Heart failure with preserved ejection fraction: dangerous, elusive, and difficult

Olav W. Nielsen¹, Lars Køber², and Christian Torp-Pedersen³*

¹Department of Cardiology, Bispebjerg University Hospital, DK-2400 Copenhagen NV, Denmark; ²Department of Cardiology, Rigshospitalet, DK-2100 Copenhagen, Denmark; and ³Department of Cardiology P, Gentofte University Hospital, Niels Andersensvej 65, DK-2900 Hellerup, Denmark

This editorial refers to ‘Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study’ by C. Tribouilloy et al.¹ on page 339

Heart failure with preserved ejection fraction has received increasing attention in the last couple of years. The study of Tribouilloy et al.¹ adds information to our understanding of the prognosis of this entity. A total of 800 consecutive patients hospitalized for a first episode of heart failure in a region of France were studied. Details of the ejection fraction were available in 83% of patients, and half of these patients had preserved ejection fraction. During a follow-up of 5 years, patients with preserved ejection fraction had a survival of 43%, similar to patients with reduced left ventricular function. The entity of heart failure with preserved ejection fraction remains dangerous, but also elusive and difficult.

Dangerous

The observation that heart failure with preserved ejection fraction is dangerous has now been confirmed in a range of systematic surveys. In a study of 2801 patients from Canada,² patients with preserved/reduced ejection fraction had 1-year mortalities of 22/26%, in a study of 4596 patients from Minnesota, USA, the 1-year mortalities were 29/32%,³ in a study of 1720 patients from California, USA,⁴ the 1-year mortalities were 27/36%, and in a study of 5491 Danish patients,⁵ the 1-year mortality was 19% among patients with preserved ejection fraction and ~25% among the majority of patients with reduced ejection fraction. The high mortality in patients with preserved compared with reduced ejection fraction is still evident when the event rates are adjusted for available covariates. The picture is not completely without exceptions, and the study of Ahmed et al.⁶ using data from a large clinical trial of patients with heart failure with preserved ejection fraction found a lower mortality than when the ejection fraction was reduced. As well illustrated in the study of Tribouilloy et al.,⁷ patients with preserved ejection fraction are older and more often female. The aetiology of heart failure differs, with hypertension being dominant in patients with preserved ejection fraction and ischaemic heart disease predominant among those with reduced ejection fraction. Co-morbidities are remarkably similar in these two groups and do not explain the high mortality in patients with preserved ejection fraction.

Elusive

In the studies described above, the proportions of patients with preserved ejection fraction were 31% in Canada, 47% in Minnesota, 55% in California, and 40% in Denmark—compared with 56% in the study of Tribouilloy et al.¹ Therefore, heart failure with preserved ejection fraction appears to occur in a large proportion of patients admitted with heart failure. These patients would thus appear to be easy to identify for trials as patients with reduced ejection fraction. In the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) trials, the same centres enrolled patients in the CHARM-Preserved—where an ejection fraction >40% was one of the entry criteria—and the CHARM-Added which required a reduced ejection fraction. Given the results of the studies cited above, the mortality should be roughly equal in these two studies, but the mortality in the CHARM-Preserved study was half that in CHARM-Added. Secondly, recruitment of patients in the Charm-Preserved study took almost twice as long as in the Charm-Added trial, which indicates that patients with preserved ejection fraction more often had exclusion criteria. A remarkably low 1-year mortality of heart failure patients with preserved ejection fraction was also noted in the study by Cleland et al.,⁷ of perindopril in patients with echocardiographic signs of diastolic dysfunction. In a study of irbesartan in patients with heart failure and preserved ejection fraction,⁸ many centres found it difficult even to identify patients, but the risk is as yet unknown. Such results give heart failure with preserved ejection fraction an important elusive aspect. Apparently this high risk condition disappears once it is systematically looked for. Many trials exclude patients with co-morbidity, but according to the demographic data of Tribouilloy et al.,⁷ it is difficult to explain the elusiveness by a much higher degree of co-morbidity.

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

* Corresponding author: Tel: + 45 39773343, Fax: + 45 39760107. Email: ctp@heart.dk

† doi:10.1093/eurheartj/ehm554

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2008. For permissions please email: journals.permissions@oxfordjournals.org
Difficult

Heart failure with preserved ejection fraction is not difficult to understand when there is significant aortic or mitral valve disease, when there is significant left ventricular hypertrophy, or the rare cases of restrictive cardiomyopathy. Also understandable is heart failure secondary to poorly regulated atrial fibrillation. In all these cases the substrate for increased diastolic pressure and hence increased venous pressure in the pulmonary circulation leading to pulmonary congestion is obvious. However, the bulk of heart failure cases with preserved ejection fraction do not fall into these categories. The study of Tribouilloy adds to this notion. While 36% of patient had atrial fibrillation and 53% had hypertensive heart disease, left ventricular hypertrophy was only present in 17% of cases and valvular disease in only 13% of cases. The question automatically arises as to whether the results of this and other surveys is an indication of misdiagnosis in many cases. Heart failure is a notoriously difficult diagnosis and there are countless individual cases of pulmonary disease being confused with cardiac disease over many years. None of the symptoms of heart failure is specific and, as in most other studies, the study of Tribouilloy et al. used a definition based on exclusion instead of confirmative investigation of diastolic function. Determination of the plasma concentration of brain-derived natriuretic protein (BNP) and tissue Doppler echocardiography are available bedside tools, which may help physicians to establish a diagnosis of systolic or diastolic heart failure.9,10 Such methods expand the classification of heart failure, but it is still premature to predict how these criteria will alter the prevalence and mortality of heart failure in epidemiological studies.

Each finding available in daily clinical practice associated with heart failure is uncertain—and the echocardiographic examination can also be erroneous, in particular when the imaging situation is less than perfect. In Table 3, Tribouilloy et al. provide data that demonstrate the possibility of erroneous diagnosis contributing to the frequency of heart failure with preserved ejection fraction. Among those who died, a number of non-cardiac diagnoses were more common, including cancer and obstructive pulmonary disease.

Solution/implication

The study of Tribouilloy adds important data to the notion that heart failure with preserved ejection fraction apparently is as common and as dangerous as heart failure related to left ventricular systolic dysfunction. However, the elusiveness of the diagnosis when sought for clinical trials and the many indications that an unknown fraction of the cases may not be heart failure call for studies to clarify the pathology of heart failure with preserved ejection fraction. More surveys are needed, but different types of surveys. What we need are studies that systematically evaluate series of cases of heart failure with preserved ejection fraction with a range of advanced examinations which could include newer tissue Doppler studies, heart catheterizations, as well as thoracic studies of competing causes of dyspnoea. Examination during physical exercise may also be relevant as patients with heart failure and preserved ejection fraction have a limited functional capacity, and even with low level exercise patients with heart failure and preserved ejection fraction have a lower cardiac index, impaired arterial vasodilation, and reduced heart rate response compared with control subjects.11 Such studies could clarify whether the diagnosis is truly as common as it appears to be and could explain the pathological processes in the heart for the difficult cases without an obvious substrate for pulmonary congestion. While heart failure with reduced ejection fraction may appear to be relatively homogenous and to be amenable to well documented life-saving treatment, the condition may in fact turn out to be a more heterogeneous disease, which will have important repercussions on the treatment strategy. Thus, a simplistic approach using one medical treatment will most probably not be rewarding.

Competing interests: none declared.

References
