The clinical significance of tricuspid regurgitation (TR) has long been ignored, because it is a common echocardiographic finding observed in 80–90% of healthy individuals and TR may have been tolerated for years. In addition, attention has not been paid to the right-side of the heart compared with the left side. However, TR has received a lot of attention in recent years as a predictor and/or a contributor of clinical outcomes in patients with heart failure (HF). TR has primary and secondary etiologies. Primary TR is uncommon and attributed to intrinsic lesions of the tricuspid valve (TV). Secondary TR, also known as functional TR, is the most common form, which is mainly caused by left-sided HF and mitral valve surgery.

In left-sided HF, elevated left atrial pressure (LAP) is transmitted through the lungs as pulmonary hypertension (PH), classified as group 2 PH. In the early stage of group 2 PH, pulmonary artery pressure (PAP) is elevated by passive downstream elevation in LAP with normal pulmonary vascular resistance (PVR), known as passive PH. When functional and structural abnormalities occur in the pulmonary vasculature, PVR is elevated and causes an increased transpulmonary gradient (TPG), called reactive PH. When the right ventricle (RV) is subjected to elevated afterload by PH, it initially dilates and may chronically adapt to PH with hypertrophy. The dilatation of the RV eventually leads to tricuspid annular dilatation, resulting in impaired tricuspid annular contraction and functional TR. Once the TV is dilated, it continues to dilate the RV further and worsen the TR, which eventually results in RV dysfunction. Thus, elevated LAP induces passive and subsequent

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Department of Medicinal Biochemistry, Osaka University Graduate School of Medicine, Suita (O.T.); Department of Clinical Medicine and Development, National Cerebral and Cardiovascular Center, Suita (M.K.), Japan
Mailing address: Osamu Tsukamoto, MD, PhD, Department of Medicinal Biochemistry, Osaka University Graduate School of Medicine, Suita 565-0871, Japan. E-mail: tsuka@medbio.med.osaka-u.ac.jp
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reactive PH, functional TR, and RV dysfunction, all of which are linked in a vicious cycle. RV function is essential to maintaining cardiac output and preventing venous congestion under the conditions of impaired LV systolic or diastolic function. RV dysfunction is as an independent predictor for poor outcome in patients with left-sided HF, irrespective of it being HF with reduced ejection fraction (HFrEF) or HF with preserved EF (HFpEF). Importantly, RV dysfunction is associated with the TPG, but not PA wedge pressure, in HFpEF, indicating that the development of reactive PH is critical for its prognosis.5 The prevalence of reactive PH is similar between HFrEF and HFpEF.6 Now, the question arises if secondary TR has a similar effect on prognosis in patients with left-sided HF irrespective of LVEF.

In this issue of the Journal, Santos et al8 report their interesting analysis of the effect of secondary TR in more than 800 patients with HFrEF and more than 1,000 patients with HFpEF who were prospectively studied for 1-year all-cause mortality in a non-selected cohort of patients with acute HF. The association between TR severity and 1-year survival was significant only in patients with HFpEF, with increasing mortality risk as TR worsens. A significant positive association between TR severity and mortality was not found in the HFrEF patients.

Why did the effect of functional TR differ between HFrEF and HFpEF? To answer this question we should consider the differences between them because HFpEF is not a transitory stage to HFrEF but a distinct entity (Figure).9 In HFrEF, myocardial remodeling is triggered by progressive loss of cardiomyocytes caused by ischemia, infection, and toxicity,10 resulting in increased wall stress in the LV and decreased LVEF. Excessive wall stress shifts the balance between collagen deposition in increased wall stress in the LV and decreased LVEF. Excessive wall stress shifts the balance between collagen deposition and degradation in the extracellular matrix, leading to LV dilatation and eccentric LV remodeling. Subsequent elevation in left-sided heart pressure is transmitted back into the pulmonary circulation and the RV, which results in PH, functional TR, and RV dysfunction, depending on the severity of the underlying LV systolic dysfunction. Accordingly, the severity of functional TR is a reflection of the severity of left-sided HF in HFrEF, although a systemic inflammatory state is also provoked by the reactive response to the severity of HF in advanced stages of HFrEF. In contrast, HFpEF is a condition with impaired relaxation and stiffening of the myocardium and arterial system,11 which is driven by a systemic proinflammatory state induced by multiple noncardiac comorbidities.10,12 A proinflammatory state causes coronary microvascular endothelial inflammation and suppression of the NO-cGMP-protein kinase G pathway in adjacent cardiomyocytes,12 which promotes cardiomyocyte hypertrophy, increases the resting tension of cardiomyocytes, and increases myocardial collagen deposition by proliferating fibroblasts and myofibroblasts. Consequent stiff cardiomyocytes and interstitial fibrosis contribute to concentric LV remodeling and diastolic dysfunction in HFpEF. In addition, multiple comorbidities such as obesity, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, anemia, and chronic kidney disease are more prevalent in HFpEF than HFrEF patients.8 These comorbidities may cause adverse effects on RV function through not only cardiovascular remodeling but also systemic and pulmonary hemodynamic disturbances. Thus, the severity of functional TR in HFpEF is not just a simple reflection of the severity of left-sided HF, but may be an integrated reflection of the severity of cardiac and noncardiac pathophysiological conditions. In fact, the proportion of noncardiovascular deaths among HFpEF patients is higher than in HFrEF, although mortality rates are similar in both groups.9,12

Other differences also exist between HFrEF and HFpEF. Narrow and elongated cardiomyocytes and reduced myofibrillar density are observed in HFrEF, whereas an increased diameter of cardiomyocytes and an increased ratio of the stiffer isoform of titin (N2B/N2B) is present in HFpEF.10,11 Treatment with vasodilators induces greater blood pressure reduction and less stroke volume enhancement in HFpEF than in HFrEF.7 Furthermore, the use of statins reduces the incidence of sudden death and noncardiovascular death in HFpEF patients, although cardioprotective drugs beneficial for HFpEF have failed.32 These properties might also contribute to the differential effect of functional TR between HFrEF and HFpEF.

In summary, the clinical implication of functional TR may differ in HFrEF and HFpEF. Especially, the severity of TR may reflect the combined burden of underlying HF and multiple comorbidities that cause reactive PH and RV dysfunction in HFpEF, although the precise mechanisms remain largely unknown. Future studies are required to clarify the mechanism, which will result in better understanding of HFpEF.

References