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Editorial Comment

Microvascular Dysfunction and Heart Failure with Preserved Ejection Fraction in Senescence

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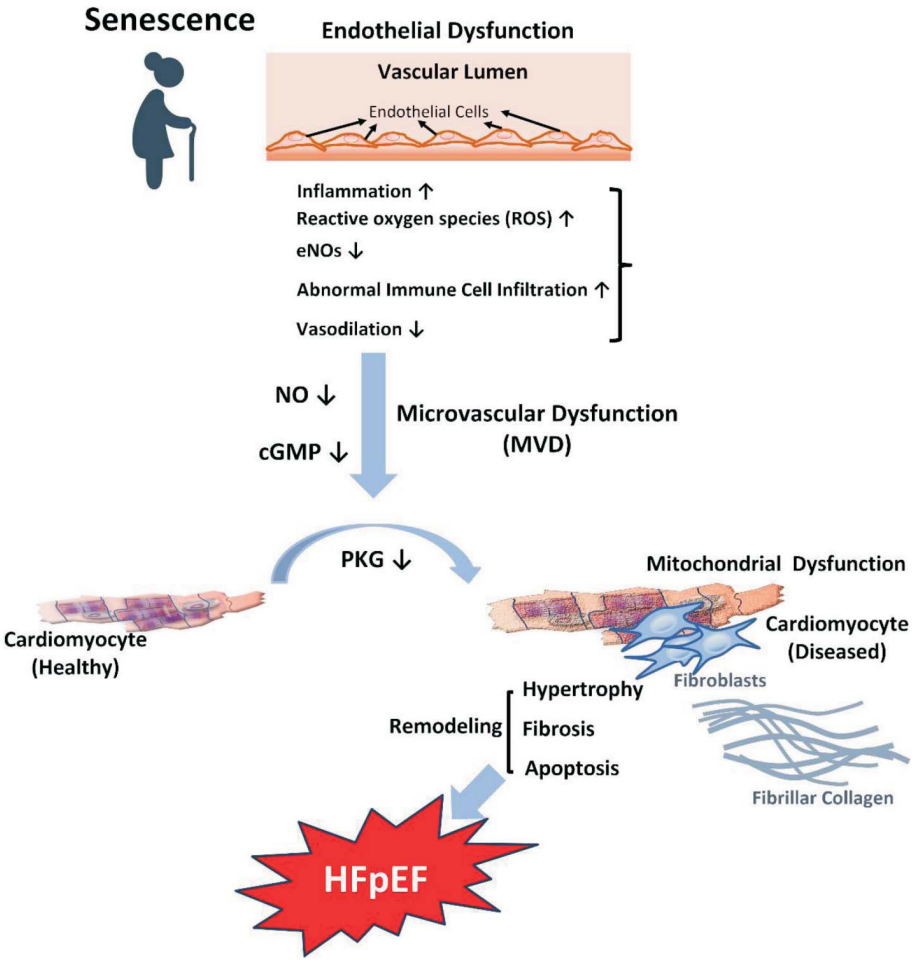

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Central Illustration. Schematic illustration for senescence-related cascades and mechanisms of microvascular dysfunction driving the pathogenesis of HFpEF. cGMP: cyclic 3′-5′-cyclic guanosine monophosphate; eNOs: endothelial nitric oxide synthase; HFpEF: heart failure with preserved ejection fraction; MVD: microvascular dysfunction; NO: nitric oxide; PKG: protein kinase G; ROS: reactive oxygen species.

Taiwan has been considered an aging society since 2018 and is expected to become a “super-aged” society by 2025. According to the 2023 White Paper of the Ministry of Health and Welfare, 17.6% of the total population is elderly and face a high burden of comorbid conditions and disabilities.[1] Aging and cell senescence leads to dysfunction in several organs, including heart failure (HF) and chronic kidney disease, or frailty. A recent nationwide survey showed there has been a > 2-fold increase in the lifetime risk of HF in individuals aged ≥ 70 years.[2] Although the precise mechanisms underlying such relationships are complex, microvascular dysfunction (MVD) has emerged as a novel and important factor driving the clinical pathological implications of HF, especially in HF with preserved left ejection fraction (HFpEF).[3] Microcirculation comprises small arterioles and extensive vascular beds that regulate blood flow to match regional perfusion.[4] To stabilize oxygen exchange and nutrient supply, regional blood flow is maintained through dynamic yet complex physiological conditions involving both shear stress (flow-mediated dilation) and pressure-dependent (myogenic) responses.[4]

Senescence can impact several biological and physiological aspects that may impair microvascular structures and function.[3] Overproduction of reactive oxygen species and reduced antioxidant ability are the primary causes of endothelial dysfunction and arterial stiffness.[5] Further, an increase in mitochondrial reactive oxygen species can induce apoptosis.[5] Senescence also inactivates endothelium-derived nitric oxide, thereby decreasing vasodilatory ability.[5] The progressive accumulation of senescent cells in tissues can trigger inflammatory responses. Chronic inflammation, common in individuals with HFpEF, impedes cardiac systolic and diastolic functions and contributes to pathological changes in myocytes or atherogenesis.[3] Autophage is a physiological process that maintains cellular homeostasis by controlling the degradation of components such as proteins and damaged organelles involved in aging processes by phenotypic changes in vascular smooth muscle cells and endothelial cells.[6] Morphological and physiological changes in vascular smooth muscle and endothelial cells contribute to atherosclerosis, arterial stiffness, and cardiac fibrosis.[6]

Substantial evidence supports the existence of a pathological continuum between MVD and HFpEF. Several studies have demonstrated a high prevalence of MVD in the elderly and those with HFpEF,[3] and coronary MVD can be considered an independent risk factor for the development of HF.[7] Currently, both invasive and non-invasive measurements provide reliable information on quantitative regional blood flow or vasodilatory ability, aiding in understanding MVD.[4] In one previous study, individuals with coronary MVD, defined as coronary flow reserve < 2, showed a 2.5-fold increased risk of HFpEF hospitalization during a median 4.1 years follow-up compared with those with normal coronary flow reserve.[7] The risk of HFpEF hospitalization was more than five-fold higher among individuals with both coronary MVD and diastolic dysfunction (E/e′ > 15) than among those without MVD and diastolic dysfunction (E/e′ < 15).[7] The PROMIS-HFpEF study showed that impaired coronary flow reserve correlated with left ventricle and left atrial strain.[3] Thus, coronary MVD affected the sub-endocardium early and predominantly, as evidenced by longitudinal systolic function. Poor diastolic function of increasing E/e′ was associated with coronary MVD and implicated in a higher risk of major adverse cardiovascular events. A recent study by Souza et al. attempted to elucidate the importance between coronary MVD and body composition. Deficient muscularity, not excess adiposity, is independently associated with coronary MVD [adjusted odds ratio: 1.38, 95% confidence interval (CI): 1.08–1.75, p = 0.009], which was detected using cardiac stress Positron Emission Tomography.[8] Both worse MVD and sarcopenia, but not visceral adipose tissue, were independently associated with adverse cardiac events, including death, hospitalization for nonfatal myocardial infarction, or HF. Notably, there was a strong interaction between coronary MVD and skeletal muscle mass (p = 0.026), with patients manifesting coronary MVD and concomitant sarcopenia having the highest risk of adverse events. Sarcopenia plays a critical role in the pathological processes of aging and HF.[9] Such a concept of sarcopenic MVD provides a convincing pathological axis for sarcopenia-MVD-HF. Given the fundamental role of malnutrition in sarcopenia, the concept of sarcopenic MVD is also supported by our recent studies, highlighting the importance of the pathological axis of malnutrition-MVD-HF.[10] Thus, presence of coronary or systemic MVD should be regarded as a preclinical or disease-progressing marker for the development of HFpEF. The early detection of MVD aids in risk stratification and aggressive treatment of comorbid cardiovascular diseases. This finding is consistent with the role of microalbuminuria in diabetes mellitus. Moreover, therapeutic targets for MVD may be effective and should be developed for patients with HFpEF. With a better understanding of the pathophysiological mechanisms underlying senescence and HFpEF, we will be able to advance into a “super-aged” society.

Conflicts of interest

All authors declare no conflicts of interest.

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