Heart failure with preserved ejection fraction — coming to terms with an oxymoron

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Many patients with heart failure do not have reduced left ventricular ejection fraction, and it is not yet clear whether their treatment should be the same as that of patients who do

The syndrome of heart failure is one that is familiar to most clinicians. The cardinal symptoms of dyspnoea and fatigue when combined with signs of fluid retention — lung crackles, elevated jugular venous pressure and peripheral oedema — usually lead one to the diagnosis. Indeed, the Framingham criteria for diagnosis of heart failure are based largely on clinical findings that can be elicited at the bedside.[1] When combined with what most of us have been taught in medical school, namely, that heart failure is usually caused by the loss of the pumping capacity of the left ventricle (eg, after myocardial infarction or due to cardiomyopathy), clinicians have become familiar with the concept that most cases of heart failure are associated with impaired left ventricular systolic function, shown by a reduction in the left ventricular ejection fraction (LVEF). As if to reinforce this mindset, major trials of new treatments for heart failure have historically focused on the group of patients with reduced LVEF.

Applying echocardiography and other diagnostic imaging modalities to patients with heart failure has led to the realisation that many patients, as many as half in some series, do not have a reduced LVEF. Several terms have been used to describe this population, such as "diastolic heart failure'", "heart failure with normal systolic function" and "heart failure with preserved systolic function". All three terms are problematic. Diastolic dysfunction is common in patients with impaired LVEF[2] and many patients with preserved LVEF have unequivocal evidence of systolic dysfunction.[3] My personal preference is for the term "heart failure with preserved ejection fraction" (HFPEF), as it makes no assumptions about the pathophysiology of heart failure in affected patients. Even this descriptor is not without its problems, as different investigators appear to have differing opinions as to what should be considered a "preserved" LVEF. Investigators in different studies have drawn the line between preserved and reduced LVEF at 50%,[4] 45%,[5,6] 40%,[7] or even 35%.[8] Needless to say, this diagnostic confusion does nothing to help clinicians who are trying to care for these patients. Is it important to distinguish HFPEF from heart failure with reduced ejection fraction (HFREF)? Are they simply different ends of a continuous disease spectrum, or do they represent distinct entities with different causes and different natural histories? Given that they present with the same clinical syndrome, should they be treated the same way? These are important questions for which we currently lack answers.

Multiple studies that have compared the demographics and natural history of HFPEF and HFREF have now been published,[9] including the study by Wong and colleagues in this issue of the Journal (*page 9*).[10] A reasonably consistent finding across these studies has been that, compared with patients with HFREF, patients with HFPEF were older, more likely to be female and more likely to have pre-existing hypertension and atrial fibrillation. Conversely, ischaemic heart disease was more common in those with HFREF. Comparison of the survival of patients with HFPEF versus HFREF has produced conflicting data. While some studies have suggested that those with HFPEF have better survival than those with HFREF, others, including Wong et al,[10] have shown no difference in survival. A recently published meta-analysis of the natural history of HFPEF compared with HFREF collected data from 17 studies that included 24 501 patients.[9] In that analysis, patients with HFPEF had a significantly better survival than those with HFREF, although it is noteworthy that over an average follow-up of 47 months, almost a third of those with HFPEF had died, indicating that the life expectancy of this group of patients is far below that of the healthy age-matched population. The poor survival of patients with HFPEF was also emphasised in the study by Wong et al,[10] and in another recent publication from the Framingham investigators.[6]

An important observation made by Wong and colleagues is that comorbid conditions and psychosocial factors are important determinants of the outcome of patients with HFPEF.[10] They found that anaemia, chronic obstructive pulmonary disease, cancer and dementia were all more common in patients with HFPEF compared with those with HFREF.[10] A higher rate of comorbid conditions in patients with HFPEF has also been noted by other investigators.[6] In addition, patients with HFPEF had fewer social supports, were more likely to live in nursing homes, and were more likely to require readmission to hospital — mainly for management of comorbid conditions rather than for heart failure.

The prognosis and quality of life for patients with HFREF has been markedly improved by the implementation of evidence-based treatments including therapy with β-blockers and inhibitors of the renin–angiotensin–aldosterone system. On the other hand, no treatment

has been proven to alter the natural history of HFPEF. Treatment remains empirical, and is aimed at controlling associated conditions such as hypertension and symptoms and signs of fluid retention. Thiazide diuretics, a class of drugs that has largely fallen out of favour for treating hypertension and HFREF, may yet prove to be the most effective drug class for preventing HFPEF. In a recent analysis of the very large ALLHAT trial of patients with hypertension and aged over 55 years,[4] antihypertensive treatment with chlorthalidone was associated with a lower risk of developing HFPEF when compared with treatment with lisinopril, amlodipine or doxazosin. Therapeutic trials of other drug classes in HFPEF have been limited, and generally disappointing. Angiotensin-receptor blockers have been the most studied class of drugs, and have been shown in two large trials to have no impact on survival.[5,7] β-Blockers appear more promising. In a prespecified analysis of the SENIORS study of the vasodilating β-blocker nebivolol in older patients with heart failure,[8] the investigators reported similar benefits of nebivolol in patients with either HFPEF or HFREF; however, the definition of HFPEF in that study was an LVEF of greater than 35%. Clearly, more trials are needed.

As our population continues to age, we are facing an impending epidemic of HFPEF together with other diseases associated with ageing. More effective blood pressure control of patients with systemic hypertension stands out as the most obvious preventive strategy, but it is clear that hypertension is only one of a number of antecedents to HFPEF. There is an urgent imperative to gain a better understanding of the pathogenesis of HFPEF in order to identify additional preventive and treatment approaches. This will be particularly challenging in a population exposed to multiple comorbid conditions, increasing physical frailty, and social isolation, as highlighted by Wong and colleagues.[10] Optimal management of these patients will require a multidisciplinary approach with the general practitioner taking the central role.

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References

1 McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971; 285: 1441-1446.
2 Meta-analysis Research Group in Echocardiography (MeRGE) Heart Failure Collaborators. Independence of restrictive filling pattern and LV ejection fraction with mortality in heart failure: an individual patient meta-analysis. *Eur J Heart Fail* 2008; 10: 786-792.
3 Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. *J Am Coll Cardiol* 2009; 54: 36-46.
4 Davis BR, Kostis JB, Simpson LM, et al. Heart failure with preserved and reduced left ventricular ejection fraction in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Circulation* 2008; 118: 2259-2267.
5 Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; 359: 2456-2467.
6 Lee DS, Gona P, Vasan RS, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham Heart Study of the National Heart, Lung, and Blood Institute. *Circulation* 2009; 119: 3070-3077.
7 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: 777-781.
8 van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol* 2009; 53: 2150-2158.
9 Somaratne JB, Berry C, McMurray JJ, et al. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. *Eur J Heart Fail* 2009; 11: 855-862.
10 Wong DT, Clark RA, Dundon BK, et al. *Caveat anicula!* Beware of quiet little old ladies. Demographic features, pharmacotherapy, readmissions and survival in a 10-year cohort of patients with heart failure and preserved systolic function. *Med J Aust* 2010; 192: 9-13. ❑