Heart failure with preserved and reduced ejection fraction: different risk profiles for different diseases

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This editorial refers to ‘Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND’†, by F.P. Brouwers et al., on page 1424

Approximately 15 million Europeans and 6 million Americans suffer from heart failure (HF), with annual direct and indirect costs in the billions. About half of patients have a preserved ejection fraction (HFrEF), while the others display a reduced EF (HFrEF). Clinical trials have unequivocally shown that treatments such as neurohormonal antagonists improve outcome in HFrEF, while similar trials in HfPEF have been neutral. Several reasons have been proposed for this differential response, including unique pathophysiological features in HFrEF and HfPEF, differing degrees of neurohormonal activation, significant pathophysiological heterogeneity within the broad population of HfPEF patients, and higher non-cardiovascular mortality in HfPEF. It is also possible that the heart in HFrEF displays greater plasticity and amenability to reverse remodelling, while changes in the mechanical properties of the heart and vasculature in HfPEF might be less reversible by the time symptoms develop. Thus, interventions designed to prevent HfPEF might be more effective to reduce the global disease burden. To better inform strategies to prevent HfPEF (and HFrEF), detailed insight is needed into disease-specific risk factors.

Brouwers and colleagues have now presented exciting new data identifying common and distinct risk profiles for incident HfPEF and HFrEF. As part of the community-based Prevention of Renal and Vascular Endstage Disease (PREVEND) study, 8592 subjects living in Groningen, The Netherlands, underwent baseline medical examination along with blood testing and 24 h urine sampling. After a median follow-up duration of 11.5 years, the authors undertook the ambitious enterprise of carefully reviewing all medical records to identify subjects developing incident HF. The HF diagnosis was established according to contemporary clinical, laboratory, and radiographic criteria as adjudicated by a panel of experienced cardiologists. HFrEF was defined by EF ≤ 40% and HfPEF by EF > 50%, meaning that the ‘middle group’ (EF 41–49%) was excluded, though it is notable that only 1.3% of all HF subjects fell in this range. During the study period, 374 people developed HF (4.4%) of which 66% had HFrEF and 34% had HfPEF. The average time to diagnosis was 7.2 years, but intriguingly subjects with HfPEF were diagnosed ~2 years later than those with HFrEF. In multivariable analysis, incident HF was associated with older age, male sex, obesity, history of myocardial infarction, N-terminal pro brain natriuretic peptide (NT-proBNP) and highly sensitive troponin T (hs-TnT). These findings confirm previous studies examining risk factors for incident HF, but they say relatively little about the specific risk for the two HF phenotypes.

To explore this question, the authors then performed cause-specific hazard analyses to determine competing risk factors for HFrEF and HfPEF. In this analysis, female sex, atrial fibrillation (AF), increased urinary albumin excretion (UAE), and increased cystatin-C (a marker of decreased renal function) emerged as being preferentially associated with risk of HfPEF rather than HFrEF (Figure 1). In contrast, typical coronary risk factors, such as male sex, smoking history, hs-TnT, and prior myocardial infarction were preferentially associated with risk of HFrEF. Obesity conferred similarly increased risk in both HF types. The authors conclude that these data provide further evidence in support of the notion that HfPEF and HFrEF are distinct HF phenotypes with separate pathophysiological features. These data confirm and extend upon recent studies examining risk factors for HfPEF and HFrEF preceding and at the time of diagnosis. Strengths are the very high proportion of subjects with EF assessment (>98%), and the fact that HF was identified in both outpatients and hospitalized subjects. However, the retrospective assessment of HF status from chart review alone is a weakness.
For example, physical findings of congestion such as jugular disten-
tion or subjective complaints of exertional dyspnoea and fatigue
are easy to miss in everyday practice, or may simply not have
been documented in the clinical records. This HF under-
recognition is more common in patients with preserved EF,
where the diagnosis continues to be less seriously entertained
than when the EF is grossly reduced. Indeed, even when the
patient with dyspnoea is evaluated by a cardiologist, the diagnosis
of HFpEF can be challenging to make, often requiring invasive as-
assessment with or without provocative testing to render with con-
fidence. In PREVEND, HF was suspected in a large number of
subjects where sufficient evidence was not felt to be present or al-
ternative causes were observed (189, >50% of the HF group), and
one wonders how many of these subjects might have been reclass-
ified as HFpEF with more intensive evaluation. Presumably, the EF
was normal in all of these subjects, since the presence of dyspnoea
in a patient with low EF will invariably lead to the diagnosis of HF.
In addition to the potential underdetection of HFpEF in this retro-
spective assessment, the mean age at entry (49 years) prob-
able contributes to the lower prevalence of HFpEF relative to
HFrEF. Indeed, community-based studies from the Framingham
group have reported a mean age at diagnosis of 79 years in
HFpEF. Age was associated with increased risk for both HF
phenotypes, but the impact was significantly greater for HFpEF.
Thus, one would expect that as this population ages and is fol-
lowed for a longer duration, HFpEF will ‘catch up’ in prevalence
with HFrEF.

The findings of increased risk of incident HFpEF with female sex
and AF are in keeping with previous studies. While the
mechanisms contributing to greater risk of HFpEF in women
remain incompletely understood, there appear to be important
sexual dimorphisms in ventricular–vascular structure and function
that develop with ageing which may predispose to HFpEF in
women. The presence of AF is another consistent factor that
increases HFpEF risk. The impact of AF is even more apparent
when considering that its prevalence at entry into PREVEND
was similar in patients destined to develop HFpEF and HFrEF,
yet AF conferred greater risk only in HFpEF (hazard ratio 3.8).
These data are congruent with observations from the CHARM
programme, where the presence of AF was associated with
increased risk of HF hospitalization and death relatively more in
HFpEF than in HFrEF. It seems that the heart in patients with
HFpEF (or at risk for HFpEF) is more reliant on atrial contraction
to maintain haemodynamic compensation, and is thus more vulner-
able to the deleterious effects of AF, leading to expression of the
HF syndrome. These data support efforts to prevent the
development of AF to help prevent HFpEF, in addition to diseases such as stroke.

Brouwers and colleagues also describe two previously unidentified risk factors for HFpEF, each of which is related to renal function: increased UAE and elevation in cystatin-C. As with AF, baseline UAE and cystatin-C levels were similar in subjects who ultimately developed HFpEF and HFrEF, meaning that greater burden of renal disease does not explain the association. Hypertension and diabetes were notably not predictive of HF risk, but each of these co-morbidities is in itself associated with renal dysfunction, albuminuria and AF, and this may explain the apparent lack of association. Loss of renal ability to dispose of excess volume would be expected to increase the risk of subclinical HF becoming manifest, and it appears that this vulnerability is greater in HFpEF. In line with this finding, ancillary data from the ALLHAT trial showed that the diuretic chlorthalidone reduced incident HFpEF compared with other antihypertensives. In contrast, angiotensin-converting enzyme (ACE) inhibitors, which are well known to mitigate albuminuria, were not found to prevent HFpEF.

Brouwers and colleagues are to be congratulated for taking a major step forward in understanding the pathogenesis of HFpEF, but there is still much to learn. Within the broad category of ‘HFpEF’, there are several aetiologies that are currently defined separately in practice, and others that may require further study for proper taxonomic classification (Figure 1). For example, patients with HF caused by severe mitral insufficiency or aortic stenosis will clearly behave differently and respond to treatments differently from patients with hypertrophic cardiomyopathy, constrictive pericarditis, or high output HF. However, despite this heterogeneity, these entities continue currently to be lumped together into the category of ‘HFpEF’. As we move forward with epidemiological and physiological studies, these specific aetiologies of the HF syndrome should not be included under the broad term of HFpEF.

Even when these ‘non-HFpEF’ causes are excluded, there are likely to be additional layers of pathophysiological heterogeneity in HFpEF that require better characterization. For example, we have recently shown that on average, cardiac output reserve predominantly limits exercise capacity in HFpEF, and yet other groups have identified HFpEF patients with overly exuberant cardiac output responses, or abnormalities peripheral to the heart in the skeletal muscle and vasculature that more potently dictate functional limitation.

Some HFpEF patients seem to express predominant diastolic limitations, yet most display numerous abnormalities in cardiovascular reserve, including diastolic dysfunction, systolic dysfunction, chronotropic incompetence, abnormal vasodilation, and endothelial dysfunction. It seems likely that these different HFpEF subphenotypes might have their own unique risk factors and treatments. Future studies that more rigorously characterize the specific phenotypes within the broader population of HFpEF may hold the greatest promise finally to prevent and treat this deadly and growing disease for which there is no effective therapy.

Conflict of interest: none declared.

References


