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REVIEW ARTICLE

Importance of Vascular Function in Patients with Heart Failure with Preserved Ejection Fraction

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ABSTRACT

There had been no effective cardioprotective medications for heart failure with preserved ejection fraction (HFpEF). Therefore, treatment intervention at the hypertension (HT) stage (stage A), which is a major factor in HFpEF, is necessary. In fact, the SPRINT and STEP trials reported that strict and intensive blood pressure (BP) control was useful, reducing approximately 25% of the primary endpoints, including cardiovascular events. The effectiveness of BP reduction for HFpEF after the onset of HF (stage C or D) has been reported and shown to generally follow the J-curve phenomenon. Both left ventricular systolic/diastolic dysfunction and vascular failure are related with the pathophysiology of HF. In the case of coexisting vascular failure, BP lowering treatment is effective, because it decreases the afterload. However, BP lowering treatment has been reported to increase the incidence of renal dysfunction; therefore, paying attention to the degree of association with vascular failure, and multiple organs when determining the target BP are important to consider. The decision on the target BP and the optimal choice of cardioprotective/antihypertensive medications for HF should be based on the pathologic condition.

Key words: heart failure with preserved ejection fraction, vascular function

Introduction

The number of patients with heart failure (HF) is increasing in Japan.[1] This situation is so called HF pandemic, like infective epidemic diseases, and HF pandemic is worldwide problem.[2,3] In Japan, the total number of patients with HF is expected to increase to approximately 1.3 million by 2030 and to decrease thereafter.[1] However, the number of patients hospitalized for HF will continue to increase and peak in 2040.[4] Despite advances in HF treatment, hospitalization for HF and/or cardiac death has not decreased over time.[5] Therefore, in addition the prevention of new onset of HF, reduction of the incidence of hospitalization for HF is important.

The current guidelines classify HF into three categories of ejection fraction (EF), as follows: HF with reduced ejection fraction (HFrEF), HF with preserved EF (HFpEF), and HF with mid-range EF (HFmrEF) (**Figure 1**).[6,7] The treatment of HFrEF is different from that of HFpEF and HFmrEF. Cardioprotective medications, such as the fantastic four (i.e., renin-angiotensin-aldosterone inhibitor (angiotensin converting enzyme inhibitor (ACE-I) / angiotensin II type Ia reseptor blocker (ARB) / angiotensin receptor neprilysin inhibitor (ARNI), beta blocker, mineralocorticoid receptor antagonist (MRA), and sodium glucose cotranspoter (SGLT)-2 inhibitor),[8] are useful only for HFrEF (**Figure 2**). Although some medications, which are effective for HFpEF, have been investigated,[9] there are currently no established cardioprotective medications for HFpEF. Notably, an increase in the number of HFpEF cases has been observed in an aging society[10] and may be one of the reasons for the ongoing prevalence of HF over time. Therefore, paying attention to new onset and exacerbation of HFpEF is necessary.

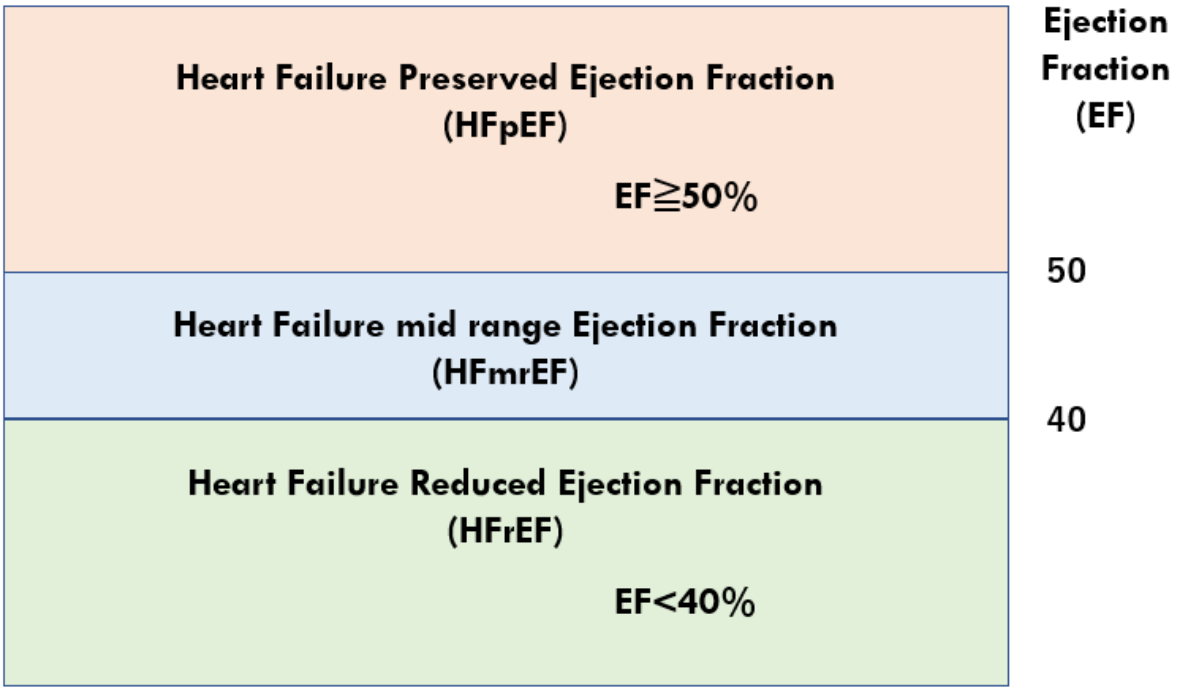

Figure 1. HF is classified into three categories

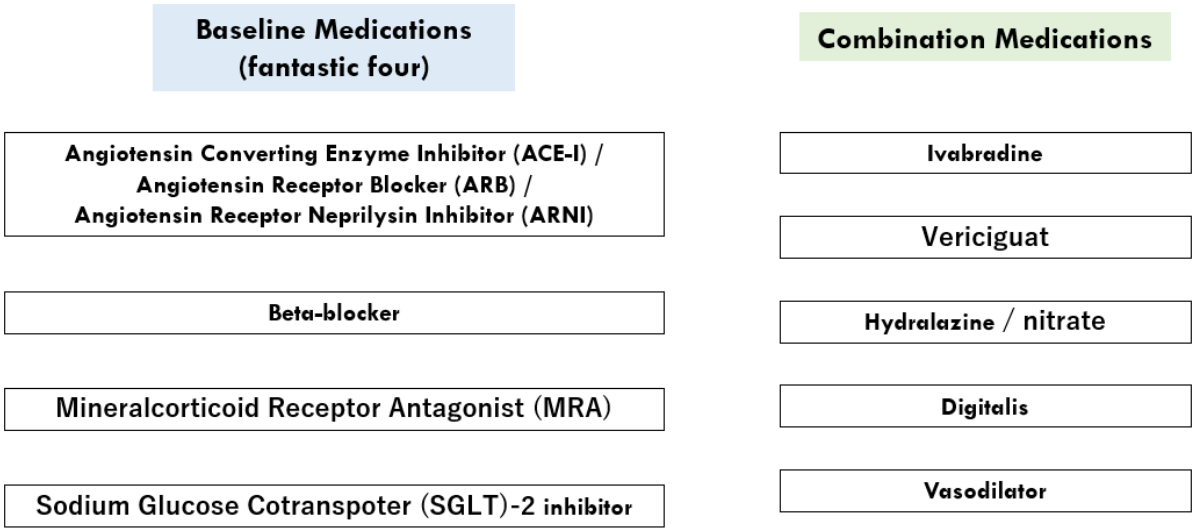

Figure 2. Recommended treatment for HFrEF

Etiology of HFpEF and prevention of new-onset HFpEF

HFpEF and HFrEF have been shown to have no difference in prognosis but have differences in the underlying heart disease and/or comorbidities.[11] Compared with HFrEF, HFpEF is more common among elderly and female patients; is associated more with comorbidities, such as anemia and atrial fibrillation; and has etiologies that more likely include cardiac hypertrophy and less likely ischemic heart disease. Hypertensive heart disease, which is common in HFpEF, often causes left ventricular diastolic dysfunction secondary to hypertension (HT).[12] Moreover, HT may directly lead to left ventricular diastolic dysfunction through neurohumoral factors and inflammation; however, it is often morphologically based on left ventricular hypertrophy (LVH) caused by pressure overload secondary to HT.[13] Because no effective cardioprotective medications for HFpEF have been identified, interventions at the stage of HT and LVH before the onset of symptomatic HF are effective.

Strict blood pressure (BP) control is effective for HT, which is stage A of HF stages and is not accompanied by cardiac structural abnormalities.[14] Studies were conducted comparing the groups between standard BP control and more strict BP control. In SPRINT and STEP studies have compared standard and stricter BP control. In the SPRINT study that was conducted mainly in the United States and Puerto Rico, control of systolic BP was controlled to approximately 135 mmHg in the standard treatment group and approximately 121 mmHg in the intensive care group.[15] As a result, it was possible to reduce the primary endpoint by groups, respectively, resulted in a 27% reduction in the primary endpoint in the intensive care group compared with the standard treatment group.15 Similarly, in the STEP study targeting Asian was also published, where systolic BP was controlled to approximately 135 mmHg in the standard treatment group and approximately 127 mmHg in the standard treatment and intensive care group.[16] Similar to the SPRINT study, the intensive care resulted in a 26% risk reduction was obtained in the primary endpoint of this study.[16] Because BP control in the intensive care group was weaker in the STEP study than in the SPRINT study, strict BP control

may be more effective in Asians than in Caucasians. [17]

Moreover, according to the SPRINT study, intensive BP lowering treatment improved LVH. [18] Control of LVH is important for the treatment of HT, because LVH is related with prognosis. [19] Therefore, intensive BP lowering treatment is recommended for patients with HT. Although various antihypertensive medications were reported to prevent new onset of HF, [20] there had been no conclusions on whether or not these medications suppressed left ventricular diastolic dysfunction. There is an ongoing prospective PREFERS Hypertension study, which aims to determine the timeline and transition from HT to HHD, including LVH and HFpEF. [21] If the patients who are prone to develop HHD and HFpEF can be identified, the optimal choice of medications for HT may change.

Pathophysiology of HFpEF

In recent years, vascular failure has attracted attention in the study on the pathophysiology of HF (Figure 3). Vascular failure not only leads to arteriosclerosis but also contributes to HF by the breakdown of the Windkessel effect. [22] During left ventricular systole, about 60% of the blood ejected from the left ventricle flows to the peripheral circulation, whereas the remaining 40% is stored in the arteries, which are elastic. The stored blood flows to the periphery organization during left ventricular diastole. If this Windkessel effect collapses, the increase in afterload by the elevated systolic BP causes exacerbation of HF. At the same time, pulse pressure (PP), which is a surrogate marker of arteriosclerosis, increases by decreasing diastolic BP. We evaluated afterload and the prognosis using Clinical Scenario (CS) HF classification categorized by BP and found that when afterload was more involved, the rate of cardiovascular death and rehospitalization for HF was relatively high in patients with more advanced vascular failure. [23] In addition, the number of cardiovascular events among patients with HFpEF was higher in those with high PP than in those with low PP. [24] The onset of HF is brought about by a combination of this cardiac pathway of left ventricular systolic and/or diastolic dysfunction and vascular failure. [25] Among the existing medications for the treatment of HF, those that are related with symptom relief are useful for both HFrEF, which presents with left ventricular systolic insufficiency, and HFpEF, which presents with left ventricular diastolic insufficiency. On the other hand, cardioprotective medications, such as β-blockers, have been shown to be effective only for HFrEF. [6, 7, 26] The different involvement of vascular failure between HFrEF and HFpEF may lead to different efficacies of cardioprotective medications between the two categories of HF. HFpEF includes various factors, and elucidation of its pathophysiology remains to be awaited from the results of several ongoing clinical studies on HF.

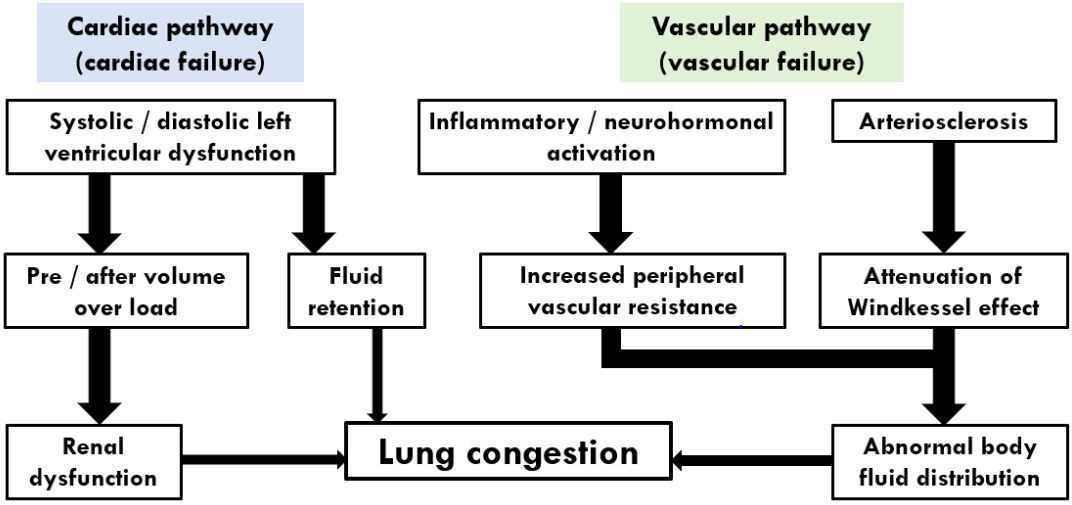

Figure 3. Two pathways involved in lung congestion

The prevention of cardiovascular events focused on treatment of hypertension

Strict BP control is one of the treatments that address increasing afterload secondary to vascular failure. A previous meta-analysis of 10 studies revealed that reduction of systolic BP by approximately 4 mmHg in patients with HFpEF resulted in an 11% rate reduction in hospitalization for HF, [27] probably through decrease in afterload. Another study showed that reduction of systolic BP was not associated with subsequent cardiovascular events. [28] However, excessive lowering of BP worsens the prognosis of HFpEF, [29] because stroke volume and BP tend to be lower in HFpEF than in HFrEF due to vasodilator use. [30] The relationship of systolic BP upon admission for acute HF and on discharge with the prognosis of HF mostly shows the J-curve phenomenon. [31] Therefore, clinicians who control the BP of patients who have previous HFpEF should always be aware of excessive BP fluctuations. In the meta-analysis mentioned above, the rate of renal dysfunction increased by approximately 52% in the intensive care group, even if the systolic BP was approximately 130 mmHg and there were no clinical findings of hypotension. When determining the target BP, the degree of association with vascular failure and the adverse effects to multiple organs are important to consider and pay attention to.

Conclusions

Both left ventricular systolic / diastolic dysfunction and vascular failure are related with the pathophysiology of HF. The optimal choice of cardioprotective / antihypertensive medications for HF should be based on the pathological condition.

Disclosure

T.I. has received Honoraria (e.g., lecture fees) from Bayer Healthcare, Ono Pharmaceutical, Co., Ltd. And, T.I. has received Subsidies or Donations from Daiichi Sankyo. The remaining authors declare that there is no conflict of interest. The authors have no conflict of interest in this manuscript.

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