# Aging and HFpEF

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Letter to the editor

# Aging and HFpEF: Are we running out of time?

*Dear editor,*

The most significant determining factor of cardiovascular health is a person's age, with cardiovascular diseases being the leading cause of death in 40% of individuals over 65 years. Especially Heart Failure (HF) with preserved Ejection Fraction (HFpEF) is strongly age related, and in fact primarily affects elderly patients, with a predominance for women, and is further associated with multiple co-morbidities. HFpEF has become a leading cause of morbidity, hospitalization and mortality in subjects at the age of >65 years [1]. These findings have led to a debate as to whether HFpEF is a specific entity or simply a combination of age-related comorbidities. While aging itself does not cause HF, it renders the heart more susceptible to HFpEF development (central figure). Therefore, there is a urgent need to understand more of the age-related precipitants and co-morbidities that play a role in HFpEF pathophysiology, as well as focus on developing novel therapeutic treatments in order to reduce this major public health burden.

*Why is HFpEF prevalence increasing?* Since 1950, the worldwide number of aged persons (60 years and over) has tripled due to increased life expectancy for men and women. Annual incidence of HF doubles with every decade after age 65 years, and community based cohort studies demonstrated age-specific prevalence of HFpEF in women, with increases in HFpEF prevalence varying from 1% in 25–49 years, to 8% for >65 years and over 10% in those above 75 years [2]. These days, HFpEF prevalence is also increasing in younger individuals, but in HF patients, HFpEF remains a disease of the elderly with only 14% of all HF diagnoses in patients <40 years, and up 59% of all HF diagnoses in patients with age > 85 years. Besides obesity and hypertension, age has thus been identified as independent risk factor for HFpEF development [3], and this age-related effect is even stronger than what is observed for HFrEF [4]. Current prevalence of HFpEF relative to HFrEF is increasing at a rate of 1% per year, indicating that HFpEF is on track to become the most common type of HF in the very near future.

*Why is HFPEF more common in elderly women?* The aging heart shows typical HFpEF changes such as cardiac hypertrophy, diastolic dysfunction and worsened myocardial performance. Older women tend to have higher left ventricular (LV) ejection fraction and, as a response to pressure overload, demonstrate more concentric cardiac remodeling (whereas in men it rather is eccentric), with absence of chamber dilatation. The long-term cost of this adaption may render the female aged heart more susceptible to functional reserve impairment, with diastolic dysfunction and a stiffer ventricle. In addition, vascular and endothelial insufficiency during exercise is more common in females and contribute to typical symptoms, such as dyspnea and exercise intolerance. Intriguingly, with normal aging, women exhibit more age-associated inability to enhance preload and contractility or to increase heart rate in response to exercise when compared to men. Clearly, this remodeling pattern in women will more easily result in an HFpEF phenotype than an HFrEF phenotype, contributing to greater susceptibility to clinical HFpEF.

*Should we include aging as main HFpEF driver in preclinical science?* A key obstacle for exploring new pathophysiological mechanisms and testing new treatment strategies is the availability of suitable animal models that realistically reflect the effect of aging in HFpEF development. Recently, multi-hit mouse models that included aging were developed, and these models were able to recapitulate most of major cardiometabolic features of this complex syndrome. Consistent with elder humans, male and female C56BL/6 or senescence accelerated prone (SAMP) mice show age-induced LV and atrial hypertrophy, diastolic dysfunction, worsened myocardial performance and exercise intolerance [5,6]. When combined with perturbations such as high fat diet and Angiotensin-II [7], or desoxycorticosterone pivalate [8], it mimics human HFpEF with an aged-cardiometabolic signature, including hypertension, obesity, diabetes and congestion. Studies in younger mice were not able to recapitulate these plethora of cardiac and non-cardiac symptoms, and the overlapping characteristics of cardiac aging and HFpEF, advocate that aging should always be considered in animal models of HFpEF.

*Should we target senescence to improve myocardial function during aging?* As we age, systemic and cardiac changes, including fibrosis, inflammation, stiffening and diastolic function contribute to HFpEF development. These processes are driven by molecular mechanisms, such as senescence associated secreted factors (SASP), telomere shortening or mitochondrial dysfunction. Senescence can be targeted with senolytics such as navitoclax, which reduces hypertrophy and fibrosis and rescues age-associated decline in diastolic function in aged-24 month-old mice [9,10]. However, these experiments were performed in mice with telomere attrition or after acute infarction or isoproterenol induced stress. We are not aware of any senolytica that have been tested in recent HFpEF animal models and further research is warranted to corroborate these findings in HFpEF. Although experimental work suggest that it may be possible to specifically target cardiac senescence, we believe that there should also be focus on co-morbidities that accelerate the aging process. Obesity and hypertension are already present before the age of 65 and these "accelerators" present an easier target than the process of aging itself. Ultimately, here lies the challenge for early diagnosis of HFpEF and prevention: to treat the "relative" young HFpEF patient who in fact has aged, so that his or her health span can be extended (central figure).

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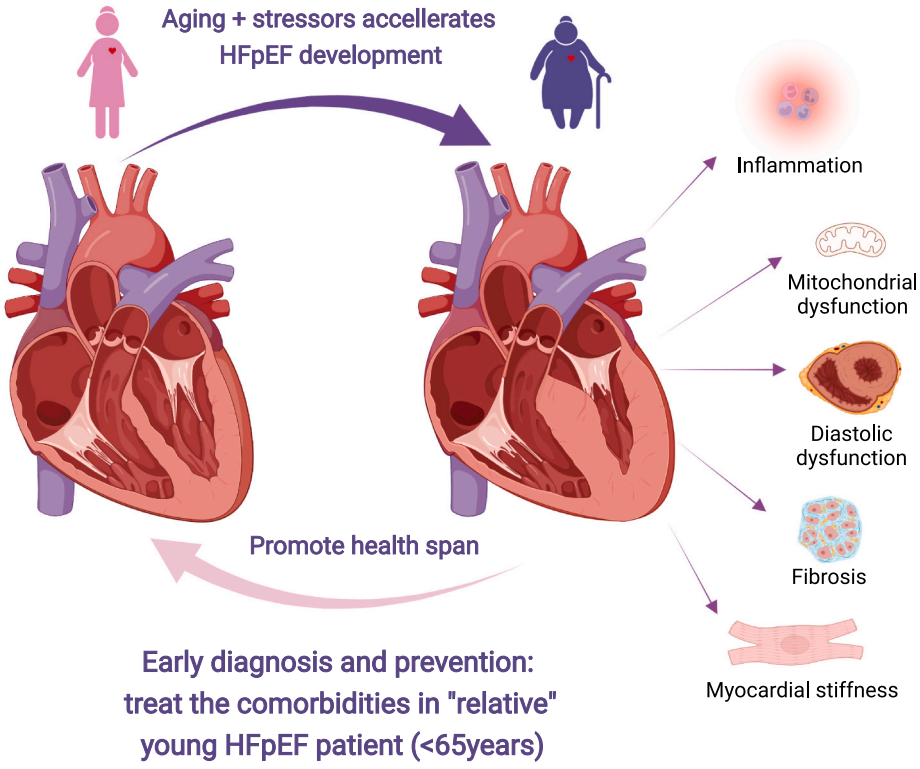


**Central Figure** Age-acquired stressors, such as hypertension, diabetes and obesity accelerate aging by enhancing inflammation and increasing the risk for HFpEF development. These co-morbid driven processes synergize with fundamental mechanisms of aging, such as cardiac cellular senescence and decline in mitochondrial function, resulting in a stiffer and hypertrophied heart with diastolic dysfunction. To promote health span of the old HFpEF patients, treatment of co-morbidities, that accelerate the aging process, should be started in the relatively young HFpEF patients (<65 years). Created with BioRender.com.

## Disclosures

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