

# Failing older hearts? Of myths and left-overs

The failing heart is the common end-point of all cardiac disease. While the syndrome of 'heart failure' encompasses both left and right heart dysfunction, impairment of left ventricular (LV) function carries the greatest consequences. Failure of contraction, or LV systolic dysfunction, is usually the result of epicardial coronary artery occlusion, with resultant muscle necrosis and myocardial scarring. Failure of myocardial relaxation, loosely termed 'diastolic' heart failure, usually results from connective tissue changes. These are typically seen in chronic hypertension and result from mechanical load disturbance but may also be the result of chronic metabolic imbalance – possibly through long-term small-vessel ischaemia.

While systolic dysfunction is easily categorized by reduction in ejection fraction (EF) at echocardiography, diastolic dysfunction is much harder to define leading to the description of 'heart failure with preserved systolic function'. Uncertainty stems from ongoing attempts to retrospectively fit echocardiographic assessment of LV function (a relatively recent technique) into the original descriptive clinical syndrome of heart failure.

## Increased prominence of heart failure

The overall awareness of heart failure has increased for several reasons. The introduction of echocardiography highlighted the link between symptoms, prognosis and systolic LV impairment. This in turn drove 20 years of randomized controlled trials, which established angiotensin-converting enzyme (ACE) inhibitors and more recently beta-blockers (and aldosterone antagonists) as the cornerstones of therapy. Possibly uniquely for a medical condition these treatments make patients feel better and live longer. They also reduce hospitalization.

In addition heart failure is becoming more prevalent. A 55-year-old man has a one in three lifetime risk of developing

heart failure (Bleumink et al, 2004). This is in part because of demographic changes, since heart failure is more prevalent in older populations. However, advances in the management of ischaemic heart disease, while reducing immediate mortality, are also creating an enlarging cohort of patients with impaired LV function (Stewart et al, 2003).

It is known that patients with heart failure consume a significant and increasing financial resource, of which two thirds is the result of repeated hospitalization, while less than 10% comes from drug costs. The benefit, especially through reduced hospitalization, of organized but often complex treatment, particularly when delivered by multidisciplinary teams, has not gone unrecognized by the government. Heart failure is increasingly seen as an archetypal chronic disease suitable for protocol-based managed care programmes in the community.

Yet the evidence base is poorest in the population most at risk. Repeated broader community studies of both prevalence and incidence of heart failure have found that the average age at presentation is 76 years with approximately 40% women (Cowie et al, 1999; Davies et al, 2001). Furthermore up to half of the patients in these studies had heart failure with preserved systolic function (usually defined as an EF >40%) (Study Group of Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology, 2003a). Older, hypertensive females predominate in this latter group.

In addition while older patients have the worst prognosis with mortality approaching 30% at 1 year, they also receive the least treatment (Study Group of Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology, 2003b). Yet the evidence base for treatment is almost irrelevant to this target population. Patients included in the major studies of ACE inhibitors were, on average, less than 60 years of age with an EF less than 30%. Over 80%

were male. The situation is no different for beta-blockers. In previous major studies, involving 12 500 patients, four-fifths were male with an average age of 61 years. The average EF was again less than 30%.

## Ageism in cardiology

Why has there been such a focus on younger men with systolic dysfunction? There are three reasons: the age of the patients, the influence of echo with the ease of defining systolic dysfunction and the focus, until recently, upon heart failure as a hospital-based illness. Ageism in cardiology may not be new (Bowling, 1999). It is argued that compliance is poorer in older patients, perhaps as a result of cognitive impairment. They may find travel difficult and not wish to take part in complicated studies. At least as importantly, from a sponsor's perspective, are concerns that loss to follow up and co-morbidities may hinder interpretation of the results of any study.

The focus on systolic dysfunction reflects the lack of agreement on simple measurements of diastolic dysfunction. This is a problem if an absolute echocardiographic baseline is sought. If the population in question cannot be defined, it is argued, then it cannot be studied. Thus while there have been several trials of systolic heart failure to date there have only been two trials including patients with heart failure and preserved systolic function. The recent awareness of the broader burden of heart failure may stem from greater access to echo within the community and the move away from perceiving coronary artery disease as a condition of younger men.

## The need for better evidence

Thus the treatment of the population most at risk from heart failure is the least understood from two perspectives: age and cardiac dysfunction. Treatment is based upon the assumption of the treating physician both of extrapolated benefit and

of patient 'need' – in effect making-do with the left-overs from someone else's evidence.

The recently published SENIORS study of older patients with heart failure therefore deserves scrutiny (Flather et al, 2005). It took straight aim at the population at risk and gave them a beta-blocker (nebivolol) or placebo, up-titrated over a 2–4-month period. A total of 2135 patients over the age of 70 years (average 76 years, range 70–95 years; 37% women) were included if there was a history of heart failure, defined either as hospital admission for heart failure – according to the enrolling physician – within 1 year, or an recorded EF of <35% within the previous 6 months. Importantly patient's echocardiography was not a necessary condition of inclusion.

At baseline the average EF was 36% with a range from 14–75%; 37% of patients had an EF of >35%. Over 21 months of follow up 35.3% of patients in the placebo group experienced the primary endpoint (all-cause mortality or cardiovascular hospitalization) compared with 31.1% in the nebivolol group (a relative reduction of 14%;  $P=0.039$ ). Death from any cause occurred in 18.1% and 15.8% respectively (a relative reduction of 12%;  $P=0.21$ ). Tolerability was the same as placebo with 65% taking the study drug and 64.2% taking placebo at the end of the study. Two thirds of patients reached the intended dose of nebivolol (10 mg). Discontinuation was usually at the patient's request with no significant excess of adverse events with the beta-blocker.

The 4% absolute risk reduction in the primary endpoint over 21 months is important, given that both the older age

group and the lack of EF cut-off will have 'diluted' the result in comparison with other studies of beta-blockade in heart failure. It shows that it is possible to conduct a valid, positive study in a representative elderly population. Concerns regarding the patients' ability to participate were not borne out: a total of 37 patients were untraced (1.7%). Furthermore beta blockade was given on top of baseline medication that included ACE inhibitor or angiotensin receptor blocker in more than 88% with a further 27% on an aldosterone antagonist and nearly 40% taking a cardiac glycoside. Similar benefit was seen in men and women and in those under and over 75 years of age.

In post-hoc analysis, benefit was present in patients with an EF both above and below 35%, suggesting that treatment with beta-blockade should not be confined to patients with heart failure in whom there is definite reduction in systolic function. This is not to negate the value of echocardiography, which should continue to be performed in all patients with heart failure. However, for those with preserved systolic function there is now an evidence base for beta-blockade, in addition to an angiotensin receptor blocker, which reduced hospitalization in a younger population, in the CHARM study (Yusuf et al, 2003).

## The future

What next? We do not fully understand heart failure with preserved systolic function. The Gaussian distribution of EF in the SENIORS study (and others) shows EF to be a continuous and not a dichotomous variable. The choice of arbitrary

cut-off values to define systolic dysfunction may be misleading and deny potential benefit to patients. More thought is needed.

## Conclusions

It is now known that for the typical population with heart failure, treatment based around ACE inhibitors and beta-blockers is practical and reduces death and hospitalization. The impact upon quality on life and symptom perception may be as, or even more important, than mortality benefit in the truly elderly and needs urgently to be studied. The myth that age alone is an obstacle to research can also be dispelled. **BJHM**

## Hugh F McIntyre

Consultant Physician  
The Conquest Hospital  
Hastings  
East Sussex TN37 7RD

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## KEY POINTS

- The prevalence of heart failure is increasing as a result of better care of ischaemic heart disease and an ageing population.
- Treatment of the population most at risk from heart failure is the least understood from two perspectives: age and cardiac dysfunction.
- Trials to date have focussed on younger patients with systolic left ventricular dysfunction.
- A recent study has shown that beta blockade is both feasible and beneficial in an older population with a broad range of left ventricular dysfunction.
- The mechanisms and treatment of heart failure with preserved systolic function remain poorly understood.