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EDITORIAL COMMENT

Heart failure with preserved ejection fraction: A moving target☆

Insuficiência cardíaca com fração de ejeção preservada: um alvo em movimento

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The signs and symptoms associated with heart failure (HF) were traditionally considered to be the result of pump failure due to depressed cardiac contractility, which could be quantified by assessing ejection fraction. However, some patients with hypertrophic cardiomyopathy or coronary artery disease presented normal ejection fraction and a clinical setting compatible with HF; these were considered to have diastolic HF.

However, in the last twenty years, our understanding of HF has changed radically, a significant percentage of patients presenting HF with preserved ejection fraction (HFPEF), but who do not fit into previously established categories. Although such individuals account for an increasing proportion of HF patients (rising from 38% to 54% between 1987 and 2001, and increasing by around 1% a year),[1,2] little is known concerning this entity.

What is reasonably sure is that such patients are predominantly female and older, are more likely to have hypertension and atrial fibrillation but less likely to have coronary artery disease, and have more comorbidities, than patients with HF with reduced ejection fraction (HFREF). Beyond that, little is known for certain.

Despite the large number of patients with HFPEF, there is still no consensus on the mortality associated with this entity. For years, it was considered to be similar to that of patients with HFREF,[2] but a 2012 meta-analysis of randomized clinical trials involving over 40 000 patients showed lower mortality in HFPEF (adjusted for age, gender, etiology, and history of hypertension, diabetes and atrial fibrillation).[3] However, a presentation by the Canadian Heart Failure Network at the European Society of Cardiology's Heart Failure Congress 2013 reported no difference in survival between HFPEF and HPREF patients in a study of approximately 10 000 individuals.

Although these results appear contradictory, certain considerations should be borne in mind. HFPEF patients tend to have more comorbidities, which may affect mortality, and in fact cardiac death is less common in this patient group. The variability of results may thus be due to differences in the number and severity of comorbidities.

The prognosis of HFPEF has not changed in recent years, in contrast to that of HFREF, in which advances in medical therapy and devices have led to reductions in morbidity and mortality. There is as yet no evidence that any drug or device reduces mortality in HFPEF.[4–6] There are various possible reasons for the failure of randomized clinical trials to demonstrate any benefit, but inappropriate patient selection will certainly have played a part. In the

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PEP-CHF (Perindopril in Elderly People with Chronic HF) study, the diagnosis of diastolic dysfunction was established by pulsed Doppler, and the mean age of the population was 78 years, which calls into question the reliability of this assessment. In the CHARM-Preserved Trial (Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction), an echocardiographic sub-study showed diastolic dysfunction in only 67% of the patients. In the I-PRESERVE trial (Outcome of heart failure with preserved ejection fraction in a population-based study), which included patients with dyspnea compatible with HF in NYHA class II-IV, the fact that 41% of patients had a body mass index of $\geq$30 kg/m^2 and that the 25th percentile of N-terminal pro-brain natriuretic peptide (NT-proBNP) was 139 vs. 131 pg/ml (irbesartan vs. placebo) raises the possibility that etiologies other than HF may have caused dyspnea.[7]

Review of the characteristics of patients included in these large studies suggests that there was considerable potential for inappropriate patient selection. Nevertheless, a more important problem is the limited understanding of HFPEF.

There is growing evidence that it is not merely a question of diastolic dysfunction. Tan et al.[8] found that, following thorough echocardiographic evaluation at rest and during exercise, HFPEF patients presented multiple changes in systolic (lower radial and longitudinal strain, apical rotation and mitral annular velocities) and diastolic function (reduced and delayed untwisting and reduced LV suction) at rest, which were more marked during exercise.

However, abnormalities in this syndrome are not limited to systolic and diastolic function; there are other changes that are manifested during exercise, including chronotropic incompetence,[9] vasodilatory disturbances and pulmonary hypertension.[10] During physical exertion, cardiac output increases through integrated enhancements in venous return, contractility, heart rate, peripheral vasodilation and diastolic function. Borlaug et al., in a landmark article published in *Circulation* in 2006, described HFPEF as a syndrome of impaired cardiac reserves, since all these parameters are altered.[11]

This lends weight to the idea that HF should be considered a syndrome rather than a diagnosis, and that patients with HFPEF have a variety of clinical and risk profiles, far more heterogeneous than those with HFREF. Decision trees that reflect the above-mentioned alterations may be more successful in arriving at a correct diagnosis, as well as in guiding appropriate treatment.

Natriuretic peptide measurement is now widely used and its value in HFREF patients is undisputed. Recent studies suggest that it may also be useful in diagnosis and prognostic assessment of HFPEF.

Until the publication of the latest European guidelines on HF, the BNP and NT-proBNP cutoffs for exclusion of HF were 100 and 400 pg/ml, respectively. According to some studies, these values are too high and have low sensitivity for a diagnosis of HF. However, it should be noted that most studies on BNP measurement have focused on patients with acute symptoms seen in the emergency department, whose BNP levels reflected a different setting from that of outpatients with milder symptoms.

The latest ESC guidelines (2012) suggest different cutoffs for BNP and NT-proBNP depending on whether dyspnea is of acute or non-acute onset (100 and 300 pg/ml for acute onset, and 35 and 125 pg/ml for non-acute situations, respectively). However, the data on which these recommended values are based are limited and not specific to patients with preserved ejection fraction. Krishnaswamy et al.[12] assessed 400 individuals with HF and showed that a BNP cutoff of 57 pg/ml identified 100% of patients with diastolic dysfunction.

In a study presented in this issue of the *Journal*, Jorge et al. assessed 161 outpatients with suspected HFPEF and analyzed the correlation between clinical, electrocardiographic and echocardiographic characteristics and BNP levels. HFPEF was confirmed in 49 individuals, and the best BNP cutoff for the diagnosis was 51 pg/ml. These results are in agreement with other studies in similar patients. The interest of the study lies in its suggestion that lower BNP levels should be used for screening outpatients with suspected HF. However, these levels are higher than those used for a diagnosis of HFREF.

To summarize, after more than twenty years of research into this entity, few results with clinical impact have been forthcoming. Recent discoveries concerning the pathophysiology and diagnosis of HFPEF may prove fruitful in the near future. In the meantime, it will continue to be termed heart failure with preserved ejection fraction, as the latter is the only characteristic common to all such patients.

Conflicts of interest

The author has no conflicts of interest to declare.

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