Heart failure is currently divided by ejection fraction (EF) into 2 categories: heart failure with reduced EF (HFrEF) or preserved EF (HFpEF). The principal reason for this categorization is that the effects of medical interventions are likely different between the 2 phenotypes. Although angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, mineralocorticoid receptor blockers and β-blockers are effective for patients with HFrEF, previous randomized trials have failed to demonstrate their benefits in HFpEF. In addition, there are several characteristic differences. As compared with HFrEF patients, those with HFpEF are more frequently female and elderly. Risk factors for the development of each phenotype are different.¹ Worsening of HF more frequently occurs as clinical scenario 1 (ie, with an increase in blood pressure) in HFpEF than in HFrEF.²

However, both phenotypes have left ventricular (LV) hypertrophy and fibrosis, and the distribution of EF among patients hospitalized for HF is unimodal. Many patients of both phenotypes have similar risk factors for cardiovascular disease.

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**Figure.** The 3 patterns of heart failure (HF). First phenotype is continuous HF with reduced ejection fraction (HFrEF). When the EF is further decreased, there is an associated increase in LV end-diastolic and end-systolic volumes (LVEDV, LVESV, respectively). Second phenotype is continuous HF with preserved EF (HFpEF). There is no change in EF, LVEDV or LVESV. Third phenotype is HFrEF evolved from HFpEF. The decrease in EF is accompanied by an increase in LVESV but not LVEDV.
such as hypertension and diabetes mellitus, and malnutrition is an independent risk factor for poor prognosis in HFrEF as well as HFrEF. Although some studies have reported that the mortality of HFrEF and HFrEF is similar, other studies have come to the different conclusion that HFrEF has a poorer prognosis than HFrEF. The mode of death is also different. The prevalence of cardiovascular death is lower in HFrEF than in HFrEF. Thus, some may argue that HFrEF and HFrEF are on the same continuum, and that HFrEF is a less ill stage before the development of HFrEF.

These arguments are not necessarily supported. The cohort study at Olmsted County demonstrated that EF followed a bimodal distribution among patients with HF, and EF at the trough between 2 peaks was approximately 45%, which is one of the cut-off values to divide HF into HFrEF and HFrEP. That result indicates the unique pathophysiology of the 2 phenotypes of HF. One of the characteristic differences is that HFrEF is associated with LV dilatation in contrast to the absence of LV dilatation in HFrEF. Although LV diastolic dysfunction is common in both HFrEF and HFrEP, there is a difference in LV systolic function. Indeed, there is controversy about the systolic function of HFrEP. Some studies have shown that systolic function is preserved in HFrEP, and others have reported its impairment. These contradictory results may at least partly stem from the different rules for systolic function used in each study. Another important issue is that abnormal factors in HFrEP are not equal to the determinants of its pathophysiology. The comparison between normal controls and HFrEP demonstrates what is abnormal in HFrEP, but does not necessarily answer what induces HFrEP. During the progression from cardiovascular disease to HF, there is a transit stage with asymptomatic cardiac dysfunction. For example, more than half of subjects with EF ≤50% are asymptomatic in the community, and these subjects are not defined as having HF. What plays roles in the progression from asymptomatic cardiac dysfunction to symptomatic stage with HF may be our therapeutic target. A previous study showed that the progression from asymptomatic diastolic dysfunction stage to HFrEP stage was not associated with further deterioration of systolic function but was accompanied by exacerbation of LV distensibility. This suggests that LV systolic dysfunction does not play a principal role in the pathophysiology of HFrEP. In contrast, several studies have reported the important role of non-cardiac factors (eg, vascular dysfunction) in the pathophysiology of HFrEP.

However, recent studies have turned our attention to systolic dysfunction with regard to the progress following the incident HFpEF. Although the data from a small number of patients show that HFpEF did not progress to systolic dysfunction, Dunlay et al reported that the EF of HFpEF patients decreased over time. They found that the decrease in EF over time was greater in HFpEF patients with higher age or coronary artery disease, and that the decline in EF over time was statistically significant in patients with an EF of 50–69% and ≥70% at diagnosis.

In contrast, Ueda et al report in this issue of the Journal that EF decreased in patients with baseline EF >50% and ≤55% and not in patients with baseline EF >55%. They also demonstrate that the decrease in EF in patients with baseline EF >50% and ≤55% was caused by the increase in LV end-systolic volume and was not necessarily related to the increase in LV end-diastolic volume. The further decrease in EF in HFrEF is usually associated with an increase in LV end-diastolic volume. Even if EF does not decrease, LV end-diastolic volume increases without anti-HF therapy in HFrEF. These different processes involving LV geometry suggest that HFrEP with progressive decline of EF should not be simply categorized to HFrEF. Ueda et al report that the baseline LV end-diastolic volume/dimension was larger in HFrEP patients with future decline of EF than in those without the decline. Dunlay et al showed that baseline LV end-diastolic dimension was not related to changes in EF in HFrEP, but their data for LV volume at follow-up were absent. Further studies are necessary to bridge the gap between Dunlay et al’s and Ueda et al’s studies.

Ueda et al raise the possibility of a third phenotype of HF in which HFpEF evolves from HFpEF without the increase in LV end-diastolic volume (Figure). The third phenotype (HFrEF evolved from HFpEF) may respond differently to medical intervention than continuous HFpEF. In future, we may have to divide HF into 3 categories (Figure) rather than just the 2 of HFrEF and HFrEP.

References