Aging and Disease
www.aginganddisease.org

Early access date: May 2, 2026
http://dx.doi.org/10.14336/AD.2026.0265

Review

HFpEF, Aging, Inflammaging, and the Future of Anti-Inflammatory: Therapy in Heart Failure with Preserved Ejection Fraction

Arkadiusz Grzeczka[1], Szymon Graczyk[1], Jan Gröschel[2,3,4,5], Sebastian Spethmann[2,4,5], Pawel Kordowitzki[1,6,7*]

[1]Department for Basic and Preclinical Sciences, Faculty of Biological and Veterinary Sciences, Nicolaus Copernicus University in Torun, 87-100 Torun, Poland; [2]Charité—Universitatsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany; [3]Working Group on Cardiovascular Magnetic Resonance, Experimental and Clinical Research Center, a Joint Cooperation Between Charité Medical Faculty and the Max-Delbrück Center for Molecular Medicine, Berlin, Germany; [4]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany; [5]Deutsches Herzzentrum der Charité—Department of Cardiology, Angiology and Intensive Care Medicine, Berlin, Germany; [6]Department of Gynecology, Berlin, Germany; [7]Department of Cell Biology, Blavatnik Institute, Harvard Medical School, Boston, USA

[Received March 3, 2026; Revised April 4, 2026; Accepted April 5, 2026]

ABSTRACT: Aging is the dominant risk factor for heart failure with preserved ejection fraction (HFpEF), a condition increasingly recognized as a manifestation of maladaptive cardiovascular aging. This review summarizes current evidence linking inflammaging, a chronic, low-grade inflammatory state driven by immunosenescence, mitochondrial dysfunction, and cellular senescence, to progressive myocardial fibrosis, diastolic stiffness, and HFpEF development. We discuss mechanistic pathways connecting fibroblast activation, extracellular matrix remodeling, adipose tissue–driven inflammation, and phenotype-specific inflammatory signatures, as well as the role of multimodality imaging in detecting early fibrotic and inflammatory changes. Finally, we critically evaluate emerging immunometabolic therapies, highlighting the limitations of single-cytokine blockade and the disease-modifying potential of SGLT2 inhibitors and GLP-1 receptor agonists in targeting HFpEF.

Keywords: Cardiac aging, Inflammaging, HFpEF, Cardiac fibrosis

1. Introduction

Cardiac aging is a multifaceted and progressive process. It involves a wide spectrum of structural, functional, and molecular alterations within the heart. The increasing prevalence of age-related cardiac disease both in the United States and globally underscores the urgent need for innovative therapeutic approaches [1, 2]. With age, changes occur at both the macroscopic level (e.g., myocardial hypertrophy) and the microscopic and cellular levels, including myocardial fibrosis and associated remodeling of the extracellular matrix (ECM) [3]. These include cardiomyocytes, cardiac fibroblasts, endothelial cells, and immune cells residing in myocardial tissue. Functional impairments often accompany these structural changes, notably reduced diastolic compliance, diminished myocardial flow reserve, and eventual diastolic dysfunction, which commonly precede the development of heart failure with preserved ejection fraction (HFpEF) [4–8]. At the molecular level, cardiac

***Correspondence should be addressed to:** Dr. Pawel Kordowitzki, Department for Basic and Preclinical Sciences, Faculty of Biological and Veterinary Sciences, Nicolaus Copernicus University in Torun, 87-100 Torun, Poland. Email: p.kordowitzki@umk.pl.

aging is driven by cumulative oxidative stress, mitochondrial dysfunction, epigenetic drift, cellular senescence, and dysregulated intercellular signaling [9, 10].

Older people are also particularly vulnerable to age-related conditions such as obesity, diabetes, and renal disease, which are all associated with chronic inflammation. These often coexist with geriatric frailty syndrome, an important risk factor for cardiovascular events [11–15]. These factors contribute to a chronic, low-grade inflammatory state, often referred to as inflammaging, that significantly influences the cardiac microenvironment [16].

One of the key pathological processes exacerbated by cardiac aging is cardiac fibrosis, a maladaptive form of tissue remodeling traditionally viewed as a reparative response to sustained injury or stress [3]. Fibrosis contributes significantly to myocardial stiffness, electrical conduction abnormalities, and ultimately, compromised cardiac output. The interplay between fibrogenic and pro-inflammatory mechanisms points to a potential link between senile cardiac fibrosis and inflammaging, suggesting that cardiac fibrosis in the elderly is not merely a structural adaptation but also an immunologically active process [17]. This evolving understanding reinforces the rationale for therapeutically modulating inflammatory and immunometabolic pathways. Consequently, there is growing interest in cardioprotective agents with anti-inflammatory and immune-modulating effects that may attenuate fibrotic progression and improve broader cardiovascular outcomes in aging populations.

We propose inflammation as a central axis along which both physiological cardiac aging and its accelerated form, manifesting as HFpEF, progress, shaped by age and the cumulative burden of comorbidities. We outline the biological basis of inflammaging and its effects on cardiac remodeling, focusing on fibroblast activation, extracellular matrix dysregulation, diastolic stiffness, and imaging approaches. We then discuss key inflammatory and immunometabolic pathways in HFpEF, including cytokine signaling, inflammasome activation, and excess adiposity. Finally, we review existing and emerging anti-inflammatory therapies, highlighting their mechanisms, clinical efficacy, limitations, and future directions.

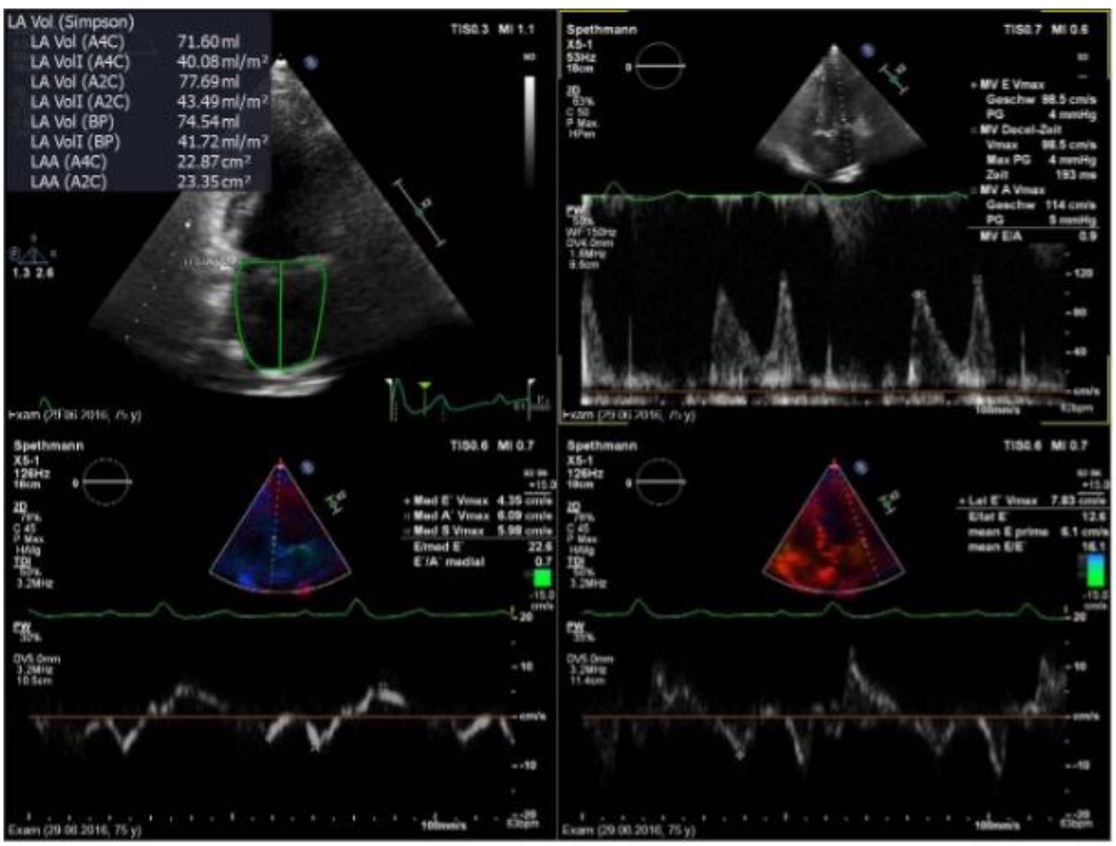

Figure 1. Diastolic dysfunction assessment in transthoracic echocardiography. Images showing the assessment of diastolic dysfunction in transthoracic echocardiography. In clockwise order, starting on the upper left: measurement of left atrial end-diastolic volume index (LAVI) in an apical two-chamber view. Upper right: Mitral inflow spectrum of a pulsed wave Doppler. Lower right: measurement of lateral e'. Lower left: measurement of septal e'. Note that, according to the latest guidelines for the assessment of diastolic dysfunction, the latter two parameters have gained importance (40617625).

2. Imaging in aging-related cardiac fibrosis and HFpEF

Cardiac fibrosis and cardiac dysfunction

Imaging plays a central role in assessing heart structure and function in aging populations, particularly in the context of HFpEF and myocardial fibrosis [Fig. 1, Fig. 2]. A multimodal approach combining echocardiography, cardiac magnetic resonance imaging (CMR), and new techniques such as molecular imaging provides valuable insights into the fibrotic and inflammatory changes associated with cardiac aging [18, 19] [Fig. 3 (F-K)]. Echocardiography is the first-line tool for assessing diastolic function [20]. However, according to current diagnostic algorithms, the diagnosis of HFpEF requires not only the structural and functional echocardiographic findings described above, but also clinical symptoms and/or signs of heart failure with increased natriuretic peptides in cases presenting with an LVEF => 50% (2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure). It is important to note that normal ranges are not necessarily equivalent to 'optimal' values, as the aging process itself can influence diastolic function. However, the use of age-specific normal ranges can improve the clinical interpretation of diastolic indices and has now become standard practice in echocardiographic measurements of cardiac structure and function [21], with growing evidence suggesting that circulating inflammatory markers should be considered complementary age-related parameters in the clinical evaluation of HFpEF, reflecting the contribution of inflammaging to myocardial remodeling and disease progression [22].

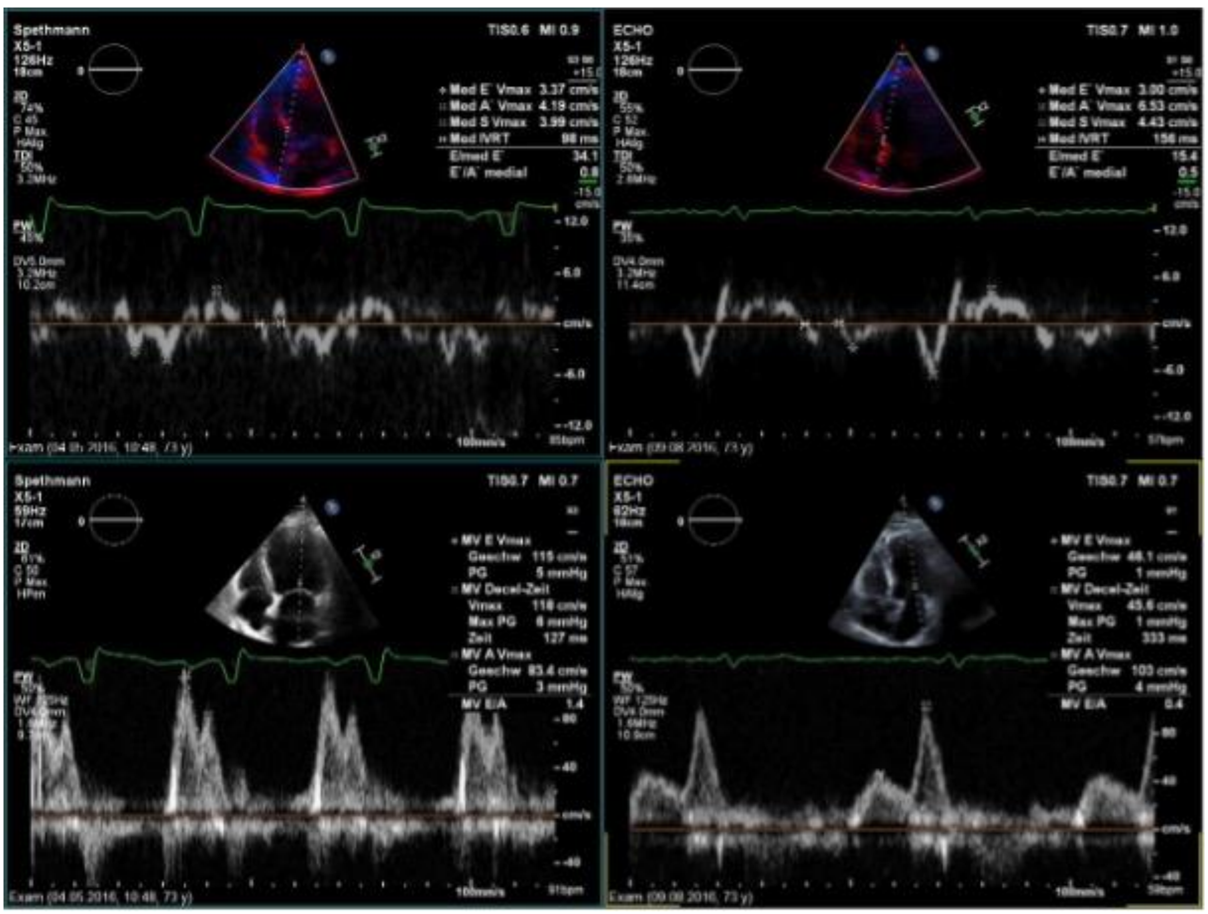

Figure 2. Effect of guideline-directed heart failure therapy on transthoracic echocardiography markers of diastolic dysfunction. Images on the left side represent a patient with heart failure with reduced ejection fraction. Shown are septal e' (upper panel) and mitral inflow (lower panel). On the left side are images after initiation of heart failure therapy, especially sacubitril/valsartan (Entresto). Note the improved septal e' (upper right panel).

Key findings in LV diastolic dysfunction include reduced early diastolic mitral annular velocity (E′) and elevated E/E′ ratio, reflecting impaired relaxation and increased filling pressures [23, 24] [Fig. 3 (A-E)]. Importantly, these echocardiographic alterations align with the pathophysiological framework of inflammaging, in which chronic, low-grade inflammation drives progressive myocardial remodeling. In population-based analyses, circulating interleukin-6 (IL-6) levels correlate inversely with E′ and directly with E/E′ ratio, as well as with other indices of diastolic filling, supporting a link between systemic inflammation and impaired ventricular relaxation [25]. Mechanistically, inflammatory signaling promotes endothelial dysfunction and activates pro-fibrotic pathways, leading to extracellular matrix deposition and increased myocardial stiffness. In line with this, studies in hypertrophic cardiomyopathy demonstrate that inflammatory mediators, including IL-6 and TNF-α, are associated not only with diastolic dysfunction parameters but also with both regional and diffuse myocardial fibrosis [26]. This inflammation–fibrosis axis provides a direct mechanistic link to HFpEF, in which increased ventricular stiffness and elevated filling pressures are central features of the clinical phenotype. Thus, alterations in E′ and E/E′ can be interpreted not merely as functional markers, but as integrative readouts of inflammation-driven fibrotic remodeling characteristic of HFpEF in the context of inflammaging.

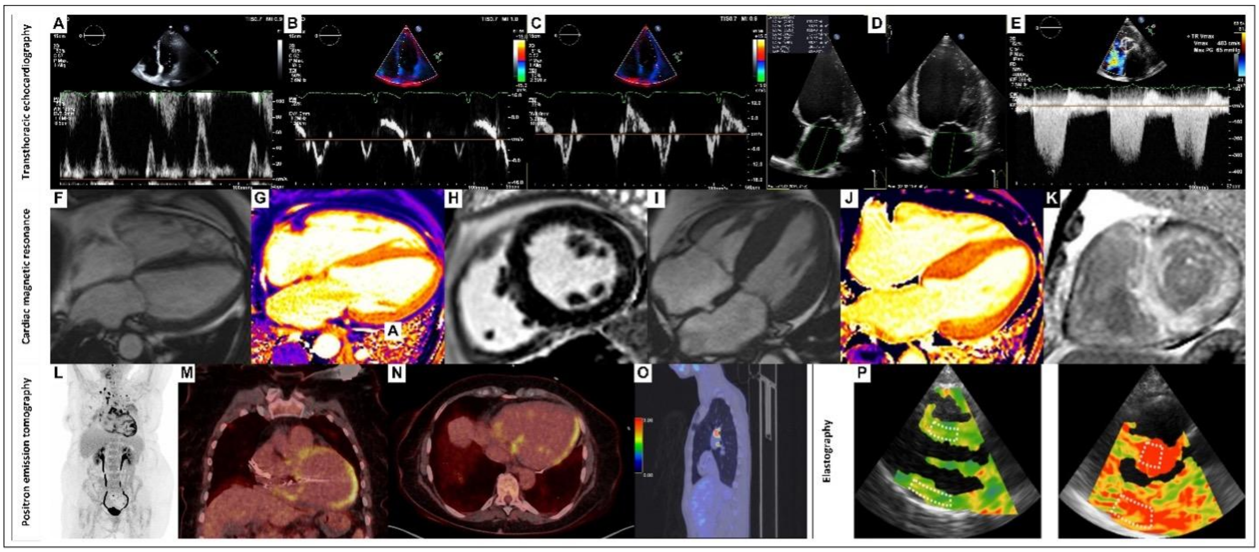

Figure 3. Multimodality assessment and visualization of direct and indirect signs of cardiac fibrosis. The upper row **(A-E)** shows transthoracic assessment of indices for a diastolic dysfunction, commonly encountered in association with cardiac fibrosis. A: Mitral inflow spectrum of a pulsed wave Doppler. B: septal e’ C: lateral e’ D: measurement of left atrial end-diastolic volume index (LAVI) in apical four- and two-chamber views. E: continuous Doppler assessment of tricuspid regurgitation in a four-chamber view. Middle Panels **(F-K)** show examples of cardiovascular magnetic resonance in a patient with hypertensive heart (F-H) and a patient with cardiac amyloidosis **(I-K)**. Shown are cine imaging in a four-chamber view (F, I), native T1 mapping in a four-chamber view **(G, J)**, and late gadolinium enhancement (LGE) in a midventricular short-axis slice **(H, K)**. Note the concentric hypertrophy, elevated T1 times (markedly higher in the patient with cardiac amyloidosis. While the LGE imaging shows no focal fibrosis in the patient with hypertensive heart disease, the patient with cardiac amyloidosis shows an abnormal enhancement, pronounced in the septum. This reflects deposition of amyloid fibrils in the myocardium. Lower row panels **(L-Q)**: PET-CT imaging in a patient with cardiac sarcoidosis. Panel A: Maximum intensity projection, coronal (M), axial fused (N), and sagittal (Q) PET/CT with 18FDG positive cardiac and lymphonodal manifestation of sarcoidosis. Panel **(P)**: Diastolic stiffness maps of the left ventricle (left: healthy volunteer; right: patient with cardiac amyloidosis), covering both the septum and posterior wall.

Tricuspid regurgitation (TR) velocity offers an easily accessible estimate of pulmonary artery systolic pressure, which, in the context of preserved ejection fraction and elevated filling pressure, suggests post-capillary pulmonary hypertension secondary to diastolic dysfunction. Importantly, emerging evidence indicates that this hemodynamic phenotype in HFpEF is closely linked to a systemic inflammatory milieu. Elevated markers of low-grade inflammation, such as high-sensitivity C-reactive protein (hs-CRP), have been shown to independently correlate with indices of pulmonary pressure response (e.g., mPAP/CO slope), supporting their role as integrative predictors of pulmonary vascular involvement [27]. This inflammatory-hemodynamic coupling is further reinforced by observations that HFpEF is characterized by an “inflammatory-metabolic” phenotype, in which low-grade systemic inflammation contributes to right ventricle-pulmonary artery uncoupling and the development of exercise-induced pulmonary hypertension [27].

Isovolumic relaxation time (IVRT) extends the assessment of early relaxation: a prolonged IVRT in the context of preserved LVEF and increased filling pressures may indicate transition from ‘aging-related slowed relaxation’ to true pathological diastolic dysfunction. Increased left ventricular mass and left atrial size are common and are often associated with increased afterload (e.g., arterial hypertension) and myocardial stiffening, suggesting underlying fibrosis [28].

CMR provides superior tissue characterization. T1 mapping and extracellular volume (ECV) quantification can identify diffuse interstitial fibrosis, which is often subtle and qualitatively not evident on late gadolinium enhancement (LGE) imaging (27899132) [29]. T2-based techniques (such as T2-weighted imaging or T2 mapping) allow for the detection of an acute myocardial inflammation (30545455) [30]. Multiple studies have shown that age-related myocardial remodeling is characterized by increased interstitial fibrosis, which can be detected and quantified using CMR tissue mapping. Specifically, native T1 mapping and ECV fraction measurements are sensitive to age-dependent fibrotic changes in the myocardium, with higher values correlating with increased collagen deposition and altered tissue composition in older individuals [31–33]. Higher ECV values are associated with diastolic dysfunction and adverse outcomes in HFpEF [29]. Importantly, increased ECV reflects expansion of the extracellular matrix and interstitial fibrosis and has been consistently associated with adverse clinical outcomes in HFpEF, including heart failure hospitalization and mortality, supporting its role as a robust prognostic biomarker [34]. In contrast, T2-based parameters capture myocardial inflammatory activity, although their sensitivity may be limited in the setting of chronic low-grade inflammation characteristic of HFpEF, underscoring the challenges in imaging inflammaging-related processes [35].

Emerging techniques such as myocardial elastography further enhance fibrosis assessment by directly evaluating myocardial stiffness. This ultrasound-based modality enables real-time visualization and quantification of regional myocardial strain and stiffness, offering potential as a non-invasive surrogate for assessing fibrotic burden. Increased myocardial stiffness, as measured by elastography, has been shown to correlate with diastolic dysfunction and adverse remodeling in aging hearts [36].

Molecular imaging techniques such as positron emission tomography (PET), using tracers for inflammation and fibrosis (e.g., 18F-FDG), offer a promising approach for visualizing active myocardial remodeling [37, 38] [Fig. 3 (L-Q)]. In addition to 18F-FDG, newer PET tracers may play a role in detecting inflammatory cardiomyopathies, particularly cardiac sarcoidosis [39]**.** Though currently limited to research, these modalities may support personalized anti-inflammatory therapies in the future.

Distinguishing between an aging heart and HFpEF

Each organ undergoes aging, leading to functional impairments. Depending on the varying rates of aging, these impairments may lead to the development of a clinical condition. HFpEF can be interpreted as a manifestation of accelerated cardiac aging, reflected by distinct echocardiographic abnormalities beyond those observed in physiological aging. Patients with HFpEF demonstrate increased left ventricular mass index (LVMI) and relative wall thickness (RWT), consistent with concentric remodeling. Shono et al. showed that although these parameters increase with age in healthy individuals, they reach significantly higher values in HFpEF, accompanied by reduced left ventricular end-diastolic volume, indicating maladaptive remodeling rather than physiological aging [40]. Notably, higher phenotypic age has been associated with increased LVMI and structural remodeling in HFpEF populations, supporting the link between biological aging and adverse cardiac geometry[41].

Diastolic dysfunction represents the dominant functional alteration. Shono et al. demonstrated a progressive decline in e′ velocity with age and a corresponding increase in E/e′ ratio, with significantly higher filling pressures observed in HFpEF compared to age-matched controls [42]. Importantly, stress testing revealed a marked increase in E/e′ and a blunted stroke volume response in HFpEF, indicating impaired preload reserve, a feature not present in physiological aging [42]. These abnormalities are more pronounced in individuals with higher phenotypic age [41].

Left atrial enlargement is another key feature, reflecting chronic elevation of filling pressures. Left atrial strain adds incremental value: reduced reservoir strain (and increased atrial stiffness) may signal elevated left atrial pressure and reflect chronic diastolic burden. In aging, this may be mildly reduced, whereas in HFpEF, the reduction is more marked and predictive of outcomes [43]. Shono et al. reported that left atrial volume index (LAVI) increases with age but is significantly higher in HFpEF patients, consistent with sustained hemodynamic burden [42].

Epicardial adipose tissue (EAT) is a metabolically active fat depot that secretes pro-inflammatory and profibrotic mediators, such as IL-6, TNF, and MCP1, which influence diastolic stiffness [44]. Increased EAT thickness correlates with systemic inflammation and fibrosis biomarkers and may assist in risk-stratifying HFpEF phenotypes [45].

Thus, the combination of increased LV mass, concentric remodeling, elevated E/e′, reduced e′ velocities, impaired preload reserve, EAT, and left atrial enlargement constitutes an echocardiographic signature of accelerated cardiac aging, distinguishing HFpEF from physiological aging processes, with phenotypic age providing an additional integrative marker linking systemic aging burden to cardiac dysfunction[41].

3. Inflammaging and HFpEF

From Immune Dysregulation to Cardiac Fibrosis: The Inflammaging Axis in Cardiac Aging

Inflammaging assumes that molecular debris physiologically generated by metabolism, cell death, microbiota activity, and mitochondrial dysfunction continuously stimulates innate immunity, but in young individuals, it is effectively neutralized by anti-inflammatory and adaptive mechanisms [46, 47]. With aging, the balance between the generation and clearance of this debris becomes disrupted, and inflammatory signals (including those propagated via exosomes) spread, leading, through context- and genetics-dependent mechanisms, to chronic, low-grade inflammation that promotes aging [46, 47]. Simultaneously, thymic involution, leading to immune aging and cellular senescence, transforms healthy cells into active cells with an arrested cell cycle that adopt a senescence-associated secretory phenotype (SASP) [48–50]. SASP describes a set of molecules, including cytokines, growth factors, and ECM-modifying enzymes, whose excessive concentration dysregulates the functions of individual cells and tissues, including in the heart [51]. The commonality among older people is that persistent low-grade inflammation is a risk factor for the development of age-related diseases, including cardiovascular disease, as a pillar of the aging process. One of the signs of the gradual deterioration in the quality and efficiency of immune cells is a conversion of the type I cytokine response to a type II cytokine response, with a simultaneous decrease in the production of anti-inflammatory cytokines [52, 53] [Fig. 4]. In individuals aged 100 years, a predominance of type 2 cytokine expression was observed in CD8+ T lymphocytes [53], with a simultaneous decrease in their absolute number and a greater proportion of cells with high SA-βGal activity during aging [54]. Ultimately, weakening immune control does not effectively remove defective cells, thus contributing to the development of certain diseases. Inflammatory and anti-inflammatory cytokines are associated with myocardial tissue remodeling and myocyte hypertrophy [55, 56]; therefore, similar changes in the heart can be expected under the influence of age-related accumulation of inflammatory mediators [57]. Therefore, elevated levels of inflammatory cytokines place excessive strain on cardiac tissue and activate fibroblasts [58]. In the context of an aging heart, prolonged myofibroblast activation leads to myocardial fibrosis.

Myofibroblast activation in the aged heart

There are three main types of cardiac fibrosis: replacement fibrosis, which typically follows cardiomyocyte death; perivascular fibrosis, localized around blood vessels; and interstitial fibrosis, which occurs in the absence of acute injury and is gradually progressive. It is this latter form, also referred to as reactive interstitial fibrosis, that is most strongly associated with aging [59]. This process is characterized by prolonged fibroblast activation and their phenotypic transition into myofibroblasts [3, 59–61]. These changes occur even in the absence of substantial cardiomyocyte loss, reinforcing the non-acute and insidious nature of age-related fibrosis [3, 59]. Myofibroblasts derived from the activation of cardiac fibroblasts, or those resulting from epithelial-mesenchymal (EMT) and endothelial-mesenchymal transitions (EndoMT), are associated with increased collagen production and expression of α-smooth muscle actin (α-SMA) [62]. The acquisition of α-SMA enables myofibroblasts to contract and form scar tissue, as seen in a post-infarction site [63]. In addition to increased collagen deposition, scar tissue is also characterized by increased stiffness, which results from the ability of α-SMA+ cells to contract [64]. The slow expansion of excessive ECM and the increased proportion of myofibroblasts in the heart are the cause of senile cardiac fibrosis and the gradual loss of myocardial elasticity [65]. An unquestionable factor that stimulates fibroblasts to transdifferentiate is the aging and damage of cardiomyocytes. These two cell types maintain communication via gap junctions, membrane nanotubes, and paracrine signaling [66–68]. As indicated, with age, changes in the expression of key connexins in the heart occur, impairing intercellular communication and leading to disturbances in the conduction of electrical impulses [69]. In three-dimensional tissue co-cultured with cardiomyocytes, aging intensifies ECM remodeling and increases cardiac fibroblast activity, disrupting interactions with cardiomyocytes and exacerbating tissue dysfunction [70]. In cardiomyocytes, aging induces DNA damage in telomeric regions regardless of telomere length or cell division, activating the p21 and p16 pathways and the pro-hypertrophic and pro-fibrotic SASP [71]. Aging cardiomyocytes, due to mitochondrial damage, are a source of large amounts of ROS, which cause oxidative stress in surrounding cells, including fibroblasts [72]. The speed of cardiac aging can be influenced by cardiotoxicity caused by drugs such as doxorubicin, leading to the accumulation of inflammatory mediators, oxidative stress, and cardiac fibrosis, which ultimately accelerates cardiac aging [73]. Pharmacological or genetic removal of aging cells reduces myocardial hypertrophy and fibrosis, alleviating age-related cardiac dysfunction [71]. At the same time, systemic inflammation affects local mechanisms in the heart. Blood vessels, from which endothelial cells can undergo EndoMT, serve as a conduit of systemic inflammation to heart tissue and are a source of myofibroblasts [74]. Coronary vessels play a key role not only as sites of fibrosis and aging cells (shortened telomeres and high SA-βGal activity in vascular wall cells), but also because they are themselves susceptible to the development of inflammatory diseases [75, 76]. Insulin resistance and metabolic status, present in aging individuals, contribute to vascular endothelial damage and the development of inflammatory foci and ROS overproduction, which affects cardiac tissue. The negative effects of elevated blood glucose and local changes in lipid metabolism in coronary vessels also contribute to the development of atherosclerotic plaques [77, 78]. Damaged endothelium is also a source of nitrosative stress, present in HFpEF, due to altered nitric oxide metabolism [79].

The sequence of changes observed in aging models is analogous to the stages of cardiac remodeling in HFpEF, as hypertrophy and cardiomyocyte damage precede overt fibrosis, which results from extracellular matrix remodeling driven by fibroblast activation (mediated by a combination of paracrine and systemic effects) [80]. Therefore, the ability to diagnose HFpEF at an early stage would be highly valuable, as timely, phenotype-tailored interventions targeting cardiomyocyte injury could prevent progression to extensive myocardial fibrosis.

Phenotype-specific inflammatory signatures in HFpEF

Acute conditions such as myocardial infarction are characterized by fibrosis, but this is different in nature from the slow expansion and growth of ECM in heart tissue during aging and is associated with the replacement of cardiomyocytes lost in the short term [3, 59]. Additionally, in patients with a history of MI and its consequences, such as heart failure with reduced ejection fraction (HFrEF), systemic inflammation is not a predictive factor [81], and IL-6 levels are not associated with new-onset HFrEF [82]. In HFpEF, increased type I collagen deposition and increased collagen cross-linking correlate with abnormal diastolic function parameters in tissue Doppler (including reduced E' and increased E/E') and greater cardiomyocyte stiffness [83, 84], which is also associated with specific clusters of biomarkers in peripheral blood, including biomarkers of fibrosis, tissue remodelling, inflammation[85], and damage [86]. Several studies have examined the strong relationship between inflammaging and HFpEF [87]. HFpEF is characterized by chronic inflammation involving macrophages, with specific pro-inflammatory subtypes that increase with age, as detected in the human heart and linked to disease progression [88]. These phagocytes regulate both the initiation and resolution of the inflammatory response, and their imbalance may contribute to the perpetuation of diastolic dysfunction and myocardial fibrosis in HFpEF [89].

NLRP3 inflammasomes, protein complexes that trigger the production and secretion of pro-inflammatory cytokines by cells, are a point of contact between HFpEF and aging [90]. Inflammasome activity increases in the heart with age [91], suggesting its important role in the pathophysiology associated with degenerative processes. Furthermore, studies have shown that inhibiting its activity leads to a noticeable reduction in myocardial fibrosis and improvement in cardiac function in aging mice [92], suggesting a potential role for the inflammasome as a therapeutic target in the context of age-related cardiac changes and the development of HFpEF. Aging cells secrete SASP, creating a long-lasting profibrotic environment. Cytokines produced in the heart muscle and circulating in peripheral blood may also sensitize fibroblasts to key activating factors, such as angiotensin [93]. For example, IL-6, produced by macrophage-stimulated cardiac fibroblasts, plays a key role in activating the TGF-β/Smad3 pathway and in the development of angiotensin II-induced cardiac fibrosis [94]. Higher levels of IL-6 were associated with a higher risk of HFpEF [81]. Another study also showed increased concentrations of soluble interleukin-1 receptor-like 1 (sST2) and high-sensitivity C-reactive protein (hsCRP), which are markers of chronic inflammation and myocardial damage [95]. In a prospective analysis of a group of participants without previous heart failure, elevated IL-6 and CRP levels were significantly associated with the subsequent development of HFpEF, emphasizing that activation of the IL-6/CRP pathway may be characteristic and specific to the pathogenesis of this form of heart failure [96]. In individuals without previous cardiovascular disease, higher cumulative hsCRP levels, indicating chronic inflammation, were associated with a higher left ventricular mass index, impaired diastolic function (reduced e', elevated E/e'). In analyses accounting for demographics, elevated hsCRP was associated with a higher risk of HFpEF [97]. These observations were confirmed in patients with HFpEF who had elevated blood CRP levels [98]. However, the lack of association between CRP levels and fibrosis markers, such as pro-collagen III N-terminal peptide and C-telopeptide of type I collagen [98], is surprising and indicates the complexity of the pathophysiological mechanisms. Moreover, in another study of patients with HFpEF, increased levels of inflammatory mediators were associated with elevated myocardial fibrosis markers and N-terminal pro-B-type natriuretic peptide (NT-proBNP), suggesting a close relationship between chronic inflammation, fibrosis, and cardiac remodeling in this group [99]. Furthermore, a study involving over 2,000 patients with heart failure showed that elevated blood concentrations of IL-17D correlate with higher NT-proBNP levels and a higher incidence of atrial fibrillation [100, 101] and renal failure, while high IL-17D levels are independently associated with a worse prognosis in patients with HFpEF. Interestingly, IL-17D was not associated with classic markers of inflammation, such as IL-6 or CRP, indicating a distinct role for this cytokine in the pathogenesis of HFpEF [102].

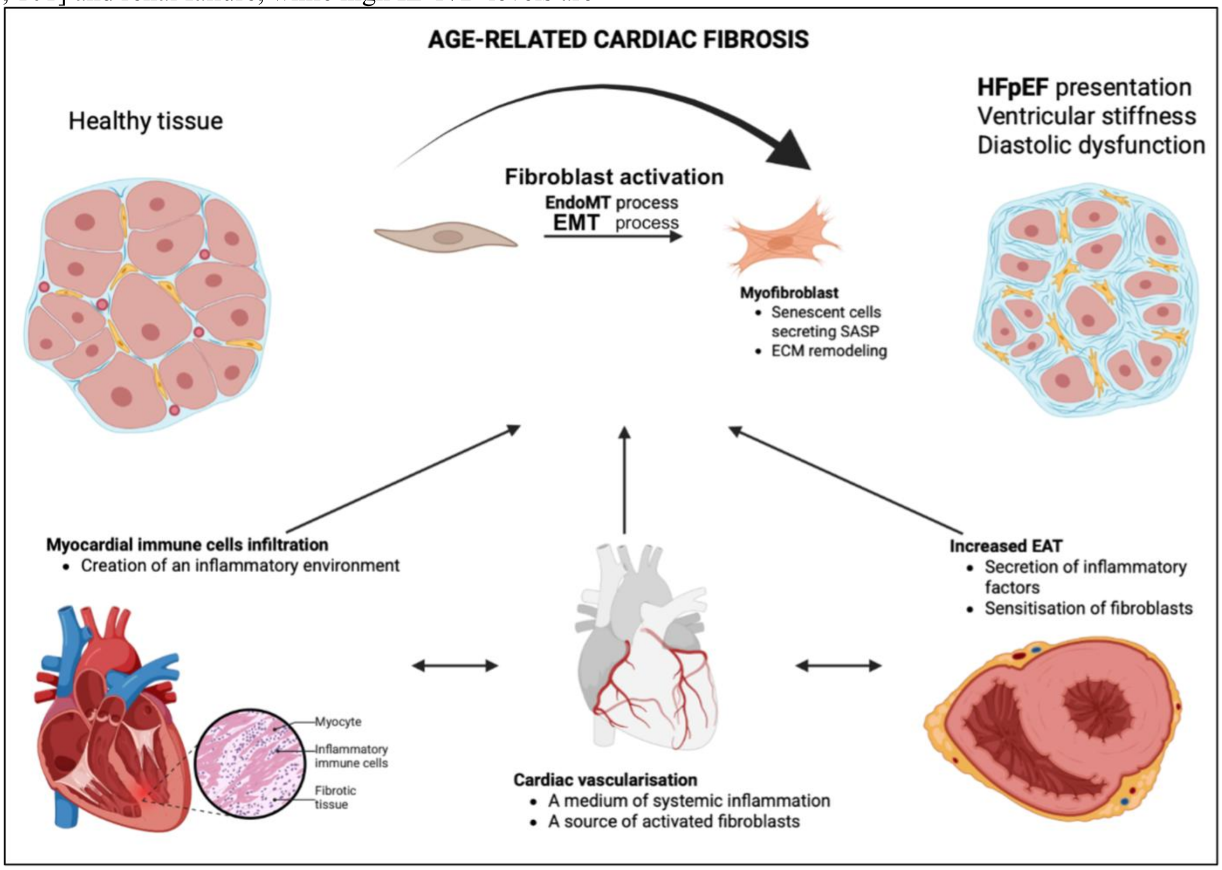

Figure 4. Mechanisms of age-related cardiac fibrosis. This process is driven by the activation of multiple cellular pathways that converge on fibroblast expansion and extracellular matrix remodeling. Resident cardiac fibroblasts become activated under the influence of pro-inflammatory and profibrotic signals, while additional myofibroblasts arise from EndoMT and EMT. These cells acquire a secretory and contractile phenotype and often exhibit features of cellular senescence, contributing to the release of SASP factors, including cytokines, growth factors, and matrix-remodeling enzymes, which further amplify local inflammation and fibrosis. Concurrently, infiltration of immune cells such as macrophages and lymphocytes into the myocardium sustains a chronic low-grade inflammatory milieu. Expansion and dysfunction of EAT provide an additional source of pro-inflammatory mediators and adipokines that act in a paracrine manner on the myocardium. Alterations in the cardiac microvasculature, including endothelial dysfunction and reduced capillary density, further exacerbate tissue hypoxia and inflammatory signaling, promoting continued fibroblast activation. The cumulative effect of these processes is excessive deposition and cross-linking of extracellular matrix components, leading to increased myocardial stiffness, impaired ventricular compliance, and progressive diastolic dysfunction-hallmark features of HFpEF.

4. HFpEF in the context of systemic aging

HFpEF and comorbidities

From a geroscience perspective, HFpEF may be viewed as a clinical manifestation of accelerated or maladaptive cardiovascular aging [103]. In this context, HFpEF lies along a continuum in which aging and age-related comorbidities converge through shared molecular and cellular pathways, including immune dysregulation, cellular senescence, and persistent activation of innate immunity [104]. Most HFpEF patients have several other age-related comorbidities in which inflammation and cellular aging are major risk factors and are key to disease progression (e.g., coronary artery disease, diabetes, arterial hypertension, atrial fibrillation/flutter, renal failure) [105–108]. The number of patients with HFpEF is increasing along with the prevalence of obesity and metabolic syndrome [109, 110]. Obesity is the predominant condition associated with HFpEF (72-

80%)[111, 112], and may lead to the disease independently of metabolic syndrome [113], which in turn increases the burden of comorbidities [109, 114]. Adipose tissue, especially when excessively accumulated, functions as an active endocrine organ that secretes numerous pro-inflammatory cytokines such as IL-6, TNF-α, and MCP-1, thereby maintaining a chronic inflammatory state within the microenvironment [115]. Therefore, obesity in patients with HFpEF may be associated with greater diastolic dysfunction and more severe exercise intolerance [111, 116]. Importantly, obesity-related inflammation may be interpreted as a potent amplifier of systemic inflammaging. Excess adipose tissue contributes to the accumulation of endogenous inflammatory signals that promote immune cell activation, fibroblast senescence, and the development of a senescence-associated secretory phenotype [117]. Sustained exposure to such a pro-inflammatory milieu may shift cardiac stromal cells toward a profibrotic state, facilitating extracellular matrix deposition and myocardial stiffening [118]. Thus, adipose tissue-derived inflammation integrates local cardiac remodeling into a broader, age-related inflammatory network that characterizes HFpEF. Prolonged exposure of fibroblasts to inflammatory mediators derived from adipose tissue may promote their transdifferentiation into myofibroblasts, leading to excessive extracellular matrix production and the development of tissue fibrosis [119–121]. Therefore, increased pericardial and peritoneal fat thickness is observed in HFpEF [122], associated with elevated inflammatory markers (CRP, IL-6) and collagen proteins (COL6A6, TNXB), which promote fibrosis and diastolic dysfunction [123, 124]. In HFrEF and in heart failure with mildly reduced ejection fraction (HFmrEF), EAT is thinner [123, 124]. A thorough INABLE study showed that HFpEF patients with the highest IL-6 levels had the highest body fat content [125].

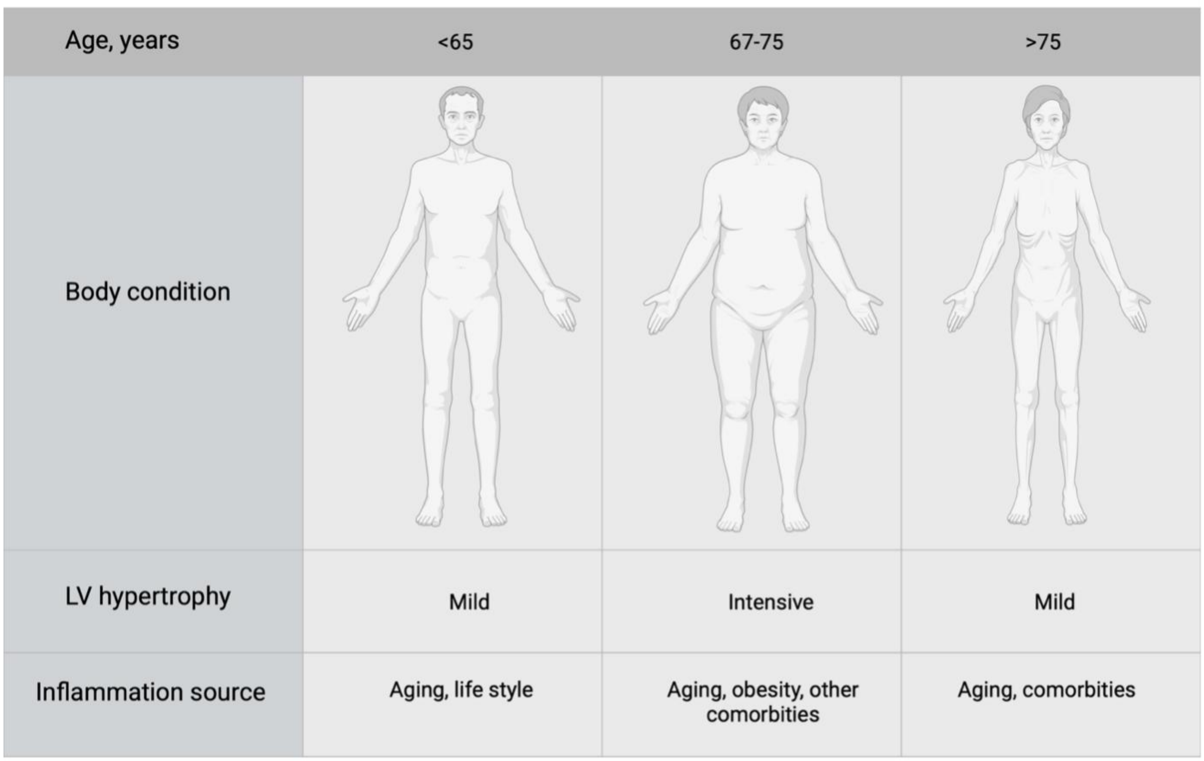

Figure 5. Conceptual schematic illustrating age-related HFpEF phenotypes. Three distinct clinical phenotypes are depicted based on age, comorbidity burden, and metabolic profile. The first phenotype represents younger patients (<65 years), typically with a history of smoking and selected comorbidities such as hypertension, but without obesity, suggesting a risk profile driven primarily by vascular and lifestyle-related factors. The second phenotype includes individuals aged 65–75 years with significant obesity and multiple comorbidities, reflecting a metabolically driven form of HFpEF characterized by systemic inflammation and immunometabolic dysregulation. The third phenotype comprises older patients (>75 years), also with coexisting comorbidities but without obesity, in whom HFpEF reflects the combined effects of advanced age, cumulative disease burden, and age-related cardiac remodeling. Together, these phenotypes illustrate the heterogeneity of HFpEF and highlight the varying contributions of accelerated versus physiological aging across patient groups.

Additionally, epicardial adipose tissue thickness and the neutrophil-to-lymphocyte ratio combined better predict hospitalization risk in patients with HFpEF [126, 127]. Obesity-related inflammation promotes fibrotic remodeling of both the atria and ventricles, leading to adverse structural changes in left atrial (LA) tissue [128, 129]. LA fibrosis predisposes to atrial fibrillation by disrupting electrical conduction and atrial architecture [129]. Atrial fibrillation is strongly associated with the subsequent development of HFpEF, often within 10 years [130]. At the same time, not all patients with HFpEF have AF, and studies across different populations report a prevalence ranging from 35% to 45% [131, 132].

A significant knowledge gap is the population of patients with HFpEF not associated with obesity [133]. It has not yet been determined whether the observed phenomenon is solely the result of aging processes or a complex interaction among multiple pathophysiological factors. Furthermore, the absence of obesity does not rule out the possibility of inflammation originating from sources other than adipose tissue, e.g., in association with rheumatoid arthritis, renal failure, or diabetes [134]. Interestingly, patients with HFpEF and obesity are more likely to have multiple comorbidities (hypertension, knee osteoarthritis, angina pectoris)[111]. Paradoxically, obesity has been shown to have a protective effect in patients with HFpEF and other comorbidities, this may be related to cardiac cachexia [134], but it may also be an error in the assessment of obesity, body composition, i.e., the actual content of adipose tissue in the body, including visceral fat, which is the main amplifier of obesity-related inflammation[135]. In their study, Cohen et al. classified the general HFpEF population into three phenotypes (F1, F2, F3-only obese) [131]. F1 and F2 patients were not obese, but the F1 population had the highest smoking rate (a well-known factor that accelerates aging). In contrast, F2 was characterized by the highest mean age and the highest prevalence of CKD and AF. Logically, the highest inflammation was observed in patients in groups F2 and F3 [131]. One HFpEF phenotype is associated with long-term inflammatory aging, while two phenotypes are linked to accelerated aging.

The difficulty in clearly defining the mechanisms underlying this phenotype stems not only from the multifactorial etiology and considerable heterogeneity of HFpEF, and from the multidimensional nature of the aging process, but also from the key role of chronic low-grade inflammation as a unifying pathophysiological axis, which damages cardiomyocytes and activates fibroblasts. This inflammatory environment may have various sources, including adipose tissue, comorbidities, and age-related immune dysregulation, among others. Nevertheless, significant advances have been made in recent years in the treatment of patients with HFpEF, both with and without obesity, which will be discussed in detail later in this article.

HFpEF and accelerated aging

The degree of biological age acceleration driven by comorbidities may vary; however, there are currently no data clearly identifying which condition exerts the strongest aging effect on the heart. It is well established, however, that key alterations occur at the level of cellular regulators of biological age, enabling the identification of epigenetic age acceleration (EAA). Population-based studies have demonstrated that higher phenotypic and epigenetic age indices are significantly associated with an increased risk of cardiovascular events and mortality, supporting their role as clinical markers of accelerated aging in HFpEF[41, 136]. In the studied population of older patients with obesity and HFpEF, a greater advancement of biological aging processes was observed, reflected by an elevated composite biomarker index. Higher index values were consistently associated with poorer physical function and exercise tolerance, including shorter distance in the 6-minute walk test, and shorter time to exhaustion [137]. Epigenetic mechanisms play a crucial role in sustaining inflammaging in HFpEF by regulating gene expression without altering the DNA sequence. Age-related changes in DNA methylation, histone modifications, and chromatin remodeling promote a shift toward a pro-inflammatory transcriptional profile, maintaining cytokine production while impairing resolution pathways [138]. Moreover, acceleration of epigenetic clocks has been shown to correlate with greater organ dysfunction and worsening cardiovascular performance, suggesting a direct contribution to HFpEF pathogenesis[136]. This process is further amplified by comorbidities such as obesity, diabetes, and hypertension, which accelerate epigenetic drift and reinforce inflammatory signaling, leading to a cumulative effect of "accelerated aging" within the cardiovascular system[41]. Consequently, epigenetic reprogramming acts as a mechanistic link between systemic aging, chronic inflammation, and myocardial remodeling in HFpEF, integrating the impact of multiple coexisting risk factors into a unified disease phenotype.

5. Anti-inflammatory therapy

Aging is not a uniform process but rather the result of a complex interplay between protective and detrimental factors, where the cumulative burden of comorbidities can shift the trajectory toward accelerated biological aging [139]. Increasing evidence suggests that the broadly defined "exposome," encompassing environmental, social, and biological influences, modulates this process and contributes to progressive functional decline. In the context of HFpEF, this supports the concept that accelerated cardiac aging, ultimately manifesting as HFpEF, is not driven by a single pathway but emerges from the coexistence of multiple comorbid conditions that collectively promote systemic inflammation, structural remodeling, and impaired cardiac reserve. Thus, age-related chronic inflammation should be viewed not as an isolated mechanism but as part of a broader, multisystem process [140].

Consequently, an important question arises: whether anti-inflammatory interventions can effectively modify the course of HFpEF, or whether their potential is inherently constrained by the multifactorial nature of accelerated aging. This perspective also highlights the need to move beyond single-pathway approaches toward therapeutic strategies that simultaneously target underlying drivers of accelerated aging, such as metabolic dysfunction or comorbidity burden, while modulating inflammatory signaling. By integrating causal and anti-inflammatory interventions, it may be possible to more effectively influence disease progression.

State-of-the-art

From the outset of research into anti-inflammatory therapies for HFpEF, various molecular targets have been pursued [141]. At the very beginning of intensive research into new anti-inflammatory therapies for heart failure, high hopes were pinned on drugs that block tumor necrosis factor alpha (TNF-α), which had shown very good results in other inflammatory diseases such as rheumatoid arthritis [142–144]. TNF-α is one of the key pro-inflammatory cytokines strongly involved in the pathomechanisms of heart failure, as it promotes cardiomyocyte apoptosis, increases oxidative stress, and exacerbates myocardial remodeling [145]. TNF-α inhibitors, such as infliximab and etanercept, were quickly introduced into clinical trials in patients with heart failure, with the hope of improving their clinical condition. Initially, positive results were obtained in animal models and in vitro studies, indicating potential benefits of TNF-α blockade in preventing adverse changes in the heart muscle. Unfortunately, the results of early clinical trials were disappointing. Not only was no improvement observed in patients, but heart function actually deteriorated, especially when high doses of infliximab were administered [142]. This paradoxical effect suggested that TNF-α also has certain protective or adaptive functions and that its complete blockade may be harmful in the context of complex pathological processes in heart failure [142, 143].

In the following years, researchers turned their attention to p38 mitogen-activated protein kinase (MAPK), a key enzyme in signaling pathways that regulate the inflammatory and stress responses of cells [146]. It has been shown that p38 MAPK is activated in response to various stressors, including cardiac pressure overload and excessive RAA activation [147]. Inhibitors of p38 MAPK kinase, such as BIRB796, were first tested in animal models, particularly in transgenic rats with overexpression of RAA receptors, where BIRB796 was shown to significantly improve animal survival, reduce myocardial fibrosis, reduce inflammatory infiltrates, and limit organ damage [148]. These effects indicated the therapeutic potential of selective suppression of inflammatory signaling pathways and highlighted the complex role of p38 MAPK in cardiac pathophysiology, especially in the context of inflammation and oxidative stress [148]. At the same time, it was confirmed that angiotensin II, one of the main mediators of the RAA system, activates p38 MAPK, leading to increased ROS production, hypertension, myocardial hypertrophy, and vascular endothelial dysfunction, which are key elements in the progression of heart failure [149]. Pharmacological blockade of p38 MAPK with the inhibitor SB239063AN effectively reduced levels of phosphorylated p38 kinase, reduced ROS production, and prevented hypertension and cardiac hypertrophy, confirming that p38 MAPK is an attractive and promising therapeutic target in cardiovascular diseases [149].

Breakthrough clinical reports from 2013 and 2014 shed new light on the role of inflammation in HFpEF. The RELAX study tested a phosphodiesterase type 5 (PDE-5) inhibitor, which had improved heart muscle function and exercise capacity in other contexts. However, despite promising preclinical data, PDE-5 inhibitor therapy did not improve exercise tolerance or clinical status after 24 weeks of treatment [150]. In a contrasting study, anakinra, a recombinant inhibitor of interleukin-1 (IL-1), a key mediator of inflammatory processes, was used. In patients with HFpEF and elevated C-reactive protein (CRP) levels, short-term anakinra therapy resulted in a significant improvement in exercise capacity, as measured by peak oxygen consumption, and a significant reduction in inflammatory markers [151]. These results highlighted the important role of inflammatory processes in HFpEF and suggested that targeted anti-inflammatory treatment may be more effective than previous strategies of NO-cGMP signaling modulation and PDE-5 blockade [151, 152]. However, in a randomized trial of 31 patients with HFpEF and elevated CRP, 12 weeks of anakinra treatment did not improve exercise capacity, despite clear reductions in hsCRP and NT-proBNP levels, suggesting an anti-inflammatory effect without clear clinical benefit [153, 154]. Notably, anakinra also did not reduce the primary endpoint in the ARAMIS trial (37640625), which included patients with myocarditis. This highlights the interspaced pathways of inflammation even in the most severe presentations, such as myocarditis.

Another key aspect in understanding inflammation in heart failure was the role of interleukin-10 (IL-10), a cytokine with potent anti-inflammatory properties [155]. The absence of IL-10 in animals with pressure overload exacerbated adverse cardiac remodeling and myocardial hypertrophy, indicating its protective role. IL-10-based therapy not only inhibited the development of these pathological changes but was also able to reverse existing left ventricular dysfunction. Mechanistically, the action of IL-10 is based on modulation of the STAT3 pathway and inhibition of the activation of the nuclear factor NF-κB, a major regulator of pro-inflammatory gene transcription [155]. These results reinforce the notion that the balance between pro- and anti-inflammatory cytokines is crucial for maintaining cardiac homeostasis and limiting pathological remodeling. The multicenter HERMES trial is currently underway to evaluate the efficacy of the human antibody ziltivekimab in patients with HFpEF [156]. Ziltivekimab is an IL-6 inhibitor; it effectively reduces hsCRP levels, thereby limiting systemic inflammation [157]. Therefore, it may be effective in patients with HFpEF.

In recent years, much attention has been paid to the inflammasome, a multiprotein complex that activates caspase-1, initiating pyroptosis, an inflammatory form of cell death, and the maturation of proinflammatory cytokines such as IL-1β and IL-18 [158, 159]. Inhibition of the inflammasome by the caspase-1 inhibitor VX-765 is a novel approach that differs from previous strategies based on blocking individual cytokines. In models of cardiac ischemia-reperfusion, administration of VX-765 in combination with a P2Y12 receptor inhibitor provided sustained protection of the heart muscle, limiting the extent of damage and improving heart function, highlighting the inflammasome as a key therapeutic target in acute myocardial infarction [160]. The NLRP3 inhibitor MCC950 also reduced IL-1β and IL-18 levels and limited systemic inflammation and myocardial fibrosis in mice after a heart attack, resulting in improved systolic and diastolic heart function [161]. In an HFpEF model, blockade of the NLRP3 inflammasome with MCC950 improved left ventricular diastolic function and reduced myocardial hypertrophy, fibrosis, and pulmonary artery remodeling. The mechanism of action involves inhibition of the NLRP3-IL-1β pathway and proinflammatory cytokine cascade, which limits the inflammatory process and reduces tissue damage [162]. In addition, MCC950 reduced the infiltration of pro-inflammatory macrophages (M1) in the heart and pericardial adipose tissue, further highlighting its immunomodulatory properties [163]. In aging mice, cardiac diastolic function deteriorates due to increased pro-inflammatory macrophages and fibrosis. The DC-SIGN ligand (DCSL1) inhibits macrophage maturation, shifts their polarisation towards an anti-inflammatory phenotype, increases IL-10, and reduces fibrosis, improving cardiac function without the need for gene exclusion [164]. Resveratrol was found to induce M1 to M2 conversion and inhibit neutrophil infiltration into heart tissue. Resveratrol modulated pathways by increasing SIRT1 activity, thereby reducing the activity of the Smad2/Smad3 fibrosis pathways [165]. Similar immunomodulatory effects were observed with propionate, a short-chain fatty acid, which reduced the number of pro-inflammatory T lymphocytes, including Th17 cells, and inhibited immune infiltration into the heart, with potential therapeutic significance in the fight against chronic inflammation and its consequences [166].

Another promising drug is colchicine, which has long been used in inflammatory diseases such as gout and coronary artery disease [167, 168]. Colchicine at a dose of 0.5 mg daily in patients after a recent myocardial infarction reduced the risk of ischaemic cardiovascular events [169]. In animal models of diet-induced HFpEF, colchicine improved heart function and reduced fibrosis and inflammation by downregulating TNFα and CCL2 expression and inhibiting NLRP3 and NF-κB pathway activity. Furthermore, it improved animal survival and physical endurance, confirming its therapeutic potential in this model [170]. However, there remains a lack of widely available clinical data confirming colchicine's efficacy in patients with HFpEF. In patients with chronic, stable HFrEF, colchicine therapy for 6 months led to a significant reduction in inflammatory markers, including CRP and IL-6 [171]. However, no improvement in physical function or reduction in the risk of death or hospitalization was observed, indicating limitations to the use of colchicine in this indication [171, 172]. Knowledge about the effect of colchicine on inflammation in HFpEF is constantly expanding. Ongoing work in the COLpEF trial (~500 patients) is evaluating whether chronic low-dose colchicine reduces systemic inflammation, as reflected by CRP levels after six months of therapy, and whether this translates into improved clinical outcomes in HFpEF-thereby clarifying its potential as a targeted immunomodulatory treatment [173].

Finally, it is worth noting the role of the enzyme myeloperoxidase (MPO), produced by neutrophils and macrophages, which generates ROS and contributes to oxidative stress [174, 175]. MPO levels correlate with the severity of inflammation, diastolic dysfunction of the heart muscle, and the endothelium. The rationale for using the MPO inhibitor mitiperstat in the ENDEAVOR study is its potential to reduce inflammation in HFpEF [176]. Specific inhibition of MPO in patients with HFpEF reduced enzyme activity by approximately 50% [177–

179]. A single 30 mg dose of mitiperstat (MPO inhibitor) did not demonstrate acute efficacy in 30 patients with HFpEF, failing to reduce exercise pulmonary wedge pressure or to beneficially affect hemodynamics, casting doubt on the immediate effect of MPO inhibition in this population [180]. Although no clear improvement in microcirculation or physical performance was observed, a positive trend in quality of life was noted, indicating the potential of this strategy in therapy [177, 178].

A new approach to inflammation and HFpEF

SGLT2 inhibitors (empagliflozin, dapagliflozin) have emerged as cornerstone therapy in HFpEF following EMPEROR-Preserved[181] and DELIVER[182] trials, which demonstrated significant reductions in heart-failure hospitalization and improved quality of life [183]. SGLT2 inhibitors exert their effects in several ways: anti-inflammatory effects, improved metabolic efficiency, and endothelial function. Preclinical and translational studies show reductions in epicardial adipose tissue, modulation of adipokine signaling, and attenuation of oxidative stress. It is noteworthy that SGLT2 inhibitors have been shown to modulate NLRP3 inflammasome signaling, thereby reducing inflammation and improving cardiac energetics [184]. Empagliflozin reduces inflammation in HFpEF by lowering proinflammatory cytokines and improving mitochondrial oxidative stress in cardiomyocytes, indicating a direct immunometabolic effect in the heart [185]. Across 23 studies including 1,008 patients with HF, SGLT2 inhibitor therapy significantly reduced left ventricular volumes, mass, and epicardial adipose tissue [186]. The results of this multicenter, randomized trial demonstrate that dapagliflozin significantly reduces myocardial fibrosis, as assessed by ECV, in patients with HFpEF and type 2 diabetes, supporting the concept that SGLT2 inhibition may exert true disease-modifying effects through direct modulation of adverse myocardial remodeling [187], it is also effective in patients without coexisting diabetes, suggesting mechanisms of action that extend beyond metabolic control alone [188]. The ongoing STADIA-HFpEF trial is designed to test the hypothesis that SGLT2 inhibition improves left ventricular stiffness in early-stage HFpEF by targeting cardiomyocyte stiffness and microvascular endothelial dysfunction, thereby providing a phenotype-guided therapeutic approach [189].

Glucagon-like peptide-1 (GLP-1) receptor agonists are incretin-based drugs recommended for patients with diabetes that also promote weight loss, making them beneficial in the treatment of HFpEF [190]. Both GLP-1 agonists (e.g., semaglutide) and drugs that combine GLP-1 and GIP activity (e.g., tirzepatide) show promising effects in patients with HFpEF, especially in cases of coexisting obesity and/or type 2 diabetes [191, 192]. In the STEP-HFpEF trial, semaglutide improved cardiac symptoms and exercise capacity while reducing C-reactive protein levels and pericardial adipose tissue burden, linking weight loss–associated attenuation of systemic inflammation to meaningful improvements in cardiac function in obese patients with HFpEF [193]. The main mechanism behind these benefits is thought to be their effect on reducing excess weight [194]. For example, tirzepatide has been shown to significantly reduce pericardial fat in patients with obesity and HFpEF [195]. However, it is worth noting that the populations in clinical trials involving patients with HFpEF to date have predominantly had a high BMI. There is still insufficient data to distinguish the effects of GLP-1 agonist treatment in patients with HFpEF according to obesity status [133]. One of the latest studies has shown a beneficial effect of GLP-1 agonist therapy, including semaglutide, in patients with HFpEF and diabetes but without obesity [196]. Similarly, a study evaluating the effect of tirzepatide in patients with and without obesity found no significant differences between the groups [197], suggesting that part of the therapeutic effect may also result from the anti-inflammatory properties of GLP-1 agonists [198]. Preclinical studies have shown that tirzepatide reduces the concentration of pro-inflammatory cytokines and decreases the infiltration of pro-inflammatory M1 macrophages by inducing their apoptosis in the adipose tissue of mice [199]. Therefore, a key direction for future research will be to determine whether a similar effect also occurs in human perivascular adipose tissue (EAT) under the influence of GLP-1 agonists [200], especially in the context of promising results indicating a reduction in inflammatory markers in peripheral blood after the use of semaglutide [201–203].

6. Deciphering the effects of anti-inflammatory treatment in HFpEF and its future

Despite the growing body of evidence implicating chronic inflammation as a key contributor to cardiac fibrosis and the pathogenesis of HFpEF, it remains unclear to what extent the observed alterations represent a direct consequence of biological cardiovascular aging versus the cumulative impact of age-related comorbidities such as obesity, diabetes, hypertension, and chronic kidney disease [204]. This unresolved interplay between "pure" aging and comorbidity burden substantially complicates the identification of patient populations most likely to benefit from anti-inflammatory therapies. A central challenge is that inflammation in HFpEF does not resemble a classical, cytokine-dominated response but rather manifests as a chronic, low-grade, multifactorial process characteristic of aging [205]. In this context, the failure of strategies targeting single cytokines, such as TNF-α or IL-1β, appears biologically plausible, as inhibition of an individual mediator does not extinguish the interconnected network underlying inflammaging, which includes parallel pathways activated by endogenous danger signals (DAMPs), Toll-like receptors, inflammasomes, mitochondrial DNA, and SASP factors released by senescent cells [206]. Moreover, TNF-α, while unequivocally pro-inflammatory, also exerts adaptive and cytoprotective effects, and its global inhibition may disrupt the delicate balance between host defense and tissue homeostasis [207]. Similarly, although IL-1 blockade effectively reduces inflammatory biomarkers, it does not consistently translate into clinical improvement, suggesting that IL-1–dependent pathways represent only one component of a redundant and compensatory signaling network driving fibrosis and diastolic dysfunction.

In the context of inflammaging, cytokines should therefore be viewed primarily as markers of an ongoing pathological process, rather than as its primary causative factors, whose secretion in degenerative diseases is induced by oxidative stress and DAMPs [208]. The principal mechanisms sustaining inflammation in HFpEF include the accumulation of molecular debris, progressive mitochondrial dysfunction, immunosenescence, oxidative stress, and the buildup of senescent cells, which together lead to persistent activation of innate immunity, cardiomyocyte injury, and myocardial fibrosis [206]. From this perspective, inflammation remains an important component of HFpEF pathophysiology, yet functions predominantly as a disease modulator rather than a factor whose isolated inhibition could reverse established structural and functional myocardial changes [80]. HFpEF is inherently a structural and biomechanical disorder: myocardial fibrosis, extracellular matrix remodeling, and left ventricular stiffening develop gradually and are maintained by fibroblast and myofibroblast senescence, rendering these alterations largely irreversible. At this stage, even biochemically effective anti-inflammatory interventions may be too late to meaningfully improve diastolic compliance, thereby explaining the observed dissociation between improvements in inflammatory biomarkers and the absence of clinical benefit [80].

Against this backdrop, immunometabolic therapies such as SGLT2 inhibitors and GLP-1 receptor agonists are particularly compelling, as they confer clinical benefits independent of classical single-cytokine suppression [209]. Preclinical and clinical data indicate that these agents modulate innate immune activity, attenuate macrophage and inflammasome activation, improve mitochondrial function, and reduce systemic inflammation, while simultaneously addressing coexisting obesity, a key driver of inflammaging [210]. An increasing body of evidence suggests that their combined anti-inflammatory and metabolic effects may influence cardiac fibrotic processes, in part by inhibiting the NLRP3–IL-1β axis and reducing oxidative stress, including via adipose tissue reduction. Nevertheless, direct evidence for fibrosis regression or slowed progression in humans remains limited and warrants further investigation [211].

From a clinical perspective, this review is positioned at the intersection of geriatric cardiology, metabolic medicine, and the immunobiology of aging, focusing on HFpEF as the dominant heart failure phenotype in older, multimorbid patients, with particular emphasis on obesity. This context is critical for clinical readers, as it underscores that the lack of efficacy of classical anti-inflammatory therapies in HFpEF reflects not merely shortcomings of individual interventions but the fundamental biological complexity of the disease itself. In clinical practice, this necessitates abandoning reductionist approaches in favor of multidimensional strategies encompassing metabolic optimization, lifestyle modification, early identification of patients with active inflammation, and the use of broad-spectrum immunometabolic agents such as SGLT2 inhibitors and GLP-1 receptor agonists, which have demonstrated tangible clinical benefits in HFpEF [211].

Future research should therefore focus on integrating clinical, imaging, and molecular data, developing tools to assess *in vivo* inflammatory activity and senescence, and designing clinical trials targeting well-defined patient phenotypes and early stages of HFpEF. Such an approach is essential to enable the effective use of anti-inflammatory and immunometabolic therapies to slow cardiac fibrosis and meaningfully alter the natural history of HFpEF in an aging population [107].

7. Conclusion

Aging-related cardiac fibrosis represents a central yet still insufficiently delineated component of HFpEF pathogenesis. Available evidence indicates that chronic, low-grade inflammation characteristic of biological aging (inflammaging) plays a critical role in fibroblast activation, ECM, and the progressive stiffening of the left ventricle. Importantly, this inflammatory state arises from mitochondrial dysfunction, immunosenescence, and senescent cell accumulation, limiting the efficacy of therapies targeting single inflammatory mediators. In this context, therapies with broad immunometabolic actions, such as SGLT2 inhibitors and GLP-1 receptor agonists, appear especially promising, as they simultaneously modulate metabolic pathways, immune responses, and the myocardial microenvironment, offering tangible clinical benefits in HFpEF.

At the same time, this analysis highlights important unresolved questions, including the lack of validated biomarkers to distinguish aging-related from comorbidity-driven inflammation, and the limited reversibility of fibrosis in advanced disease stages.

Future therapeutic strategies should therefore move away from nonspecific blockade of individual cytokines toward more precise, phenotype-guided approaches that integrate immunomodulation with metabolic control (targeting obesity, diabetes, and hypertension), assessment of active inflammation, and refined biological subtyping of HFpEF. Such strategies may enable more effective deployment of anti-inflammatory therapies to slow myocardial fibrosis and modify the natural course of HFpEF in an aging population.

Conflict of Interest

The Authors declare no Competing Financial or Non-Financial Interests.

References

[1] Atella V, Piano Mortari A, Kopinska J, Belotti F, Lapi F, Cricelli C, et al. (2019). Trends in age-related disease burden and healthcare utilization. Aging Cell, 18:e12861.

[2] Bozkurt B, Ahmad T, Alexander K, Baker WL, Bosak K, Breathett K, et al. (2025). HF STATS 2024: Heart Failure Epidemiology and Outcomes Statistics An Updated 2024 Report from the Heart Failure Society of America. Journal of Cardiac Failure, 31:66–116.

[3] Biernacka A, Frangogiannis NG (2011). Aging and Cardiac Fibrosis. Aging Dis, 2:158–173.

[4] Chiamvimonvat N (2002). Diastolic dysfunction and the aging heart. J Mol Cell Cardiol, 34:607–610.

[5] Weisfeldt M (1998). Aging, changes in the cardiovascular system, and responses to stress. American journal of hypertension, 11:41S-45S.

[6] Meschiari CA, Ero OK, Pan H, Finkel T, Lindsey ML (2017). The impact of aging on cardiac extracellular matrix. GeroScience, 39:7–18.

[7] Goyal P, Maurer MS, Roh J (2024). Aging in Heart Failure: Embracing Biology Over Chronology: JACC Family Series. JACC: Heart Failure .

[8] Konerman MC, Greenberg JC, Kolias TJ, Corbett JR, Shah RV, Murthy VL, et al. (2018). Reduced myocardial flow reserve is associated with diastolic dysfunction and decreased left atrial strain in patients with normal ejection fraction and epicardial perfusion. J Card Fail, 24:90–100.

[9] Beck J, Horikawa I, Harris C (2020). Cellular Senescence: Mechanisms, Morphology, and Mouse Models. Vet Pathol, 57:747–757.

[10] Goldstein DR, Abdel-Latif A (2023). Immune mechanisms of cardiac aging. The journal of cardiovascular aging, 3:17.

[11] Jones G, Trajanoska K, Santanasto AJ, Stringa N, Kuo C-L, Atkins JL, et al. (2021). Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women. Nat Commun, 12:654.

[12] Dance CJ, Ipser A, Simner J (2022). The prevalence of aphantasia (imagery weakness) in the general population. Consciousness and Cognition, 97:103243.

[13] Wang X, Hu J, Wu D (2022). Risk factors for frailty in older adults. Medicine, 101:e30169.

[14] Aziz T, Hussain N, Hameed Z, Lin L (2024). Elucidating the role of diet in maintaining gut health to reduce the risk of obesity, cardiovascular and other age-related inflammatory diseases: recent challenges and future recommendations. Gut Microbes, 16:2297864.

[15] Damluji AA, Chung S-E, Xue Q-L, Hasan RK, Moscucci M, Forman DE, et al. (2021). Frailty and cardiovascular outcomes in the National Health and Aging Trends Study. Eur Heart J, 42:3856–3865.

[16] Barcena ML, Aslam M, Pozdniakova S, Norman K, Ladilov Y (2022). Cardiovascular Inflammaging: Mechanisms and Translational Aspects. Cells, 11:1010.

[17] Ferrucci L, Fabbri E (2018). Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol, 15:505–522.

[18] Pagourelias ED, Alexandridis GM, Vassilikos VP (2021). Fibrosis in hypertrophic cardiomyopathy: role of novel echo techniques and multi-modality imaging assessment. Heart Failure Reviews, 26:1297–1310.

[19] Mitropoulou P, Georgiopoulos G, Figliozzi S, Klettas D, Nicoli F, Masci PG (2020). Multi-modality imaging in dilated cardiomyopathy: with a focus on the role of cardiac magnetic resonance. Frontiers in Cardiovascular Medicine, 7:97.

[20] Nagueh SF, Sanborn DY, Oh JK, Anderson B, Billick K, Derumeaux G, et al. (2025). Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography and for Heart Failure With Preserved Ejection Fraction Diagnosis: An Update From the American Society of Echocardiography. Journal of the American Society of Echocardiography, 38:537–569.

[21] Nagueh SF, Sanborn DY, Oh JK, Anderson B, Billick K, Derumeaux G, et al. (2025). Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography and for Heart Failure With Preserved Ejection Fraction Diagnosis: An Update From the American Society of Echocardiography. J Am Soc Echocardiogr, 38:537–569.

[22] Fu Z, Liu P, Gao X, Shi S, Li Y, Zhang B, et al. (2024). Association of systemic inflammatory markers with clinical adverse prognosis and outcomes in HFpEF: a systematic review and meta-analysis of cohort studies. Front Cardiovasc Med. doi: 10.3389/fcvm.2024.1461073.

[23] De Sutter J, De Backer J, Van de Veire N, Velghe A, De Buyzere M, Gillebert TC (2005). Effects of age, gender, and left ventricular mass on septal mitral annulus velocity (E′) and the ratio of transmitral early peak

velocity to E′(E/E′). The American journal of cardiology, 95:1020–1023.
[24] Kim I-S, Kim T-H, Shim C-Y, Mun H-S, Uhm JS, Joung B, et al. (2015). The ratio of early transmitral flow velocity (E) to early mitral annular velocity (E m) predicts improvement in left ventricular systolic and diastolic function 1 year after catheter ablation for atrial fibrillation. EP Europace, 17:1051–1058.
[25] Kloch M, Stolarz-Skrzypek K, Olszanecka A, Wojciechowska W, Bednarski A, Stefaniak J, et al. (2019). Inflammatory markers and left ventricular diastolic dysfunction in a family-based population study. Polish Heart Journal (Kardiologia Polska), 77:33–39.
[26] Fang L, Ellims AH, Beale AL, Taylor AJ, Murphy A, Dart AM (2017). Systemic inflammation is associated with myocardial fibrosis, diastolic dysfunction, and cardiac hypertrophy in patients with hypertrophic cardiomyopathy. Am J Transl Res, 9:5063–5073.
[27] Pugliese NR, Mazzola M, Madonna R, Gargani L, De Biase N, Dini FL, et al. (2022). Exercise-induced pulmonary hypertension in HFpEF and HFrEF: Different pathophysiologic mechanism behind similar functional impairment. Vascular Pharmacology, 144:106978.
[28] Schimmel K, Ichimura K, Reddy S, Haddad F, Spiekerkoetter E (2022). Cardiac fibrosis in the pressure overloaded left and right ventricle as a therapeutic target. Frontiers in Cardiovascular Medicine, 9:886553.
[29] Pan JA, Kerwin MJ, Salerno M (2020). Native T1 Mapping, Extracellular Volume Mapping, and Late Gadolinium Enhancement in Cardiac Amyloidosis. JACC: Cardiovascular Imaging, 13:1299–1310.
[30] Ferreira VM, Schulz -Menger Jeanette, Holmvang G, Kramer CM, Carbone I, Sechtem U, et al. (2018). Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation. JACC, 72:3158–3176.
[31] Lee LE, Chandrasekar B, Yu P, Ma L (2022). Quantification of myocardial fibrosis using noninvasive T2-mapping magnetic resonance imaging: Preclinical models of aging and pressure overload. NMR Biomed, 35:e4641.
[32] Corpataux N, Haider A, Fuentes Artiles R, Wahl A, Gebert P, Mikail N, et al. (2026). Effect of age and sex on cardiac magnetic resonance native T1 mapping and synthetic extracellular volume. Int J Cardiol, 442:133818.
[33] Liu C-Y, Liu Y-C, Wu C, Armstrong A, Volpe GJ, van der Geest RJ, et al. (2013). Evaluation of age-related interstitial myocardial fibrosis with cardiac magnetic resonance contrast-enhanced T1 mapping: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol, 62:1280–1287.
[34] Moustafa A, Khan MS, Alsamman MA, Jamal F, Atalay MK (2021). Prognostic significance of T1 mapping parameters in heart failure with preserved ejection fraction: a systematic review. Heart Fail Rev, 26:1325–1331.
[35] Emrich* T, Hahn F, Fleischmann D, Halfmann MC, Düber C, Varga-Szemes A, et al. (2020). T1 and T2 Mapping to Detect Chronic Inflammation in Cardiac Magnetic Resonance Imaging in Heart Failure with Reduced Ejection Fraction. ESC Heart Fail, 7:2544–2552.
[36] Meyer T, Wellge B, Barzen G, Klemmer Chandia S, Knebel F, Hahn K, et al. (2025). Cardiac Elastography With External Vibration for Quantification of Diastolic Myocardial Stiffness. J Am Soc Echocardiogr, 38:431–442.
[37] Kelly JM, Babich JW (2022). PET Tracers for Imaging Cardiac Function in Cardio-oncology. Curr Cardiol Rep, 24:247–260.
[38] Saraste A, Knuuti J (2017). PET imaging in heart failure: the role of new tracers. Heart failure reviews, 22:501–511.
[39] Saraste A, Knuuti J (2017). PET imaging in heart failure: the role of new tracers. Heart Fail Rev, 22:501–511.
[40] Borlaug BA (2020). Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol, 17:559–573.
[41] Xu X, Huang Z, Xu X, Liu M, Huang R, Xiong Z, et al. (2025). Biological aging, left ventricular dysfunction and mortality in patients with heart failure with preserved ejection fraction. npj Aging, 11:102.
[42] Shono A, Matsumoto K, Yamada N, Kusunose K, Suzuki M, Sumimoto K, et al. (2021). "Accelerated aging" of the heart as heart failure with preserved ejection fraction—analysis using leg-positive pressure stress echocardiography. Int J Cardiovasc Imaging, 37:2473–2482.
[43] Nagueh SF, Khan SU (2023). Left Atrial Strain for Assessment of Left Ventricular Diastolic Function: Focus on Populations With Normal LVEF. JACC Cardiovasc Imaging, 16:691–707.
[44] Iacobellis G (2022). Epicardial adipose tissue in contemporary cardiology. Nat Rev Cardiol, 19:593–606.
[45] Elsanhoury A, Nelki V, Kelle S, Van Linthout S, Tschöpe C (2021). Epicardial Fat Expansion in Diabetic and Obese Patients With Heart Failure and Preserved Ejection Fraction—A Specific HFpEF Phenotype. Front Cardiovasc Med. doi: 10.3389/fcvm.2021.720690.
[46] García-Domínguez M (2025). Pathological and Inflammatory Consequences of Aging. Biomolecules, 15:404.
[47] Xu X, Pang Y, Fan X (2025). Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances. Signal Transduction and Targeted Therapy, 10:190.
[48] Takasugi M, Yoshida Y, Ohtani N (2022). Cellular senescence and the tumour microenvironment. Molecular Oncology, 16:3333–3351.
[49] Khavinson V, Linkova N, Dyatlova A, Kantemirova R, Kozlov K (2023). Senescence-Associated Secretory Phenotype of Cardiovascular System Cells and Inflammaging: Perspectives of Peptide Regulation. Cells, 12:106.
[50] ReactomeTeam, Lynch V, Weitz E (2024). Senescence-associated secretory phenotype (SASP). .
[51] Santinha D, Vilaça A, Estronca L, Schüler SC, Bartoli C, Sandre-Giovannoli AD, et al. (2024). Remodeling of the Cardiac Extracellular Matrix Proteome During

Chronological and Pathological Aging. Molecular & Cellular Proteomics. doi: 10.1016/j.mcpro.2023.100706.
[52] Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A (2018). Inflammaging: a new immune–metabolic viewpoint for age-related diseases. Nat Rev Endocrinol, 14:576–590.
[53] Sandmand M, Bruunsgaard H, Kemp K al, Andersen-Ranberg K, Pedersen AN, Skinhøj P (2002). Is ageing associated with a shift in the balance between Type 1 and Type 2 cytokines in humans? Clinical & Experimental Immunology, 127:107–114.
[54] Martínez-Zamudio RI, Dewald HK, Vasilopoulos T, Gittens-Williams L, Fitzgerald-Bocarsly P, Herbig U (2021). Senescence-associated β-galactosidase reveals the abundance of senescent CD8+ T cells in aging humans. Aging Cell, 20:e13344.
[55] El-Menyar AA (2008). Cytokines and Myocardial Dysfunction: State of the Art. Journal of Cardiac Failure, 14:61–74.
[56] Frangogiannis NG (2014). The inflammatory response in myocardial injury, repair, and remodelling. Nature Reviews Cardiology, 11:255–265.
[57] Mesquita T, Lin Y-N, Ibrahim A (2021). Chronic low-grade inflammation in heart failure with preserved ejection fraction. Aging Cell, 20:e13453.
[58] Siwik DA, Chang DL-F, Colucci WS (2000). Interleukin-1β and Tumor Necrosis Factor-α Decrease Collagen Synthesis and Increase Matrix Metalloproteinase Activity in Cardiac Fibroblasts In Vitro. Circulation Research, 86:1259–1265.
[59] Frangogiannis NG (2021). Cardiac fibrosis. Cardiovascular research, 117:1450–1488.
[60] Biernacka A, Dobaczewski M, Frangogiannis NG (2011). TGF-β signaling in fibrosis. Growth Factors, 29:196–202.
[61] Chen W, Frangogiannis NG (2010). The role of inflammatory and fibrogenic pathways in heart failure associated with aging. Heart failure reviews, 15:415–422.
[62] Krenning G, Zeisberg EM, Kalluri R (2010). The origin of fibroblasts and mechanism of cardiac fibrosis. Journal of Cellular Physiology, 225:631–637.
[63] Ma Y, de Castro Brás LE, Toba H, Iyer RP, Hall ME, Winniford MD, et al. (2014). Myofibroblasts and the extracellular matrix network in post-myocardial infarction cardiac remodeling. Pflugers Arch - Eur J Physiol, 466:1113–1127.
[64] Shinde AV, Humeres C, Frangogiannis NG (2017). The role of α-smooth muscle actin in fibroblast-mediated matrix contraction and remodeling. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1863:298–309.
[65] Mishra S, Kass DA (2021). Cellular and molecular pathobiology of heart failure with preserved ejection fraction. Nat Rev Cardiol, 18:400–423.
[66] He K, Shi X, Zhang X, Dang S, Ma X, Liu F, et al. (2011). Long-distance intercellular connectivity between cardiomyocytes and cardiofibroblasts mediated by membrane nanotubes. Cardiovasc Res, 92:39–47.
[67] Fountoulaki K, Dagres N, Iliodromitis EK (2015). Cellular Communications in the Heart. Card Fail Rev, 1:64–68.
[68] Zhang P, Su J, Mende U (2012). Cross talk between cardiac myocytes and fibroblasts: from multiscale investigative approaches to mechanisms and functional consequences. American Journal of Physiology-Heart and Circulatory Physiology, 303:H1385–H1396.
[69] Nagibin V, Egan Benova T, Viczenczova C, Szeiffova Bacova B, Dovinova I, Barancik M, et al. (2016). Ageing related down-regulation of myocardial connexin-43 and up-regulation of MMP-2 may predict propensity to atrial fibrillation in experimental animals. Physiol Res, 65 Suppl 1:S91–S100.
[70] Li Y, Asfour H, Bursac N (2017). Age-dependent functional crosstalk between cardiac fibroblasts and cardiomyocytes in a 3D engineered cardiac tissue. Acta Biomaterialia, 55:120–130.
[71] Anderson R, Lagnado A, Maggiorani D, Walaszczyk A, Dookun E, Chapman J, et al. (2019). Length-independent telomere damage drives post-mitotic cardiomyocyte senescence. The EMBO Journal, 38:e100492.
[72] Rizvi F, Preston CC, Emelyanova L, Yousufuddin M, Viqar M, Dakwar O, et al. (2021). Effects of Aging on Cardiac Oxidative Stress and Transcriptional Changes in Pathways of Reactive Oxygen Species Generation and Clearance. Journal of the American Heart Association, 10:e019948.
[73] Linders AN, Dias IB, López Fernández T, Tocchetti CG, Bomer N, Van der Meer P (2024). A review of the pathophysiological mechanisms of doxorubicin-induced cardiotoxicity and aging. npj Aging, 10:9.
[74] Zeisberg EM, Tarnavski O, Zeisberg M, Dorfman AL, McMullen JR, Gustafsson E, et al. (2007). Endothelial-to-mesenchymal transition contributes to cardiac fibrosis. Nature medicine, 13:952–961.
[75] Ungvari Z, Tarantini S, Kiss T, Wren JD, Giles CB, Griffin CT, et al. (2018). Endothelial dysfunction and angiogenesis impairment in the ageing vasculature. Nature Reviews Cardiology, 15:555–565.
[76] Qiu C, Fratiglioni L (2015). A major role for cardiovascular burden in age-related cognitive decline. Nature Reviews Cardiology, 12:267–277.
[77] Rask-Madsen C, King GL (2007). Mechanisms of disease: endothelial dysfunction in insulin resistance and diabetes. Nature clinical practice Endocrinology & metabolism, 3:46–56.
[78] Laakso M, Kuusisto J (2014). Insulin resistance and hyperglycaemia in cardiovascular disease development. Nature reviews endocrinology, 10:293–302.
[79] Schiattarella GG, Altamirano F, Tong D, French KM, Villalobos E, Kim SY, et al. (2019). Nitrosative stress drives heart failure with preserved ejection fraction. Nature, 568:351–356.
[80] Peikert A, Fontana M, Solomon SD, Thum T (2025). Left ventricular hypertrophy and myocardial fibrosis in heart failure with preserved ejection fraction: mechanisms and treatment. Eur Heart J, ehaf524.
[81] Kalogeropoulos A, Georgiopoulou V, Psaty BM, Rodondi N, Smith AL, Harrison DG, et al. (2010).

Inflammatory Markers and Incident Heart Failure Risk in Older Adults. Journal of the American College of Cardiology, 55:2129–2137.
[82] Chia YC, Kieneker LM, van Hassel G, Binnenmars SH, Nolte IM, van Zanden JJ, et al. (2021). Interleukin 6 and Development of Heart Failure With Preserved Ejection Fraction in the General Population. Journal of the American Heart Association, 10:e018549.
[83] Kasner M, Westermann D, Lopez B, Gaub R, Escher F, K ühl U, et al. (2011). Diastolic Tissue Doppler Indexes Correlate With the Degree of Collagen Expression and Cross-Linking in Heart Failure and Normal Ejection Fraction. JACC, 57:977–985.
[84] Borbély A, van der Velden J, Papp Z, Bronzwaer JGF, Edes I, Stienen GJM, et al. (2005). Cardiomyocyte Stiffness in Diastolic Heart Failure. Circulation, 111:774–781.
[85] Mooney L, Jackson CE, Adamson C, McConnachie A, Welsh P, Myles RC, et al. (2023). Adverse Outcomes Associated With Interleukin-6 in Patients Recently Hospitalized for Heart Failure With Preserved Ejection Fraction. Circulation: Heart Failure, 16:e010051.
[86] Chirinos JA, Orlenko A, Zhao L, Basso MD, Cvijic ME, Li Z, et al. (2020). Multiple Plasma Biomarkers for Risk Stratification in Patients With Heart Failure and Preserved Ejection Fraction. Journal of the American College of Cardiology, 75:1281–1295.
[87] Sanders-van Wijk S, Tromp J, Beussink-Nelson L, Hage C, Svedlund S, Saraste A, et al. (2020). Proteomic Evaluation of the Comorbidity-Inflammation Paradigm in Heart Failure With Preserved Ejection Fraction. Circulation, 142:2029–2044.
[88] O'Rourke SA, Dunne A, Monaghan MG (2019). The role of macrophages in the infarcted myocardium: orchestrators of ECM remodeling. Frontiers in cardiovascular medicine, 6:101.
[89] DeBerge M, Shah SJ, Wilsbacher L, Thorp EB (2019). Macrophages in Heart Failure with Reduced versus Preserved Ejection Fraction. Trends in Molecular Medicine, 25:328–340.
[90] Mesquita TRR, Zhang R, de Couto G, Valle J, Sanchez L, Rogers RG, et al. (2020). Mechanisms of atrial fibrillation in aged rats with heart failure with preserved ejection fraction. Heart Rhythm, 17:1025–1033.
[91] Paneni F, Diaz CC, Libby P, L üscher TF, Camici GG (2017). The Aging Cardiovascular System. Journal of the American College of Cardiology, 69:1952–1967.
[92] Marín-Aguilar F, Lechuga-Vieco AV, Alcocer-Gómez E, Castejón-Vega B, Lucas J, Garrido C, et al. (2020). NLRP3 inflammasome suppression improves longevity and prevents cardiac aging in male mice. Aging Cell, 19:e13050.
[93] Gurantz D, Cowling RT, Varki N, Frikovsky E, Moore CD, Greenberg BH (2005). IL-1β and TNF-α upregulate angiotensin II type 1 (AT1) receptors on cardiac fibroblasts and are associated with increased AT1 density in the post-MI heart. Journal of molecular and cellular cardiology, 38:505–515.
[94] Ma F, Li Y, Jia L, Han Y, Cheng J, Li H, et al. (2012). Macrophage-Stimulated Cardiac Fibroblast Production of IL-6 Is Essential for TGF β/Smad Activation and Cardiac Fibrosis Induced by Angiotensin II. PLOS ONE, 7:e35144.
[95] Sanders-van Wijk S, Van Empel V, Davarzani N, Maeder MT, Handschin R, Pfisterer ME, et al. (2015). Circulating biomarkers of distinct pathophysiological pathways in heart failure with preserved vs. reduced left ventricular ejection fraction. European J of Heart Fail, 17:1006–1014.
[96] Albar Z, Albakri M, Hajjari J, Karnib M, Janus SE, Al-Kindi SG (2022). Inflammatory Markers and Risk of Heart Failure With Reduced to Preserved Ejection Fraction. The American Journal of Cardiology, 167:68–75.
[97] Cohen AJ, Teramoto K, Claggett B, Buckley L, Solomon S, Ballantyne C, et al. (2021). Mid- to Late-Life Inflammation and Risk of Cardiac Dysfunction, HFpEF and HFrEF in Late Life. Journal of Cardiac Failure, 27:1382–1392.
[98] DuBrock HM, AbouEzzeddine OF, Redfield MM (2018). High-sensitivity C-reactive protein in heart failure with preserved ejection fraction. PLOS ONE, 13:e0201836.
[99] Sabbah MS, Fayyaz AU, De Denus S, Felker GM, Borlaug BA, Dasari S, et al. (2020). Obese-Inflammatory Phenotypes in Heart Failure With Preserved Ejection Fraction. Circ: Heart Failure, 13:e006414.
[100] Kotecha D, Lam CSP, Van VDJ, Van GIC, Voors AA, Rienstra M (2016). Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation. JACC, 68:2217–2228.
[101] Shuai W, Kong B, Yang H, Fu H, Huang H (2020). Loss of myeloid differentiation protein 1 promotes atrial fibrillation in heart failure with preserved ejection fraction. ESC Heart Failure, 7:626–638.
[102] Baumhove L, Bomer N, Tromp J, van Essen BJ, Dickstein K, Cleland JG, et al. (2024). Clinical characteristics and prognosis of patients with heart failure and high concentrations of interleukin-17D. International Journal of Cardiology, 396:131384.
[103] Triposkiadis F, Xanthopoulos A, Parissis J, Butler J, Farmakis D (2022). Pathogenesis of chronic heart failure: cardiovascular aging, risk factors, comorbidities, and disease modifiers. Heart failure reviews, 27:337–344.
[104] Frantz S, Falcao-Pires I, Balligand J-L, Bauersachs J, Brutsaert D, Ciccarelli M, et al. (2018). The innate immune system in chronic cardiomyopathy: a European Society of Cardiology (ESC) scientific statement from the Working Group on Myocardial Function of the ESC. European Journal of Heart Failure, 20:445–459.
[105] Mentz RJ, Kelly JP, Von Lueder TG, Voors AA, Lam CSP, Cowie MR, et al. (2014). Noncardiac Comorbidities in Heart Failure With Reduced Versus Preserved Ejection Fraction. Journal of the American College of Cardiology, 64:2281–2293.
[106] Streng KW, Nauta JF, Hillege HL, Anker SD, Cleland JG, Dickstein K, et al. (2018). Non-cardiac comorbidities in heart failure with reduced, mid-range and preserved

ejection fraction. International journal of cardiology, 271:132–139.

[107] Gremese E, Bruno D, Perniola S, Ceolan J, Ferraccioli G (2025). Autoimmune inflammation as a key risk factor for heart failure with preserved ejection fraction: the different types of inflammation driving to HFpEF. Front Med. doi: 10.3389/fmed.2025.1557312.

[108] Deichl A, Wachter R, Edelmann F (2022). Comorbidities in heart failure with preserved ejection fraction. Herz, 47:301–307.

[109] Verma S, Petrie MC, Borlaug BA, Butler J, Davies MJ, Kitzman DW, et al. (2024). Inflammation in Obesity-Related HFpEF: The STEP-HFpEF Program. Journal of the American College of Cardiology, 84:1646–1662.

[110] Yu Z, Chen Y, Miranda O, Qi M, Zhang M, Feng N, et al. (2024). The Association of Long-Term Body Mass Index Variability with the Development of HFpEF and HFrEF Across Patterns of Weight Change. 2024.11.08.24317010.

[111] Zhang Y, Zhao Z, Kim S, Fabricatore AN, Iyer P (2025). The epidemiology, clinical characteristics, and burden of heart failure with or without obesity in US patients. Current Medical Research and Opinion, 41:1149–1163.

[112] Haass M, Kitzman DW, Anand IS, Miller A, Zile MR, Massie BM, et al. (2011). Body Mass Index and Adverse Cardiovascular Outcomes in Heart Failure Patients With Preserved Ejection Fraction. Circulation: Heart Failure, 4:324–331.

[113] Hobbach AJ, Brix TJ, Weyer-Elberich V, Varghese J, Reinecke H, Linke WA (2025). Obesity and Comorbidities in HFpEF: A Retrospective Cohort Analysis in a University Hospital Setting. Journal of Clinical Medicine, 14:3348.

[114] Bae JP, Kallenbach L, Nelson DR, Lavelle K, Winer-Jones JP, Bonafede M, et al. (2024). Obesity and metabolic syndrome in patients with heart failure with preserved ejection fraction: a cross-sectional analysis of the Veradigm Cardiology Registry. BMC Endocr Disord, 24:59.

[115] Harvey I, Boudreau A, Stephens JM (2023). Adipose tissue in health and disease. Advances in Surgical and Medical Specialties, 1281–1306.

[116] Reddy YNV, Lewis GD, Shah SJ, Obokata M, Abou-Ezzedine OF, Fudim M, et al. (2019). Characterization of the Obese Phenotype of Heart Failure With Preserved Ejection Fraction: A RELAX Trial Ancillary Study. Mayo Clinic Proceedings, 94:1199–1209.

[117] Frasca D, Blomberg BB (2020). Adipose tissue, immune aging, and cellular senescence. Seminars in immunopathology. Springer, 573–587.

[118] Liu Z, Wu KK, Jiang X, Xu A, Cheng KK (2020). The role of adipose tissue senescence in obesity-and ageing-related metabolic disorders. Clinical science, 134:315–330.

[119] Krishnan A, Chilton E, Raman J, Saxena P, McFarlane C, Trollope AF, et al. (2021). Are Interactions between Epicardial Adipose Tissue, Cardiac Fibroblasts and Cardiac Myocytes Instrumental in Atrial Fibrosis and Atrial Fibrillation? Cells, 10:2501.

[120] Su M, Li W, Yuan Y, Liu S, Liang C, Liu H, et al. (2022). Epididymal white adipose tissue promotes angiotensin II-induced cardiac fibrosis in an exosome-dependent manner. Translational Research, 248:51–67.

[121] Tuleta I, Hanna A, Humeres C, Aguilan JT, Sidoli S, Zhu F, et al. (2024). Fibroblast-specific TGF-β signaling mediates cardiac dysfunction, fibrosis, and hypertrophy in obese diabetic mice. Cardiovasc Res, 120:2047–2063.

[122] Ariyaratnam JP, Elliott AD, Mishima RS, Dziano JK, Emami M, Howie JO, et al. Evaluating the Impact of Obesity and Epicardial Adiposity on the Presence of HFpEF in Patients With AF. JACC: Clinical Electrophysiology. doi: 10.1016/j.jacep.2025.08.011.

[123] Gao Q, He S, Peng Y, Su P, Zhao L (2023). Proteomic profiling of epicardial fat in heart failure with preserved versus reduced and mildly reduced ejection fraction. Journal of Cellular and Molecular Medicine, 27:727–735.

[124] Sun M, Gao ,Lei, Bai ,Hongmei, Hu ,Weiwei, Zhang ,Xiaofang, Xiao ,Jin, et al. (2023). Association Between Visceral Fat, Blood Pressure and Arterial Stiffness in Patients with HFpEF: A Mediation Analysis. Diabetes, Metabolic Syndrome and Obesity, 16:653–662.

[125] Alogna A, Koepp KE, Sabbah M, Espindola Netto JM, Jensen MD, Kirkland JL, et al. (2023). Interleukin-6 in Patients With Heart Failure and Preserved Ejection Fraction. JACC: Heart Failure, 11:1549–1561.

[126] Colluoglu T, Akın Y (2023). The value of neutrophil-to-lymphocyte ratio and epicardial adipose tissue thickness in heart failure with preserved ejection fraction. Cureus 15:.

[127] Elsanhoury A, Nelki V, Kelle S, Van Linthout S, Tschöpe C (2021). Epicardial Fat Expansion in Diabetic and Obese Patients With Heart Failure and Preserved Ejection Fraction—A Specific HFpEF Phenotype. Front Cardiovasc Med. doi: 10.3389/fcvm.2021.720690.

[128] Packer M (2018). The epicardial adipose inflammatory triad: coronary atherosclerosis, atrial fibrillation, and heart failure with a preserved ejection fraction. European Journal of Heart Failure, 20:1567–1569.

[129] Pang Z, Ren Y, Yao Z (2025). Interactions between atrial fibrosis and inflammation in atrial fibrillation. Frontiers in cardiovascular medicine, 12:1578148.

[130] van Woerden G, Gorter TM, Westenbrink BD, Willems TP, van Veldhuisen DJ, Rienstra M (2018). Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. European Journal of Heart Failure, 20:1559–1566.

[131] Cohen JB, Schrauben SJ, Zhao L, Basso MD, Cvijic ME, Li Z, et al. (2020). Clinical Phenogroups in Heart Failure With Preserved Ejection Fraction. JACC: Heart Failure, 8:172–184.

[132] Mundisugih J, Franke KB, Tully PJ, Munawar DA, Kumar S, Mahajan R (2023). Prevalence and Prognostic Implication of Atrial Fibrillation in Heart Failure Subtypes: Systematic Review and Meta-Analysis. Heart, Lung and Circulation, 32:666–677.

[133] Nelson AJ, Pagidipati NJ (2025). HFpEF Without Obesity: Fallen Off the Radar? Journal of Cardiac Failure, 31:1002–1004.

[134] Yousufuddin M, Ma Z, Barkoudah E, Tahir MW, Yazdanyar A, Chikkanna R, et al. (2025). Comorbidity patterns and mortality in HFpEF: A retrospective longitudinal cohort study. International Journal of Cardiology Cardiovascular Risk and Prevention, 27:200526.
[135] Khan S, Chan YT, Revelo XS, Winer DA (2020). The immune landscape of visceral adipose tissue during obesity and aging. Frontiers in endocrinology, 11:267.
[136] Srivatsa S, Rice N, Pike JR, Smith JA, Ding J, Liu Y, et al. (2025). Epigenetic Aging Clocks and Incident Cardiovascular Outcomes: Results From the MESA. Journal of the American Heart Association, 14:e044946.
[137] Justice JN, Pajewski NM, Espeland MA, Brubaker P, Houston DK, Marcovina S, et al. (2022). Evaluation of a blood-based geroscience biomarker index in a randomized trial of caloric restriction and exercise in older adults with heart failure with preserved ejection fraction. GeroScience, 44:983–995.
[138] Liao X, Kennel PJ, Liu B, Nash TR, Zhuang RZ, Godier-Furnemont AF, et al. Effect of mechanical unloading on genome-wide DNA methylation profile of the failing human heart. JCI Insight, 8:e161788.
[139] Fabbri E, Zoli M, Gonzalez-Freire M, Salive ME, Studenski SA, Ferrucci L (2015). Aging and multimorbidity: new tasks, priorities, and frontiers for integrated gerontological and clinical research. Journal of the American Medical Directors Association, 16:640–647.
[140] Franceschi C, Campisi J (2014). Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 69:S4–S9.
[141] Taylor EB, Hall JE, Mouton AJ (2025). Current anti-inflammatory strategies for treatment of heart failure: From innate to adaptive immunity. Pharmacological Research, 216:107761.
[142] Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT (2003). Randomized, Double-Blind, Placebo-Controlled, Pilot Trial of Infliximab, a Chimeric Monoclonal Antibody to Tumor Necrosis Factor-α, in Patients With Moderate-to-Severe Heart Failure. Circulation, 107:3133–3140.
[143] Mann DL, McMurray JJV, Packer M, Swedberg K, Borer JS, Colucci WS, et al. (2004). Targeted Anticytokine Therapy in Patients With Chronic Heart Failure. Circulation, 109:1594–1602.
[144] Fox DA (2000). Cytokine blockade as a new strategy to treat rheumatoid arthritis: inhibition of tumor necrosis factor. Archives of internal medicine, 160:437–444.
[145] Frangogiannis NG, Smith CW, Entman ML (2002). The inflammatory response in myocardial infarction. Cardiovascular research, 53:31–47.
[146] Turner NA, Blythe NM (2019). Cardiac fibroblast p38 MAPK: a critical regulator of myocardial remodeling. Journal of cardiovascular development and disease, 6:27.
[147] Marber MS, Rose B, Wang Y (2011). The p38 mitogen-activated protein kinase pathway—a potential target for intervention in infarction, hypertrophy, and heart failure. Journal of molecular and cellular cardiology, 51:485–490.
[148] Park J-K, Fischer R, Dechend R, Shagdarsuren E, Gapeljuk A, Wellner M, et al. (2007). p38 Mitogen-Activated Protein Kinase Inhibition Ameliorates Angiotensin II–Induced Target Organ Damage. Hypertension, 49:481–489.
[149] Bao W, Behm DJ, Nerurkar SS, Ao Z, Bentley R, Mirabile RC, et al. (2007). Effects of p38 MAPK Inhibitor on Angiotensin II-Dependent Hypertension, Organ Damage, and Superoxide Anion Production. Journal of Cardiovascular Pharmacology, 49:362.
[150] Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, et al. (2013). Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. JAMA, 309:1268–1277.
[151] Van Tassell BW, Arena R, Biondi-Zoccai G, McNair Canada J, Oddi C, Abouzaki NA, et al. (2014). Effects of Interleukin-1 Blockade With Anakinra on Aerobic Exercise Capacity in Patients With Heart Failure and Preserved Ejection Fraction (from the D-HART Pilot Study). The American Journal of Cardiology, 113:321–327.
[152] Borlaug BA, Anstrom KJ, Lewis GD, Shah SJ, Levine JA, Koepp GA, et al. (2018). Effect of Inorganic Nitrite vs Placebo on Exercise Capacity Among Patients With Heart Failure With Preserved Ejection Fraction: The INDIE-HFpEF Randomized Clinical Trial. JAMA, 320:1764–1773.
[153] Van Tassell BW, Buckley LF, Carbone S, Trankle CR, Canada JM, Dixon DL, et al. (2017). Interleukin-1 blockade in heart failure with preserved ejection fraction: rationale and design of the Diastolic Heart Failure Anakinra Response Trial 2 (D-HART2). Clinical Cardiology, 40:626–632.
[154] Van Tassell BW, Trankle CR, Canada JM, Carbone S, Buckley L, Kadariya D, et al. (2018). IL-1 Blockade in Patients With Heart Failure With Preserved Ejection Fraction. Circulation: Heart Failure, 11:e005036.
[155] Verma SK, Krishnamurthy P, Barefield D, Singh N, Gupta R, Lambers E, et al. (2012). Interleukin-10 Treatment Attenuates Pressure Overload–Induced Hypertrophic Remodeling and Improves Heart Function via Signal Transducers and Activators of Transcription 3–Dependent Inhibition of Nuclear Factor-κB. Circulation, 126:418–429.
[156] Petrie M, Borlaug B, Buchholtz K, Ducharme A, Hvelplund A, Ping CLS, et al. (2024). HERMES: Effects Of Ziltivekimab Versus Placebo On Morbidity And Mortality In Patients With Heart Failure With Mildly Reduced Or Preserved Ejection Fraction And Systemic Inflammation. Journal of Cardiac Failure, 30:126.
[157] Ridker PM, Devalaraja M, Baeres FMM, Engelmann MDM, Hovingh GK, Ivkovic M, et al. (2021). IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. The Lancet, 397:2060–2069.

[158] Takahashi M (2019). Role of NLRP3 inflammasome in cardiac inflammation and remodeling after myocardial infarction. Biological and Pharmaceutical Bulletin, 42:518–523.
[159] Toldo S, Abbate A (2024). The role of the NLRP3 inflammasome and pyroptosis in cardiovascular diseases. Nature Reviews Cardiology, 21:219–237.
[160] Audia JP, Yang X-M, Crockett ES, Housley N, Haq EU, O'Donnell K, et al. (2018). Caspase-1 inhibition by VX-765 administered at reperfusion in P2Y12 receptor antagonist-treated rats provides long-term reduction in myocardial infarct size and preservation of ventricular function. Basic Res Cardiol, 113:32.
[161] Gao R, Shi H, Chang S, Gao Y, Li X, Lv C, et al. (2019). The selective NLRP3-inflammasome inhibitor MCC950 reduces myocardial fibrosis and improves cardiac remodeling in a mouse model of myocardial infarction. International Immunopharmacology, 74:105575.
[162] Cheng X, Zhao H, Wen X, Li G, Guo S, Zhang D (2023). NLRP3-inflammasome inhibition by MCC950 attenuates cardiac and pulmonary artery remodelling in heart failure with preserved ejection fraction. Life Sciences, 333:122185.
[163] Li S, Withaar C, Rodrigues PG, Zijlstra SN, de Boer RA, Silljé HHW, et al. (2024). The NLRP3-inflammasome inhibitor MCC950 improves cardiac function in a HFpEF mouse model. Biomedicine & Pharmacotherapy, 181:117711.
[164] Trial J, Diaz Lankenau R, Angelini A, Tovar Perez JE, Taffet GE, Entman ML, et al. (2021). Treatment with a DC-SIGN ligand reduces macrophage polarization and diastolic dysfunction in the aging female but not male mouse hearts. GeroScience, 43:881–899.
[165] Zhang L, Chen J, Yan L, He Q, Xie H, Chen M (2021). Resveratrol ameliorates cardiac remodeling in a murine model of heart failure with preserved ejection fraction. Frontiers in Pharmacology, 12:646240.
[166] Bartolomaeus H, Balogh A, Yakoub M, Homann S, Markó L, Höges S, et al. (2019). Short-Chain Fatty Acid Propionate Protects From Hypertensive Cardiovascular Damage. Circulation, 139:1407–1421.
[167] Dalbeth N, Lauterio TJ, Wolfe HR (2014). Mechanism of action of colchicine in the treatment of gout. Clinical therapeutics, 36:1465–1479.
[168] Nelson K, Fuster V, Ridker PM (2023). Low-Dose Colchicine for Secondary Prevention of Coronary Artery Disease. JACC, 82:648–660.
[169] Tardif J-C, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. (2019). Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. New England Journal of Medicine, 381:2497–2505.
[170] Shen S, Duan J, Hu J, Qi Y, Kang L, Wang K, et al. (2022). Colchicine alleviates inflammation and improves diastolic dysfunction in heart failure rats with preserved ejection fraction. European Journal of Pharmacology, 929:175126.
[171] Deftereos S, Giannopoulos G, Panagopoulou V, Bouras G, Raisakis K, Kossyvakis C, et al. (2014). Anti-Inflammatory Treatment With Colchicine in Stable Chronic Heart Failure. JACC: Heart Failure, 2:131–137.
[172] Shchendrygina A, Rachina S, Cherkasova N, Suvorov A, Komarova I, Mukhina N, et al. (2023). Colchicine in patients with heart failure and preserved left ventricular ejection fraction: rationale and design of a prospective, randomised, open-label, crossover clinical trial. Open Heart. doi: 10.1136/openhrt-2023-002360.
[173] Bourcier L, Bellemare M, Tremblay-Gravel M, Henri C, White M, Bouabdallaoui N (2023). Effects of COLchicine on inflammation, myocardial damage and microvascular dysfunction in heart failure with Preserved Ejection Fraction – the COLpEF trial. Archives of Cardiovascular Diseases Supplements, 15:53.
[174] Quinn M, Zhang RY, Bello I, Rye K-A, Thomas SR (2024). Myeloperoxidase as a promising therapeutic target after myocardial infarction. Antioxidants, 13:788.
[175] Friedrichs K, Baldus S, Klinke A (2012). Fibrosis in atrial fibrillation–role of reactive species and MPO. Frontiers in physiology, 3:214.
[176] Kittipibul V, Ambrosy AP, Greene SJ (2025). Myeloperoxidase inhibition in the landscape of anti-inflammatory therapies for heart failure with preserved ejection fraction: the ENDEAVOR trial. Heart Fail Rev. doi: 10.1007/s10741-025-10498-y.
[177] Hage C, Michaëlsson E, Kull B, Miliotis T, Svedlund S, Linde C, et al. (2020). Myeloperoxidase and related biomarkers are suggestive footprints of endothelial microvascular inflammation in HFpEF patients. ESC Heart Failure, 7:1534–1546.
[178] Lam CSP, Lund LH, Shah SJ, Voors AA, Erlinge D, Saraste A, et al. (2024). Myeloperoxidase Inhibition in Heart Failure With Preserved or Mildly Reduced Ejection Fraction: SATELLITE Trial Results. Journal of Cardiac Failure, 30:104–110.
[179] Inghardt T, Antonsson T, Ericsson C, Hovdal D, Johannesson P, Johansson C, et al. (2022). Discovery of AZD4831, a Mechanism-Based Irreversible Inhibitor of Myeloperoxidase, As a Potential Treatment for Heart Failure with Preserved Ejection Fraction. J Med Chem, 65:11485–11496.
[180] Popovic D, Reddy YNV, Omar M, Omote K, Melenovsky V, Burkhoff D, et al. (2025). Acute Effects of Myeloperoxidase Inhibition on Exercise Hemodynamics in Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. Mayo Clinic Proceedings, 100:1495–1505.
[181] Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. (2021). Empagliflozin in Heart Failure with a Preserved Ejection Fraction. New England Journal of Medicine, 385:1451–1461.
[182] Solomon SD, McMurray JJV, Claggett B, Boer RA de, DeMets D, Hernandez AF, et al. (2022). Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. New England Journal of Medicine, 387:1089–1098.
[183] Minisy MM, Abdelaziz A (2025). The role of SGLT 2 inhibitors in heart failure with preserved ejection fraction (HFpEF): a systematic review and meta-analysis of randomized controlled trials. BMC Cardiovasc Disord, 25:765.

[184] Pandey AK, Bhatt DL, Pandey A, Marx N, Cosentino F, Pandey A, et al. (2023). Mechanisms of benefits of sodium-glucose cotransporter 2 inhibitors in heart failure with preserved ejection fraction. Eur Heart J, 44:3640–3651.
[185] Kolijn D, Pabel S, Tian Y, Lódi M, Herwig M, Carrizzo A, et al. (2021). Empagliflozin improves endothelial and cardiomyocyte function in human heart failure with preserved ejection fraction via reduced pro-inflammatory-oxidative pathways and protein kinase Gα oxidation. Cardiovasc Res, 117:495–507.
[186] Leo I, Salerno N, Figliozzi S, Cersosimo A, Ielapi J, Stankowski K, et al. (2025). Effect of SGLT2 inhibitors on cardiac structure and function assessed by cardiac magnetic resonance: a systematic review and meta-analysis. Cardiovasc Diabetol, 24:345.
[187] Albulushi A, Askari KM, Al-Abedi AM, Al-Kulaibi MA, Hasan MS, Hosseini Z, et al. (2025). Impact of SGLT2 inhibitors on myocardial fibrosis in diabetic HFpEF: a longitudinal study. Eur J Med Res, 30:592.
[188] Alrasheed DA, Alshahrani AM, Alshehri AS, Ateen FM, Alqarni MA, Albandri DA, et al. (2025). Efficacy and Safety of SGLT2 Inhibitors in Non-Diabetic Patients with Heart Failure: A Systematic Review and Meta-Analysis. Vascular and Endovascular Review, 8:395–401.
[189] Scheffer M, Driessen-Waaijer A, Hamdani N, Landzaat JWD, Jonkman NH, Paulus WJ, et al. (2020). Stratified Treatment of Heart Failure with Preserved Ejection Fraction: Rationale and Design of the STADIA-HFPEF Trial. ESC Heart Fail, 7:4478–4487.
[190] Gonzales-Uribe A, Ruiz-Cortez R, Collantes-Silva N, Olivero L, Agarwal R, Arambulo-Castillo S, et al. (2025). Impact of GLP-1 receptor agonists on cardiovascular outcomes in heart failure with preserved ejection fraction (HFpEF): systematic review and meta-analysis. Clin Res Cardiol. doi: 10.1007/s00392-025-02710-8.
[191] Packer M, Zile MR, Kramer CM, Baum SJ, Litwin SE, Menon V, et al. (2025). Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. New England Journal of Medicine, 392:427–437.
[192] Vignarajah A, Thong JY, Tan MC, Vigneswaramoorthy N, Anand S, Lee JZ (2025). Effects of glucagon-like peptide-1 receptor agonists in HFpEF and obesity without diabetes mellitus. Journal of Cardiology, 86:88–89.
[193] Borlaug BA, Kitzman DW, Davies MJ, Rasmussen S, Barros E, Butler J, et al. (2023). Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial. Nat Med, 29:2358–2365.
[194] Cimino G, Vaduganathan M, Lombardi CM, Pagnesi M, Vizzardi E, Tomasoni D, et al. (2024). Obesity, heart failure with preserved ejection fraction, and the role of glucagon-like peptide-1 receptor agonists. ESC Heart Failure, 11:649–661.
[195] Kramer CM, Borlaug BA, Zile MR, Ruff D, DiMaria JM, Menon V, et al. (2025). Tirzepatide Reduces LV Mass and Paracardiac Adipose Tissue in Obesity-Related Heart Failure. JACC, 85:699–706.
[196] Khadke S, Kumar A, Bhatti A, Dani SS, Al-Kindi S, Nasir K, et al. (2024). GLP-1 receptor agonist in nonobese patients with type 2 diabetes mellitus and heart failure with preserved ejection fraction. Journal of Cardiac Failure .
[197] Lin Y-M, Liao K-M, Yu T, Wu J-Y, Lai C-C (2025). Effectiveness of tirzepatide in patients with HFpEF using a target trial emulation retrospective cohort study. Nat Commun, 16:4471.
[198] Ussher JR, Drucker DJ (2023). Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. Nat Rev Cardiol, 20:463–474.
[199] Xia Y, Jin J, Sun Y, Kong X, Shen Z, Yan R, et al. (2024). Tirzepatide's role in targeting adipose tissue macrophages to reduce obesity-related inflammation and improve insulin resistance. International Immunopharmacology, 143:113499.
[200] Malavazos AE, Iacobellis G, Dozio E, Basilico S, Di Vincenzo A, Dubini C, et al. (2023). Human epicardial adipose tissue expresses glucose-dependent insulinotropic polypeptide, glucagon, and glucagon-like peptide-1 receptors as potential targets of pleiotropic therapies. Eur J Prev Cardiol, 30:680–693.
[201] Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al. (2023). Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. New England Journal of Medicine. doi: 10.1056/NEJMoa2306963.
[202] Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, et al. (2024). Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. New England Journal of Medicine. doi: 10.1056/NEJMoa2313917.
[203] Butler J, Shah SJ, Petrie MC, Borlaug BA, Abildstrøm SZ, Davies MJ, et al. (2024). Semaglutide versus placebo in people with obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF DM randomised trials. The Lancet, 403:1635–1648.
[204] Withaar C, Li S, Meems LM, Silljé HH, de Boer RA (2022). Aging and HFpEF: Are we running out of time? Journal of molecular and cellular cardiology, 168:33–34.
[205] Loredo-Mendoza ML, Ramirez-Sanchez I, Bustamante-Pozo MM, Ayala M, Navarrete V, Garate-Carrillo A, et al. (2020). The role of inflammation in driving left ventricular remodeling in a pre-HFpEF model. Experimental Biology and Medicine, 245:748–757.
[206] Delalat S, Sultana I, Osman H, Sieme M, Zhazykbayeva S, Herwig M, et al. (2025). Dysregulated inflammation, oxidative stress, and protein quality control in diabetic HFpEF: unraveling mechanisms and therapeutic targets. Cardiovasc Diabetol, 24:211.
[207] Mann DL (2015). Innate Immunity and the Failing Heart. Circulation Research, 116:1254–1268.
[208] Bolourani S, Brenner M, Wang P (2021). The interplay of DAMPs, TLR4, and proinflammatory cytokines in pulmonary fibrosis. J Mol Med, 99:1373–1384.

[209] Saeed S, Elashery A, Bazai U (2026). Comparative Efficacy Of GLP-1 Receptor Agonists, Mineralocorticoid Receptor Antagonists, And SGLT2 Inhibitors In HFpEF: A Meta-analysis Of Cardiovascular Outcomes. Journal of Cardiac Failure, 32:252.

[210] Kim EY, Feinstein MJ (2026). Clinical knowns and mechanistic unknowns: cardioprotection and inflammation modulation of GLP-1 receptor agonists and SGLT2 inhibitors. Canadian Journal of Cardiology .

[211] Samuel AH, Kshatri AHS, Babu RN, Patel HS, Viswanathan SH, Challa MSR, et al. (2026). GLP-1 RAs vs. SGLT2is: Divergent Pathways of Cardiovascular Inflammation Control in Obesity-Associated Diabetes. Annales d'Endocrinologie. Elsevier, 102494.