Comorbidities and Differential Diagnosis in Heart Failure with Preserved Ejection Fraction

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KEYWORDS

• Prognosis • Comorbidity • HF-PEF • HF-REF

KEY POINTS

- Many patients presenting with the signs and/or symptoms of HF may have an alternative diagnosis.
- Symptoms should not be solely attributed to comorbidities as patients can also have more than one condition contributing to their symptoms.
- An alternative diagnosis, particularly heart failure with reduced ejection fraction, should be considered before arriving at the diagnosis of HF-PEF as this could dramatically alter treatment options that are available.

INTRODUCTION

Heart failure (HF) is common, affecting 1% to 2% of the general population,[1–3] with the prevalence rising to more than 10% in those aged more than 80 years.[1,4] HF has a high morbidity and reduced life expectancy, with 5- and 10-year survival rates of 50% and 10% reported in epidemiologic studies.[5,6] HF can broadly be divided into 2 groups: HF with reduced ejection fraction (HF-REF) and HF with preserved ejection fraction (HF-PEF). There is a suggestion that HF-PEF accounts for almost half of all patients with HF and that prognosis is equally poor between groups,[7,8] although a recent meta-analysis of 41,972 patients showed HF-REF to have a worse prognosis.[9] The main difference between these 2 groups is response to treatment. Where HF-REF has several evidence-based therapies proved to improve survival, no treatment has been shown to do so in HF-PEF. The HF-PEF phenotype also differs from HF-REF, with HF-PEF patients being older, more often women, obese, and with more comorbidities. HF-PEF diagnosis is challenging and essentially a diagnosis of exclusion, with comorbidities potentially making the diagnosis more difficult. This article describes the comorbidities commonly associated with HF-PEF, the potential influence of these comorbidities on morbidity and mortality, and the differential diagnosis.

COMORBIDITIES

Any description of the comorbidities in HF-PEF would ideally be based on cohorts of patients without selection bias, who have a confirmed diagnosis of HF-PEF. Furthermore, as the diagnosis of HF-PEF is difficult and one of exclusion, any study describing this population would ideally be prospective and use echocardiography and

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natriuretic peptides to confirm the diagnosis. Unfortunately, there are no such studies, possibly reflecting the evolving diagnostic criteria of HF-PEF. There are, however, several large epidemiologic/community cohorts,[10–15] hospital cohorts,[7,8,16–24] and randomized controlled clinical trials (RCTs)[25–37] available (**Table 1**). Many of these studies used different inclusion criteria and definitions of HF-PEF, reflecting different eras of recruitment. However, useful comparisons and observations can still be made from the large number of patients enrolled in these different settings. The most obvious comparison would be with HF-REF patients. Patients with HF-PEF are consistently older, regardless of whether the cohort is based in the community, hospital, or an RCT. Another striking difference in demographics is the proportion of female patients, with HF-PEF having much higher prevalence of women. Women generally accounted for more than half of HF-PEF patients, whereas the converse is true in HF-REF. Of the HF-PEF studies with more than 1000 participants, only 4 studies had less than 50% women. These were the DIG (Digoxin Investigation Group) ancillary trial,[31] CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity)-preserved trial,[36] the DIAMOND-CHF (Danish Investigations of Arrhythmia and Mortality) study,[16] and the population-based study by Ather and colleagues.[12] Even then, women accounted for a much higher proportion compared with HF-REF in the DIG (41% vs 23%), CHARM (40% vs 26%), and DIAMOND-CHF (49% vs 33%) cohorts. One notable exception is the study by Ather and colleagues, with only 9% women, although this is not unexpected as this was a study of Veterans. Again the proportion of women was higher in the HF-PEF group compared to HF-REF (9% vs 4%). There are other similarities between the different HF-PEF cohorts other than age and sex, namely type and frequency of comorbidities.

CARDIOVASCULAR COMORBIDITIES

Hypertension

Hypertension (HT) is the most common comorbidity associated with HF-PEF (see **Table 1**). Community cohorts report HT prevalence between 44% and 86%, with a higher proportion of HF-PEF with HT than HF-REF. Hospital cohorts and registries report similarly high proportions of HT, up to 80%. Again, HT would appear more common in hospitalized HF-PEF patients compared to HF-REF. Tribouilloy and colleagues[20] reported a marked difference between HF-PEF and HF-REF (74% vs 48%). Only the DIAMOND-CHF registry reported less than 50% HT.[16] RCTs report even higher proportions of HT, with the recent I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function) and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trials reporting HT prevalence of 88% and 91%, respectively.[28,30] Although HT was also common in the HF-REF arms of several comparison studies, there was a much higher prevalence in HF-PEF.

The high prevalence of HT is not surprising, given increased left ventricular (LV) stiffness and impaired LV relaxation, often associated with concentric left ventricular hypertrophy (LVH), resulting in impaired diastolic dysfunction are thought to be key components in the pathophysiologic process of HF-PEF.[38] Indeed, the presence of LVH is now a component of the European Society of Cardiology Guidelines diagnostic pathway for HF-PEF.[39]

There would appear to be more to HF-PEF than old age, female sex, HT, and LVH. Comparisons can be made between large RCTs of HT and HF-PEF, which reported heart failure hospitalization (HFH) and overall mortality rates per 1000 patient years (**Table 2**).[31,40–50] Four HT trials enrolled elderly cohorts with mostly women: the HYVET (Hypertension in the Very Elderly Trial) trial had a mean age of 84 years, with 60% women[41]; the ANBP-2 (Second Australia National Blood Pressure) trial had a mean age of 72 years, with 51% women[45]; the LIFE (Losartan Intervention for Endpoint reduction in hypertension) trial had a mean age of 67 years, with 54% women[43]; and the STOP-2 (Swedish Trial in Old Patients with Hypertension) trial had a mean age of 76 years, with 67% women.[40] The 3 HF-PEF trials enrolled similar proportions of female patients and were also elderly: the DIG ancillary trial had a mean age of 67 years, with 41% women; the CHARM-preserved trial had a mean age of 67 years, with 40% women; and the I-PRESERVE trial had a mean age of 72 years, with 60% women. These 3 trials had a high prevalence of HT, 60%, 64%, and 68%, respectively. Despite the HT trials enrolling older patients with more HT, the overall mortality rates and HF hospitalization rates were still higher in the HF-PEF trials (see **Table 2**).

Although abnormal LV geometry and mass are thought to be important in the pathogenesis of HF-PEF, this does not wholly account for the morbidity and mortality. Despite similar LV mass in HT patients with LVH, HF-PEF patients have been shown to have worse diastolic function, lower LV cavity size, and stroke volume.[51] Both I-PRESERVE and LIFE published echocardiography substudies, with LIFE reporting a higher LV