Noncardiac Comorbidities in Heart Failure With Preserved Ejection Fraction
– A Commonly Ignored Fact –
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It has been well described that many patients with heart failure (HF) have a normal left ventricular ejection fraction. This entity has been termed “heart failure with preserved ejection fraction (HFPEF)”\(^1\). Significant advances have been made in understanding the clinical characteristics of HFPEF over the past 2 decades on the basis of large HF registries and randomized clinical trials. However, most multicenter clinical trials that investigated medical therapies in HFPEF have yielded disappointing results. HFPEF being a clinical syndrome involving multiple organ systems may be a potential explanation for treatment failure. In this review we discuss the prevalence of noncardiac comorbidities in HFPEF patients as well as their effect on the prognosis of HFPEF. (Circ J 2015; 79: 954–959)

**Key Words:** Diastolic dysfunction; Ejection fraction; Heart failure; Morbidity

Heart failure (HF) is a global disease and still on the rise, affecting approximately 2% of the Western population, with prevalence increasing sharply from 1% in 40 year-old individuals to 10% in those over 75 years.\(^1\) Although HF was traditionally labeled as ‘pump failure’ or reduced left ventricular ejection fraction (LVEF), it has become widely recognized that HF can occur even in patients with relatively normal or preserved EF, a condition called HF with preserved EF (HFPEF).\(^2\) HFPEF is a complex syndrome characterized by signs and symptoms of HF and a relatively normal LVEF. Studies have reported the prevalence of HFPEF ranging from 30% to 70% among HF patients cohorts.\(^3\)–\(^5\)

Over the past 2 decades, significant advances have been made in understanding the epidemiology and pathophysiology of HFPEF, based on large HF registries and randomized, controlled clinical trials. Cardiovascular risk factors are found to be highly prevalent in HFPEF in population-based studies and registries, which include obesity in 41–46%, coronary artery disease in 20–76%, diabetes mellitus in 13–70%, atrial fibrillation in 15–41%, and hyperlipidemia in 16–77%, which is similar to HF with reduced EF (HFREF).\(^1\)

Intriguingly, drugs that improve outcomes in HFREF have not been shown to be similarly beneficial for HFPEF in multicenter clinical trials such as DIG,\(^6\) PEP-CHF,\(^7\) I-PRESERVE,\(^8\) CHARM-Preserved\(^9\) and TOPCAT.\(^10\) Potential contributors to treatment failure may include suboptimal study design or inadequate statistical power, but the involvement of multiple organ systems rather than only the cardiovascular system in HFPEF is possibly the most relevant. Noncardiovascular comorbidities appear to be prevalent in HFPEF, which may at least partially be explained by the more advanced age of this population. They include renal impairment, chronic lung diseases, anemia, cancer, liver disease, peptic ulcer disease and hypothyroidism.\(^6\)–\(^10\) Published mortality data showed that patients with HFPEF had a higher proportion of noncardiovascular deaths when compared with those with HFREF.\(^3\)–\(^10\)–\(^12\) The relative effects of these comorbidities on morbidity and mortality in HFPEF compared with HFREF have not yet been well studied.

In this review we summarize the prevalence of the wide range of noncardiac comorbidities in HFPEF patients as well as their relative effects on morbidity and mortality of HFPEF (Table, Figure). We also discuss the underlying mechanism of these comorbidities contributing to poor outcomes of HFPEF patients.

**Noncardiac Comorbidities in HFPEF**

**Renal Dysfunction**
The critical effect of renal function on mortality of HFPEF is not well established.\(^13\) It was found that approximately 51–58.5% of HFPEF patients had an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m\(^2\).\(^14\)–\(^16\) In fact, lower admission eGFR is a predictor of all-cause mortality and hospitalizations at 12–22 months of follow-up, even after adjustment for covari-
Noncardiac Comorbidities in HFPEF

Hyponatremia

Traditionally, hyponatremia is a predictor of adverse short-term outcomes in patients with acute HF. Hyponatremia (sodium <136 mmol/L) was present in approximately 12.9–25.4% of patients with HFPEF. Recently, the prognosticator role of hyponatremia in the long-term survival of HFPEF patients has attracted attention. A cohort with 2–7 years follow-up demonstrated that baseline hyponatremia was associated with an increased risk of all-cause and cardiovascular mortalities. The presence of hyponatremia in HFPEF patients was independently related to younger age, diabetes, lower systolic blood pressure, anemia, body mass index (BMI) <30 kg/m², as well as spironolactone use. However, it is still unclear about the mechanism of hyponatremia in the onset and progression of HFPEF. The OPTIMIZE-HF and EFFECT studies found that the unadjusted relationship between serum sodium and in-hospital mortality was present regardless of LV function, which may indicate that the mechanism and effect of hyponatremia are similar in HFREF and HFPEF.

Hyponatremia can be classified as hypervolemic, hypovolemic or euvolemic. In the setting of HF, hyponatremia at admission is most likely to be hypervolemic because of fluid overload. In one of these studies, 16.6% of HFPEF patients showed deteriorated in eGFR of at least 25% after 1 year of follow-up. These patients were more likely to be diabetic. However, a more recent study observed a U-shaped relationship between the level of renal function and death, and to a lesser extent between the level of renal function and all-cause hospitalization. Development of eGFR >130 ml/min/1.73 m² during follow-up was also independently associated with worse outcomes in HFPEF patients.

Renal dysfunction may be prerenal, renal or post-renal. Prerenal reasons include inadequate renal perfusion as the reason of low cardiac output and/or excessive vasoconstriction and adverse effects of anti-HF medications (angiotensin-converting enzyme inhibitors, diuretics, etc). These reasons may be the cause of renal dysfunction in both HFREF and HFPEF. Patients with HFPEF are typically older, and frequently have hypertension and diabetes. As a result, they may have significant pre-existing intrinsic renal diseases. Renal dysfunction in HFPEF could also be a marker of more generalized and advanced vascular disease. Although the prevalence of renal vascular disease in HF has been poorly delineated, it is probably high, and bilateral renal artery stenosis with rapid-onset pulmonary edema is a well-recognized cause of HFPEF. Evaluation of the renal arteries should be considered in patients presenting with the triad of hypertension, renal dysfunction and HFPEF.

### Table. Studies of Noncardiac Comorbidities in Patients With HFPEF

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence in HFPEF</th>
<th>Effect on outcomes of HFPEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rusinaru et al</td>
<td>53%</td>
<td>↑ Worsening renal function</td>
</tr>
<tr>
<td>Casado et al</td>
<td>58.2%</td>
<td>↑ 1-year all-cause mortality</td>
</tr>
<tr>
<td>McAlistier et al</td>
<td>51%</td>
<td>↑ All-cause mortality</td>
</tr>
<tr>
<td>Smith et al</td>
<td>53.5%</td>
<td>U-shape relationship between eGFR and all-cause mortality</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rusinaru et al</td>
<td>25.4%</td>
<td>↑ In-hospital and 7-year overall mortality</td>
</tr>
<tr>
<td>Bavishi et al</td>
<td>12.9%</td>
<td>↑ 2-year all-cause mortality</td>
</tr>
<tr>
<td>OPTIMIZE-HF</td>
<td>20.8%</td>
<td>↑ 1-year all-cause mortality</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uthamalingam et al</td>
<td>19.1%</td>
<td>No effect on 1-year mortality</td>
</tr>
<tr>
<td>Liu et al</td>
<td>28%</td>
<td>↑ 1-year all-cause mortality</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SENIORS study</td>
<td>10%</td>
<td>↑ All-cause mortality and cardiovascular hospital admission</td>
</tr>
<tr>
<td>Maurer et al</td>
<td>NA</td>
<td>↓ Stroke volume</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kapoor et al</td>
<td>44%</td>
<td>U-shape relationship between BMI and 1-year all-cause mortality</td>
</tr>
<tr>
<td>I-PRESERVE trial</td>
<td>41.3%</td>
<td>U-shape relationship between BMI and 6-year primary composite endpoint</td>
</tr>
<tr>
<td>MAGGIC meta-analysis</td>
<td>29.6%</td>
<td>U-shape relationship between BMI and 3-year all-cause mortality</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herrschel et al</td>
<td>54%</td>
<td>NA</td>
</tr>
<tr>
<td>Bitter et al</td>
<td>39.8%</td>
<td>NA</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwon et al</td>
<td>NA</td>
<td>↑ All-cause mortality</td>
</tr>
<tr>
<td>Rusinaru et al</td>
<td>16.5%</td>
<td>↑ All-cause mortality</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selvaraj et al</td>
<td>22%</td>
<td>NA</td>
</tr>
</tbody>
</table>

BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HFPEF, heart failure with preserved ejection fraction.
and hypervolemic hyponatremia may also act as a marker of neurohormonal activation in patients with HFREF. Furthermore, increased activation of the renin-angiotensin-aldosterone system and excessive or inappropriate arginine vasopressin release in response to nonsmotic stimuli may be the main mechanism responsible for hyponatremia in patients with HFREF. Hyponatremia may be a consequence of excessive diuretic therapy and may also have an important pathogenic effect. Patients with HFPEF are particularly sensitive to hypervolemia because the underlying impairment of HFPEF is LV abnormal relaxation and increased chamber stiffness, which may induce fluid redistribution and the symptoms of volume overload.

Hypoalbuminemia
Uthamalingam et al found that the prevalence of hypoalbuminemia (defined as a serum albumin ≤34 g/L) was 54% of acute decompensated HF patients in a cohort of 438; intriguingly, it was predictive of outcome but mainly in those with HFREF but not HFPEF. Our group also studied 576 consecutive HFPEF patients and found that hypoalbuminemia (serum albumin ≤34 g/L) was detected in 160 (28%) at admission. It was observed that hypoalbuminemia, history of cerebrovascular disease and older age were the most powerful independent predictors of all-cause mortality in HFPEF patients at 1 year.

Albumin is a hepatic protein, and its plasma concentration is mainly influenced by several factors, including the rate of albumin synthesis, exogenous albumin loss and dilution. Synthesis of albumin is affected by nutritional intake, colloid oncotic pressure variations, and liver function. The mechanism of hypoalbuminemia in HFPEF is not clear. A low plasma level of albumin in HFPEF probably has multiple causes including malnutrition, reduced synthesis related to hepatic congestion, hemodilution, increased metabolic activity, inflammation and proteinuria.

Anemia
Anemia also is another common comorbidity of HFPEF. Anemia was found similarly common between patients with LVEF ≤35% and those with LVEF >35% (19.0 vs. 18.7%, P=0.89) in the SENIOR study. Anemic patients were older, had lower diastolic BP and worse renal function (all P<0.05). After multivariable adjustment, hemoglobin remained an independent predictor of all-cause mortality and cardiovascular hospital admission (time to first event) in this cohort of patients. In another trial of HFPEF, treatment with epoetin α resulted in significant increases in hemoglobin level and decreases in stroke volume after 6 months, although there was no significant change in LV end-diastolic volume, LV mass and 6-minute hall-walk distance.

A number of risk factors such as female sex, advanced age, chronic kidney disease and poor nutritional status have previously been reported to predispose patients with HFREF to develop anemia in the course of the disease. All these may be also the mechanisms of anemia in patients with HFPEF, though further studies are warranted to confirm this hypothesis.

Obesity
Obesity is associated with an increased risk for HF. In general, patients with HFPEF are more often obese than are patients with HFREF, and the prevalence of diastolic dysfunction is increased in obese persons. Overweight (BMI 24.9–29.9 kg/m²) and obesity (BMI >30 kg/m²) were present in 26–44% of patients with HFPEF. A meta-analysis demonstrated that obese
HFPEF patients were younger, more likely to receive cardiovascular drug treatment, and had higher comorbidity burdens than those without obesity. Independent of other key prognostic variables for HFPEF patients, there was a U-shaped relationship, with the greatest rate of adverse outcomes in the lowest and highest BMI categories, which was called the “obesity paradox”.

Although the pathophysiology behind the obesity paradox is unknown, several possible explanations have been proposed. Patients able to maintain a healthy BMI may harbor a favorable inflammatory, hormonal, and metabolic milieu and avert a catabolic state. Soluble tumor necrosis factor α receptors, which are elevated in HF, are produced by adipose tissue and may neutralize the untoward cardiac effects of tumor necrosis factor α. Elevated levels of catecholamines, tumor necrosis factor, and interleukin-1 have been associated with the wasting syndrome of cardiac cachexia observed in advanced HFREF. Cardiac cachexia falls short of a complete explanation for the obesity paradox, because adverse outcomes have also been seen in nonachecatic patients with a low BMI.

Obesity not only imposes an adverse hemodynamic load on the heart but also is a source of a large number of biologically active peptide and nonpeptide mediators, many linked to chronic inflammation. Studies using tissue Doppler imaging or invasive LV pressure measurement have reported an association between diastolic dysfunction and obesity, even in the absence of a diagnosis of HF.

As nutrition status is likely associated with the outcomes of HFPEF patients, the geriatric nutritional risk index (GNRI) has been used to assess nutritional risk of patients with HFPEF. GNRI was calculated as follows: (14.89×serum albumin (g/dl)+41.7×BMI)/22. Kinugasa et al studied 151 patients with HFPEF and found lower GNRI predicted increased mortality independent of age, sex, prior HF hospitalization, and higher blood urea nitrogen and B-type natriuretic peptide (BNP) concentration (P<0.01) after 2.1 years’ follow-up. Considering such a counteracting effect, GNRI as a combined index of albumin and BMI may lead to minimization of the effect of fluid status and identify nutritional risk better than each of them.

Sleep-Disordered Breathing
Diastolic dysfunction is commonly associated with obstructive sleep apnea (OSA). Conversely, sleep-disordered breathing (SDB) was prevalent (69–80%) in HFPEF. Among SDB, 40–62% had OSA and 29.5% had central sleep apnea (CSA). Moreover, exercise capability, including both cardiopulmonary exercise test and 6-minute hall-walk test, was worse in patient with SDB. Partial pressure of CO2 was lower in CSA, whereas exercise test and 6-minute hall-walk test, was worse in patients with OSA. Partial pressure of CO2 was lower in CSA, whereas

Chronic Obstructive Pulmonary Disease
There also have been several studies aiming to illustrate the relationship of chronic obstructive pulmonary disease (COPD) and the prognosis of HFPEF patients. COPD was found coexistent in 16.5–19.5% of patients with HFPEF. Cardiopulmonary and pulmonary event-free survival of HFPEF was found to be similar to that of HFREF over 3 years’ follow-up. Global initiative for chronic obstructive lung disease (GOLD) stage (III vs. I) or presence of COPD was found to be an independent predictor of event-free survival in HF patients with preserved as well as reduced EF.

HFPEF and COPD are 2 increasingly prevalent conditions associated with premature mortality and poor quality of life in elderly people. High prevalence of COPD in HFPEF may be related to increasing age. COPD has been shown to increase the risk of cardiovascular disease 2–3-fold in a previous study of HFPEF. Furthermore; pulmonary hypertension is a predictor of poor prognosis in HFPEF.

Subclinical Pulmonary Dysfunction
Impairment of parameters of lung function test has been found to be common and related to adverse outcome in patients with HFPEF. Andrea et al found that 94% of the patients had at least 1 abnormal parameter in lung function measurements obtained in patients with HFPEF. Among them, spirometry was abnormal in 59%, diffusing capacity of the lungs for carbon monoxide was abnormal in 83% and arterial hypoxemia were present in 62% of patients. Lower ratio of forced expiratory volume in 1 s to forced vital capacity and lower hemoglobin concentrations were associated with increased risk of HF in a study (including both HFREF and HFPEF).

Pulmonary function has a direct effect on the manifestation of dyspnea. Subclinical pulmonary dysfunction is characterized by low-grade inflammation and may contribute to progression of atherosclerosis and myocardial dysfunction. Of note, even mild airflow obstruction is associated with abnormal LV diastolic filling.

Thyroid Dysfunction
Thyroid dysfunction is not uncommon in HFPEF. In one study, 22% of patients with HFPEF had reduced total triiodothyronine (T3) levels. Patients with reduced T3 levels were older, more symptomatic, had higher prevalences of hyperlipidemia and diabetes, and higher BNP levels. In addition, lower T3 levels was associated with more severe LV diastolic dysfunction with higher mitral E velocity and shorter deceleration time (ie, towards more restrictive physiology of filling), as well as higher pulse pressure/stroke volume ratio. Conversely, Masaki et al showed that patients with subclinical hypothyroidism had impaired LV diastolic function and elevated NT-proBNP when compared with euthyroid patients.

It is possible that the HFPEF may cause lower T3 levels, which in turn exacerbate HF symptoms and create a vicious cycle.

Several previous studies had investigated the mechanisms of low T3 in HF, which include upregulation of type III deiodinase enzyme that converted T3 to its inactive counterpart as shown in a rat model and increased levels of pro-inflammatory cytokines in human subjects. Even when levels of T3 are “normal” in HF patients, the downstream effects of T3 may be blunted by the upregulation of certain repressor proteins.

On the other hand, Kinugasa et al summarized the mechanism of the development of HF in patients with subclinical hypothyroidism, including impaired LV function, increased vascular stiffness and the ventricular-arterial interaction.
Other Comorbidities

The prevalence of peptic ulcer disease was higher in patients with HFPEF than those with HREF (8.1% vs. 6.0%, P<0.001) in a cohort study. However, there was no significant relationship between the presence of peptic ulcer disease and higher mortality of patients with HFPEF. There are some studies of the relationship between rheumatoid arthritis (RA) and HFPEF. A study demonstrates that patients with RA have a higher prevalence of diastolic dysfunction than those without RA. RA duration and interleukin-6 concentration are independently associated with diastolic dysfunction, suggesting the effect of chronic autoimmune inflammation on myocardial function in RA.62

Conclusions

It appears that HFPEF is a heterogeneous disorder with variable noncardiovascular comorbidities that are common and closely related to adverse outcome of HFPEF. However, unlike the wealth of clinical studies for HREF, there is a need for more clinical research to guide the treatment of noncardiac comorbidities and the effect on the outcome of patients with HFPEF.

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References


