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COMMENT

Resveratrol supplementation: a therapeutic potential for cardiac remodeling in hypertensive heart disease

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Hypertension (HT) is the leading risk factor for life-threatening cardiorenovascular diseases, such as stroke, heart disease, and kidney disease. To prevent the onset and progression of these complications, proper management is required. Elevated blood pressure (BP) has a negative effect on the heart by increasing pressure load, abnormal calcium handling, and contractile protein abnormalities *via* chronic activation of neurohumoral factors such as the renin-angiotensin-aldosterone system and the sympathetic nervous system. As a result, cardiac remodeling, including cardiac hypertrophy and myocardial fibrosis, occurs [1]. In addition, HT causes atherosclerosis and is known to be a risk factor for coronary artery disease, along with dyslipidemia and diabetes mellitus (DM). These changes induce structural and functional changes in the heart, resulting in hypertensive heart disease (HHD), which eventually progresses to heart failure (HF) with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). Because HF reduces healthy life expectancy, lowers quality of life, and raises medical costs, adequate and persistent BP reduction is necessary. According to the Framingham Heart Study, HT increases the risk of developing HF by two-fold in men and three-fold in women, and 91% of new cases of HF have a history of HT [2]. Furthermore, the incidence of HF is significantly lower by 38% in the strict treatment group with a target systolic blood pressure (SBP) less than 120 mmHg than in the standard treatment group with a target SBP less than 140 mmHg [3]. Antihypertensive therapy is expected to prevent the development of left ventricular (LV) diastolic dysfunction (LVDD) by reducing cardiac hypertrophy and myocardial fibrosis. In the real clinical setting, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) are often used in hypertensive patients with LV hypertrophy. However, a significant number of cases of LVDD still exist even after adequate BP reduction. Hence, antihypertensive therapies with greater cardioprotective effects on cardiac remodeling and LVDD are required.

Resveratrol (RES) is a non-flavonoid polyphenol naturally present in red wine, berries, and grapes, with well-known anti-apoptotic, antioxidant, and anti-inflammatory effects [4]. Until now, RES replacement therapy has been shown to be potentially effective for stroke, HT, DM, and HF. For instance, Rivera et al. reported that RES significantly lowered SBP in the obese Zucker rat, which is used as an animal model of obesity and type 2 DM and exhibits many of the characteristics of the human metabolic syndrome [5]. In addition, RES has been shown to ameliorate myocardial hypertrophy, mitochondrial dysfunction, fatty acid oxidation, and cardiac dysfunction [6]. The antihypertensive effects of RES are thought to be mediated *via* AMP-activated protein kinase (AMPK) and SIRT-1. The activation of SIRT-1 and AMPK increases endothelial nitric oxide synthase (eNOS) expression and activity, resulting in nitric oxide (NO) production. NO produced by vascular endothelial cells relaxes vascular smooth muscle and dilates blood vessels, lowering BP. In terms of HF and cardiac hypertrophy, RES is thought to have favorable effects *via* several mechanisms, including eNOS and AMPK activation and sarco/endoplasmic reticulum calcium ATPase 2a expression [4]. RES is well tolerated by humans; however, few studies have demonstrated cardioprotective effects in humans.

In this issue of the Journal, Zheng et al. investigated the cardioprotective effects of RES in patients with essential

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HT [7]. The patients were divided into two groups: the RES group, which was treated with RES orally and basic anti-hypertensive therapy, and the control group, which was treated with anti-hypertensive therapy alone. The use of ACE inhibitors, ARBs, CCBs, beta-blockers, and diuretics did not differ between the two groups. First, they found that E/e', left atrial (LA) diameter, and global longitudinal strain (GLS) were improved in the RES group compared to the control group. Meanwhile, the interventricular septum thickness, LV internal diastolic diameter, LV posterior wall thickness at end diastole, and LV mass index did not improve. HHD develops as a compensatory response to chronic LV pressure overload and is often asymptomatic. Soma et al. previously reported that LV systolic function (LVSD) was preserved for a long time; however, LVDD was impaired in patients with HT at an early stage [8]. Therefore, it is important to assess LVDD and LVSD by echocardiography. The E/e' ratio is used to estimate LV filling pressure and is considered a useful prognostic parameter in conditions such as acute myocardial infarction, LVSD, atrial fibrillation, and HFpEF. The LA enlargement progresses as LVDD progresses, making LA size a sensitive indicator of LV overload. In addition, it has been reported that GLS can assess not only minute changes in LV contractility but also LV diastolic function. Moreover, Zheng et al. [7] found that RES replacement therapy improved E/e', LA diameter, and GLS after six months of treatment, implying that the therapy is effective in improving LVDD and LVSD in patients with essential HT at an early stage. Currently, an algorithm that integrates multiple parameters such as E/e', e', tricuspid regurgitation velocity, and LA volume index (LAVI) is recommended to assess LVDD in patients with preserved LV ejection fraction [9]. Furthermore, Tsang et al. elucidated that LAVI is a more sensitive risk marker for predicting cardiovascular events than LA diameter or area in patients with sinus rhythm [10]. Therefore, future studies are required to validate the effect of RES replacement therapy on LAVI.

Second, they revealed that serum procollagen type I C-peptide (PICP) and galectin-3 levels were lower in the RES group and that the change in E/e' was positively correlated with the change in PICP and galectin-3 levels. Serum PICP is generated when collagen type I is produced from procollagen type I and is thought to be a biomarker for a variety of cardiac diseases, including cardiac fibrosis and myocardial infarction. Serum PICP levels have been found to correlate with the collagen type I volume fraction in HF and to be associated with mortality in HFpEF [11]. Furthermore, collagen type I fibers contribute to the increased stiffness in HFpEF and are overproduced in HF with HHD [11]. In addition, galectin-3, a member of the beta-galactoside-binding animal lectin family, has been approved as a prognostic biomarker of HF, and its level is correlated with disease severity. Its expression has recently been found to increase in many human fibrotic diseases, including cardiac fibrosis [12]. Furthermore, it is suggested that increased myocardial stiffness derived from the excessive accumulation of collagen and extracellular matrix causes LVDD [11]. Thus, their findings are extremely promising for the development of drugs to mitigate the progression of LVDD.

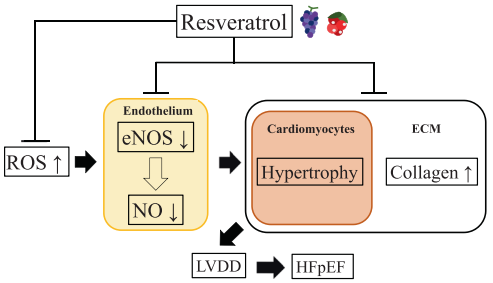

Fig. 1 Possible mechanisms of action of resveratrol on left ventricular diastolic dysfunction (LVDD) and heart failure with preserved ejection fraction (HFpEF). ECM extracellular matrix; eNOS endothelial nitric oxide synthase; HFpEF heart failure with preserved ejection fraction; LVDD left ventricular diastolic dysfunction; NO nitric oxide; ROS reactive oxygen species

Globally, the number of patients with HF, a terminal cardiovascular disease, is increasing. HF is characterized by high mortality and rehospitalization rates. Hence, the most important medical and social strategy is to prevent the development of HF. The number of hospitalizations due to HFrEF has not changed significantly, whereas the number of hospitalizations due to HFpEF has increased significantly [13], possibly due to the fact that the pathogenesis of HFpEF is still unknown and effective treatments are currently unavailable. Recently, a complex combination of microvascular inflammation, myocardial hypertrophy, fibrosis, endothelial dysfunction, and increased myocardial stiffness has been shown to result in a variety of clinical forms of HFpEF [14]. Until now, the only drug that has demonstrated cardioprotective effects against HFpEF is the sodium-glucose co-transporter-2 inhibitor. Therefore, it is necessary to further develop therapeutic agents with new mechanisms that can ameliorate the complex pathogenesis of HFpEF while also treating comorbidities. Zheng et al. [7] indicated the relationship between the LVDD index and fibrosis in patients with HT, as well as the effects and mechanisms of RES replacement therapy. However, the limitation of the study is the small number of patients and the short follow-up period. Hence, further studies are needed to determine the long-term prognosis, safety, and efficacy of RES replacement therapy in HF, as well as its appropriate dosage in humans. We believe that their work could provide a novel perspective on the future treatment of LVDD and HFpEF (Fig. 1).

Compliance with ethical standards

Conflict of interest KJ declares no competing interests. AT has received honoraria from Boehringer Ingelheim and research funding from GlaxoSmithKline, Takeda, Bristol Myers Squibb, and Novo Nordisk. KN has received honoraria from MSD, Astellas, AstraZeneca, Novartis, Ono, Daiichi Sankyo, Mitsubishi Tanabe, Eli Lilly, Boehringer Ingelheim, and Takeda; research grants from Asahi Kasei, Astellas, Mitsubishi Tanabe, Teijin, Terumo, Boehringer Ingelheim, Eli Lilly, and Company, Mochida, and Fuji; and scholarships from Daiichi Sankyo Healthcare, Teijin, Medtronic, and Bayer.

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