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REVIEW

Systemic aging fuels heart failure: Molecular mechanisms and therapeutic avenues

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Abstract

Systemic aging influences various physiological processes and contributes to structural and functional decline in cardiac tissue. These alterations include an increased incidence of left ventricular hypertrophy, a decline in left ventricular diastolic function, left atrial dilation, atrial fibrillation, myocardial fibrosis and cardiac amyloidosis, elevating susceptibility to chronic heart failure (HF) in the elderly. Age-related cardiac dysfunction stems from prolonged exposure to genomic, epigenetic, oxidative, autophagic, inflammatory and regenerative stresses, along with the accumulation of senescent cells. Concurrently, age-related structural and functional changes in the vascular system, attributed to endothelial dysfunction, arterial stiffness, impaired angiogenesis, oxidative stress and inflammation, impose additional strain on the heart. Dysregulated mechanosignalling and impaired nitric oxide signalling play critical roles in the age-related vascular dysfunction associated with HF. Metabolic aging drives intricate shifts in glucose and lipid metabolism, leading to insulin resistance, mitochondrial dysfunction and lipid accumulation within cardiomyocytes. These alterations contribute to cardiac hypertrophy, fibrosis and impaired contractility, ultimately propelling HF. Systemic low-grade chronic inflammation, in conjunction with the senescence-associated secretory phenotype, aggravates cardiac dysfunction with age by promoting immune cell infiltration into the myocardium, fostering HF. This is further exacerbated by age-related comorbidities like coronary artery disease (CAD), atherosclerosis, hypertension, obesity, diabetes and chronic kidney disease (CKD). CAD and atherosclerosis induce myocardial ischaemia and adverse remodelling, while hypertension contributes to cardiac hypertrophy and fibrosis. Obesity-associated insulin resistance, inflammation and dyslipidaemia create a profibrotic cardiac environment, whereas diabetes-related metabolic disturbances further impair cardiac function. CKD-related fluid overload, electrolyte imbalances and uraemic toxins exacerbate HF through systemic inflammation and neurohormonal renin-angiotensin-aldosterone system (RAAS) activation. Recognizing aging as a modifiable process has opened avenues to target systemic aging in HF through both lifestyle interventions and therapeutics. Exercise, known for its antioxidant effects, can partly reverse pathological cardiac remodelling in the elderly by countering processes linked to age-related chronic HF, such as mitochondrial dysfunction, inflammation, senescence and declining cardiomyocyte regeneration. Dietary interventions such as plant-based and ketogenic diets, caloric restriction and macronutrient supplementation are instrumental in maintaining energy balance, reducing adiposity and addressing micronutrient and macronutrient imbalances associated with age-related HF. Therapeutic advancements targeting systemic aging in HF are underway. Key approaches include senomorphics and senolytics to limit senescence, antioxidants targeting mitochondrial stress, anti-inflammatory drugs like interleukin (IL)-1β inhibitors, metabolic rejuvenators such as nicotinamide riboside, resveratrol and sirtuin (SIRT) activators and autophagy enhancers like metformin and sodium-glucose cotransporter 2 (SGLT2) inhibitors, all of which offer potential for preserving cardiac function and alleviating the age-related HF burden.

Keywords anti-aging therapy; exercise; heart failure; inflammaging; metabolic aging; systemic aging; vascular aging

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Introduction

Heart failure (HF), a condition in which the heart is unable to pump enough blood to meet the body's demands, results in a significant number of deaths annually, particularly among patients above the age of 50.[1,2] This issue is particularly concerning in the United States, where the population aged 65 and over has seen substantial growth and is projected to reach 95 million by 2060.[3] Hence, the aging population presents a formidable challenge to global healthcare, necessitating an in-depth understanding of age-related HF.

Systemic aging, impacting various organs and physiological processes, contributes to structural and functional alterations in the aging heart, rendering older adults more vulnerable to HF.[4,5] While resting cardiac function may not exhibit significant impairment, subclinical diastolic and systolic dysfunction ensues with age.[5] Heightened susceptibility to chronic HF in the elderly is linked to prolonged exposure to detrimental stimuli, including genomic, epigenetic, oxidative, autophagic, inflammatory and regenerative stresses, along with the accumulation of senescent cells in the heart.[6] Vascular aging, characterized by endothelial dysfunction and arterial and capillary stiffness, places additional strain on the heart, creating an environment conducive to the development of chronic HF.[7] Aging in other organs, especially metabolic organs like the liver, kidneys, adipose tissue and skeletal muscles, further exacerbates heart dysfunction through endocrine signalling.[8,9] The age-related accumulation of systemic low-grade chronic inflammation, coupled with the senescence-associated secretory phenotype (SASP), promotes cardiac dysfunction.[6,10] Age-related comorbidities such as coronary artery disease (CAD), atherosclerosis, hypertension, obesity, diabetes and chronic kidney disease (CKD) further exacerbate the scenario,[11] resulting in a greater impairment of cardiac tissue and an elevated risk of HF in the aging population.

Recent insights challenge the traditional perception of aging as an inevitable consequence of chronological time, revealing a variable rate of age-related deterioration across species, individuals and organs.[12,13] This shift in perspective acknowledges aging as a mutable process, suggesting that age-related pathways could be targeted to counteract and potentially reverse structural and functional changes associated with age-related pathologies, including HF.[6,12] Lifestyle interventions, particularly exercise, emerge as protective measures against physiological decline, potentially prolonging cardiac health. Exercise mitigates age-related intermediate phenotypes such as oxidative stress, cellular senescence and inflammation, contributing to the modulation of age-related cardiac decline that precedes chronic HF development. The physiological effects of exercise further aid in the development of interventions to curb or reverse age-related functional decline in the heart.[14] Ongoing research is exploring multiple therapeutic options targeting aging-related pathways, including senescence, oxidative stress and inflammation, and promoting metabolic dysfunction and autophagy in HF, and the future holds great promise for achieving personalized interventions targeting aging processes in chronic HF patients.[15,16]

Here, we present systemic aging as the key culprit fuelling HF, providing a comprehensive overview of age-related pathophysiological and molecular changes in the heart from the perspective of cardiac, vascular, metabolic and inflammaging factors leading to HF, with aging-related comorbidities further exacerbating the scenario. Subsequently, we highlight exercise and dietary interventions as strategies to modulate aging, aiming to alleviate heart dysfunction in HF. Finally, we discuss ongoing therapeutic advancements potentially targeting systemic aging mechanisms in the context of HF.

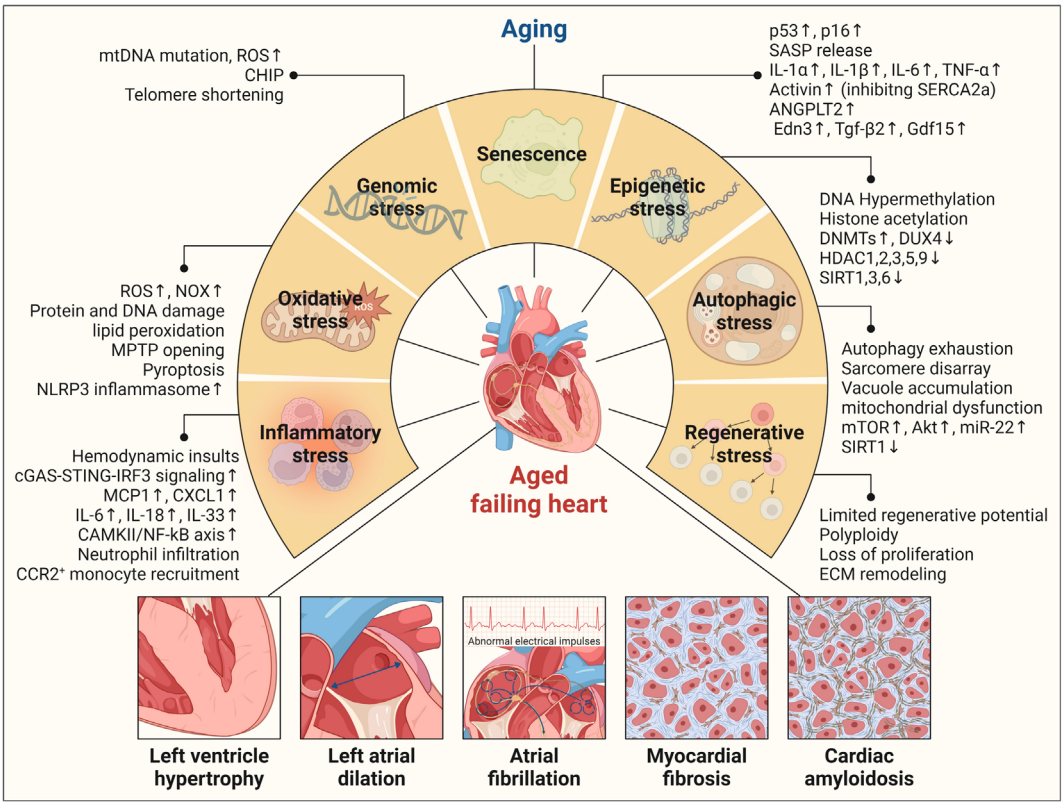
Cardiac aging: Intrinsic culprit driving HF

The aging process is intertwined with the physiological minutiae of the heart, and as the cardiovascular system matures, its structural and functional attributes undergo profound changes.[6] In this section, we first present the structural and functional decline observed in the aging heart, followed by dissecting the intrinsic molecular mechanisms that propel the aging heart towards chronic HF (Figure 1).

Structural and functional decline

Several cardiac changes occur in aging individuals, heightening the risk of HF. These alterations encompass an increased incidence of left ventricular hypertrophy, a decline in left ventricular diastolic function, left atrial dilation, atrial fibrillation, myocardial fibrosis and cardiac amyloidosis, though the ejection fraction is generally preserved (Figure 1).[5] The increase in the left ventricular mass-to-volume ratio with aging is accompanied by a decline in stroke volume due to both systolic and diastolic dysfunctions.[17] While diastolic dysfunction is uncommon in early to middle age, its prevalence and severity significantly rise thereafter with age.[18] Aging results in a

Figure 1 Cardiac aging and heart failure (HF). Lifetime molecular and cellular stresses such as genomic, epigenetic, oxidative, autophagic, inflammatory and regenerative stresses, along with the accumulation of senescent cells, drive cardiac aging and lead to structural and functional changes such as left ventricular hypertrophy, left atrial dilation, atrial fibrillation, myocardial fibrosis and amyloidosis, culminating in HF. Cardiac aging-related molecular mechanisms involved in HF are listed. CHIP, clonal haematopoiesis of indeterminate potential; DNMT, DNA methyl transferase; ECM, extracellular matrix; HDAC, histone deacetylase; MPTP, mitochondrial permeability transition pore; ROS, reactive oxygen species; SASP, senescence-associated secretary phenotype; ↑, up-regulated; ↓, down-regulated.



reduction in maximal heart rate, attributed to both decreased intrinsic heart rate and diminished responsiveness to β-adrenergic stimulation.[19] This, coupled with decreased left ventricular stroke volume and elevated left ventricular filling pressure due to impaired relaxation and compliance,[20] leads to a diminished maximal cardiac output, ultimately compromising cardiac reserve.[21] The aging myocardium also undergoes intrinsic electrophysiological alterations influenced by the cardiac autonomic nervous system, increasing the elderly's susceptibility to arrhythmic risk.[22] Elderly individuals often exhibit degenerative abnormalities associated with severe aortic stenosis.[23] Age-related increases in left atrial maximal and minimal volume are evident, while longitudinal strain and radial motion fractions during both reservoir and conduit phases decrease with age.[24] Left atrial dilation and mechanical dysfunction emerge as significant risk factors for atrial fibrillation and HF.[25] Mild increases in pulmonary artery pressure and vascular resistance impact the right ventricle during aging. Although both right and left ventricular ejection fractions (LVEF) remain relatively preserved, right ventricular diastolic dysfunction develops over time.[26] In addition, right atrial volume increases with age, and the elderly experience more frequent right atrial flow disturbances.[27] Aging is also linked to myocardial fibrosis, marked by excessive collagen deposition, which contributes to cardiac dysfunction and chronic HF risk.[28] Furthermore, cardiac amyloid deposition increases with age, leading to elevated ventricular wall thickness and myocardial stiffness, contributing to HF risk.[29]

Molecular bases of cardiac aging in HF

The information theory of aging posits that the loss of youthful epigenetic information drives the aging process, which can potentially be slowed down or even reversed by improving the function of damaged and aged tissues via epigenetic reprogramming.[30] A recent investigation has underscored the pivotal role of faithful DNA repair in fostering aging at physiological and molecular levels through mechanisms including erosion of the epigenetic landscape, progression of the DNA methylation clock, cellular de-differentiation and

senescence.[31] The aging myocardium undergoes a complex interplay of molecular events in response to a plethora of exogenous and endogenous stresses, including genomic, epigenetic, oxidative, autophagic, inflammatory and regenerative stresses, governing its trajectory towards functional decline and senescence and subsequent progression towards HF. Here, we delve into these molecular intricacies that underlie the aging process within cardiac tissues, particularly those contributing to HF (Figure 1).

Genomic stress

Somatic DNA mutations, a hallmark of aging, are implicated in cardiac aging and diseases, with mitochondrial DNA mutations being particularly prominent due to the high mutation rate and limited repair capacity.[32] These mutations compromise mitochondrial integrity, impairing mitochondrial biogenesis and increasing reactive oxygen species (ROS) production.[33] 'Mutator' mice harbouring homologous mutations in mitochondrial polymerase gamma ($Polg^{m/m}$) demonstrate compromised mitochondrial function and oxidative damage and develop premature aging phenotypes exhibiting cardiac hypertrophy, dilated cardiomyopathy and fibrosis, with an average lifespan of 12 months.[34,35] Crossing the $Polg^{m/m}$ model with antioxidant catalase (mCAT)-overexpressing mice partially rescues these cardiac aging and HF phenotypes.[36] Similarly, myocardial twinkle (Twnk) helicase overexpression in mice leads to accelerated mtDNA deletions, resulting in arrhythmias during aging.[37] Conversely, mutating the ROS production-related $p66^{Shc}$ gene reduces mitochondrial ROS (mtROS), improves resistance to ROS-mediated apoptosis and extends lifespan.[38] These findings underscore the pivotal role of mtDNA mutations in cardiac aging and HF. Clonal expansion of haematopoietic cells with somatic mutations, a phenomenon termed clonal haematopoiesis of indeterminate potential (CHIP), increases with age and correlates with elevated mortality.[39] CHIP in peripheral blood cells is associated with a doubled risk of coronary heart disease or early-onset myocardial infarction.[40,41] Given the common occurrence of CHIP in asymptomatic, cancer-free older individuals, its association with cardiac diseases suggests a potential causal link between somatic mutation and age-related chronic HF.[40,42]

Telomeres are protective caps at chromosome ends that maintain genomic integrity. Telomeres are synthesized by telomerase, comprising an RNA component (TERC) and catalytic subunit [telomerase reverse transcriptase (TERT)], and are safeguarded by the shelterin protein complex. Telomeres undergo shortening with cell division and aging and in response to stressors like oxidative stress and inflammation. Critically shortened telomeres destabilize the shelterin complex, disrupting telomeric DNA and leading to DNA damage, cell cycle arrest, cellular senescence and cell death.[43] Therefore, telomere length serves as a prominent cellular marker of aging.[12] Despite low rates of cardiomyocyte division in adults, animal studies have consistently emphasized the crucial role of telomere shortening in cardiac aging and disease. For instance, Mus musculus castaneus (CAST), having naturally short telomeres, exhibits a premature cardiac aging phenotype.[44] Similarly, TERC-deficient mice experience critical telomere shortening, exhibit heightened p21-dependent cell cycle arrest in cardiomyocytes and manifest cardiac aging and dysfunction.[45,46] Conversely, impeding telomere shortening appears to protect the heart from pathological stress. Partial aortic constriction in mice reduces telomeric repeat-binding factor 2 (Trf2), a shelterin protein, resulting in telomere shortening and cardiomyocyte apoptosis, whereas Tert or Trf2 overexpression mitigates the condition.[47] Despite this, the role of telomere shortening in human cardiac aging and HF is contentious. While it is observed that human myocardial telomere length decreases with age[48] and there are associations between shorter telomeres, decreased TRF2 and increased cardiac apoptosis in end-stage HF patients,[47] conflicting findings suggest that telomere shortening in HF patients may not reflect normal cardiac aging as it is associated with extensive DNA damage in cardiomyocytes.[49] Furthermore, age-related mitochondrial dysfunction and oxidative stress induce telomere damage specifically in cardiomyocytes, suggesting that telomere damage in these cells may occur independently of telomere length during cardiac aging.[50] These diverse perspectives underscore the complexity of the relationship between telomere dynamics, cardiac aging and chronic HF in humans.

Epigenetic stress

Epigenetics encompasses mutation independent, somatic or inherited modifications in gene function resulting from changes in DNA methylation, histone modifications, chromatin remodelling and RNA editing. Epigenetic changes are recognized as a hallmark of aging and are believed to play a role in cardiac aging and cardiovascular diseases (CVDs), including HF.[51] DNA methylation increases with age, constituting an 'epigenetic clock' serving as a marker for chronological and biological age.[52] Left ventricular tissue from HF patients exhibits global methylation differences in promoter CpG islands, intragenic CpG islands and gene bodies compared with healthy controls. In particular, mimicking differential DNA methylation of the double homeobox 4 (DUX4) locus through gene knockdown displays reduced cardiac cell viability in vitro, suggesting a potential causal role for DUX4 in cardiac dysfunction.[53] Similarly, differential methylation patterns are evident in peripheral blood from left ventricular HF patients compared with controls as well as among genomic regions of cardiomyocytes from neonatal, healthy adult and adult failing hearts.[54,55] Hypermethylation is also apparent in hearts from rats with norepinephrine-induced cardiac hypertrophy, with inhibition of DNA methyl transferase (DNMT) reducing hypertrophy and HF.[56] Furthermore, METTL3-mediated N^6-methyladenosine methylation regulates cardiac hypertrophic

response, with enhanced methylation resulting in compensated cardiac hypertrophy and diminished methylation inducing cardiac dysfunction,[57] highlighting the significance of age-related DNA methylation in cardiac disease.

Histone proteins play a crucial role in preserving chromatin structure, safeguarding genomic integrity and enabling dynamic gene regulation.[58] Post-translational histone modifications, including acetylation/deacetylation and methylation/demethylation, are implicated in disease-associated cardiac dysfunction during aging.[59] In line with this, loss of histone deacetylases (HDACs) such as HDAC1, 2, 3, 5 and 9 promotes aging-like features including cardiac hypertrophy, dysfunction and vulnerability to cardiac injury, along with a shortened lifespan.[60–62] Sirtuins (SIRTs) constitute a specialized class of HDACs with NAD^+ dependency and are implicated in age-related cardiac dysfunction and CVDs.[63] Decreased SIRT1 expression in cardiomyocytes from advanced HF patients and rat models is linked to enhanced oxidative stress, inflammation and apoptotic death.[64,65] SIRT1 attenuates oxidative stress in cardiomyocytes through reduction of manganese superoxide dismutase (MnSOD), thioredoxin1 (TRX1) and Bcl-xL[64] and diminishes cardiomyocyte apoptosis through the nuclear factor kappa B (NF-κB) p65/miR-155/brain-derived neurotrophic factor (BDNF) pathway, alleviating HF in rats.[66] SIRT3 deficiency may impair cardiac mitochondrial function and exacerbate HF during aging. SIRT3 also regulates endothelial metabolism and angiogenesis, impacting HF occurrence and development. Endothelial-specific SIRT3 knockout disrupts glucose transport, decreases cardiomyocyte glucose utilization and sensitizes pressure-overload-induced HF in vivo.[67,68] Similarly, SIRT6 exhibits protective effects in HF, with decreased expression observed in chronic HF patients and animal models. SIRT6 overexpression increases the survival of HF mice, potentially through telomerase up-regulation.[69,70] These findings underscore the role of age-related epigenetic stress in cardiac dysfunction and chronic HF.

Oxidative stress

Mitochondria, serving as the heart's primary energy source, play a pivotal role in cardiomyocyte survival by producing adenosine triphosphate (ATP). The aging heart experiences a decline in mitochondrial function, contributing to HF. Recent insights into mitochondrial dysfunction align with the oxidative stress hypothesis of aging, proposing that excessive ROS from mitochondria induces oxidative damage to mtDNA and redox-sensitive mitochondrial proteins. This creates a self-perpetuating cycle of oxidative damage that contributes to cellular and organ functional decline, limiting health and lifespan.[71,72] Mitochondrial dysfunction can alone trigger functional decline in the heart, as knocking out peroxisome proliferator-activated receptor-gamma co-activator 1 alpha (Pgc-1α), a key regulator of mitochondrial biogenesis, in mice introduces cardiac dysfunction as early as 7–8 months of age.[73] MtROS may induce mitochondrial respiratory chain defects, causing oxidative stress, protein and DNA damage, lipid peroxidation and mitochondrial permeability transition pore (MPTP) opening. Subsequently, cytochrome C release drives chronic proteome remodelling and apoptosis, leading to acute cardiovascular events and chronic HF.[74] Moreover, mtROS may induce NLRP3 inflammasome activation and cardiomyocyte pyroptosis in dilated cardiomyopathy, unveiling a novel event in HF initiation and progression.[75] Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) is a predominant source of ROS that induces lipid peroxidation of the mitochondrial membrane and opens a redox-sensitive mitochondrial K^+ channel, resulting in mtROS generation from the electron transport chain.[76] Conversely, mitochondria-specific overexpression of antioxidant mCAT prolongs lifespan through attenuation of cardiac aging phenotypes attributed to reduced oxidative damage to mtDNA and proteins.[77,78] Hence, alleviating oxidative stress during age-related cardiac dysfunction and chronic HF offers a potential avenue for preserving cardiac function.

Autophagic stress

Autophagy, a cellular process responsible for organelle turnover and the recycling of damaged components, is vital for maintaining cellular homeostasis. Under normal conditions, autophagy is tightly controlled by the mammalian target of rapamycin (mTOR) complexes. Nutrient deprivation activates AMP-activated protein kinase (AMPK), which inhibits mTORC1 and initiates autophagy. Key regulators in the transcriptional control of autophagy include transcription factor EB (TFEB) and FoxO, primarily transcribing autophagy-related genes (ATGs).[79] Age-related exhaustion of the autophagic response (autophagic stress) due to mitochondrial dysfunction and oxidative stress in aging hearts leads to structural and functional damage.[80] mTOR activation,[81,82] or inhibition of autophagy activators like SIRT1,[83] contributes to autophagic stress and cardiac dysfunction in the heart. Atg5 knockout mice display disorganized sarcomere structures and collapsed mitochondria, leading to cardiomyopathy and systolic dysfunction in aged animals.[80] Inducible conditional knockout of Atg5 or Atg7 in cardiomyocytes leads to cardiomyopathy, severe contractile dysfunction and premature death in mice.[84,85] Mice with lysosome-associated membrane protein 2 (Lamp2) knockout exhibit cardiac dysfunction along with pathological changes in various organs, including arteries, skeletal muscle, pancreas and liver, resulting in premature mortality.[86] Knocking out glycogen synthase kinase 3 alpha (Gsk3α) endorses vacuole accumulation and sarcomere disarray, hallmarks of autophagic stress, and disrupts mitochondria, leading to cardiomyopathy and a shortened lifespan.[87] Mice with the heat shock protein family B (HSPB6)^{S10F} mutation undergo autophagic stress due to impaired HSPB6 and Beclin-1 (Becn1) interactions, leading to HF and early death.[88] Paradoxically, Becn1 expression is implicated in enhancing hypertrophy, fi-

brosis and pressure-overload-induced chronic HF.[89] Chronic protein kinase B (Akt) activation in cardiomyocytes suppresses autophagy, causing aging-associated cardiac hypertrophy, fibrosis and contractile dysfunction in transgenic mice.[90] Age-related and p53-dependent up-regulation of microRNA (miR)-22 induces autophagic stress, cardiac remodelling and dysfunction. Furthermore, elevated circulating miR-22 in HF patients is associated with early mortality.[91] Hence, mitigating autophagic stress in age-related cardiac dysfunction and chronic HF presents a potential avenue for maintaining cardiac function.

Inflammatory stress

Age-related haemodynamic insults, encompassing injury, pressure overload, volume overload and ischaemia, can initiate cardiac remodelling. This adaptive mechanism induces hypertrophy and fibrosis, serving to maintain cardiac function and compensate for the potential loss of cardiomyocytes. Successful compensation resolves inflammatory responses; however, persistent stimuli may lead to dysregulated immunity, causing sustained, low-grade inflammation and adverse cardiac remodelling (cytokine hypothesis) that culminates in chronic HF.[92,93] During the acute inflammatory phase, the self-DNA, released from dying cardiomyocytes, is identified by the cytosolic pattern recognition receptor, known as cyclic GMP-AMP synthase (cGAS), that initiates an inflammatory response through signal transduction along the cGAS–STING–IRF3 pathway.[94] In addition, cardiomyocytes express cytokines like monocyte chemoattractant protein-1 (MCP1), chemokine (C–X–C motif) ligand 1 (CXCL1), interleukin (IL)-6, IL-18 and IL-33 via CaM kinase II (CaMKII)-mediated NF-κB activation.[93] Cardiomyocyte-released chemokines and cytokines may circulate, facilitating the recruitment of monocytes and neutrophils and activating tissue-resident macrophages.[95] Neutrophils play a crucial role in transitioning from acute inflammation to the reparative phase, marked by macrophage-mediated tissue clearance, profibrotic cytokine production and monocyte recruitment.[96] These responses are critical for cardiac repair and border zone cardiomyocyte survival,[97] though they may flood the systemic circulation due to massive injury or chronic inflammatory conditions, resulting in adverse remodelling.[98] Crosstalk between stressed cardiomyocytes and neighbouring immunoreactive cells, such as fibroblasts, endothelial cells and resident immune cells, may contribute to the persistent, low-grade inflammation characteristic of chronic HF.[99,100] Prolonged stress and inflammatory responses drive the transition to adverse remodelling, and HF, marked by hypertrophy and excessive fibrosis, necessitates the infiltration of CC motif chemokine receptor 2 ($CCR2^+$) monocyte-derived macrophages, replacing the resident macrophages.[101] Given that infiltrated neutrophils precede recruited $CCR2^+$ monocytes, there is a potential synergistic recruitment by resident macrophages and infiltrated neutrophils.[101] Failure to resolve stress leads to para-inflammation and exacerbates adverse remodelling, culminating in chronic HF.[93] Overall, targeting inflammatory processes emerges as a direct strategy to attenuate cardiac immune responses during aging and alleviate HF.

Regenerative stress

Adult cardiomyocytes renew at a rate of 0.5%–2% per year, indicating some, albeit limited, endogenous regenerative potential.[102,103] This cardiomyogenesis potential primarily stems from the division of pre-existing cardiomyocytes, not through the differentiation of stem cells.[104] Furthermore, this renewal rate tends to decline with age, suggesting a diminished ability to compensate for cardiomyocyte loss, a critical factor given that even minimal experimentally induced cardiomyocyte loss results in cardiomyopathy and death.[105] Conditions in failing hearts, such as ischaemia, hypertrophy and atrophy, can reactivate foetal gene programmes, partially reversing morphological and metabolic processes.[106] Despite the loss of functional cardiomyocytes, failing hearts display increased cell cycle activity following cardiac injury,[107] resembling neonatal cardiomyocytes that can duplicate and contribute to cardiac regeneration.[108,109] However, the transition to postnatal maturation induces significant changes in cardiomyocyte characteristics, leading to a gradual loss of proliferative capacity.[110] Unfortunately, increased cell cycle activity in diseased and injured hearts typically results in polyploidy rather than substantial cardiomyocyte proliferation.[111] Additionally, the extracellular matrix (ECM) composition plays a crucial role in regulating cardiomyocyte maturation and cell cycle activity, though it is often compromised in cardiac pathologies.[112,113] Hence, there is a need for therapeutic interventions to promote endogenous regenerative capacity in the heart, potentially tilting the homeostatic balance and improving cardiac performance in aging and failing hearts.

Senescence

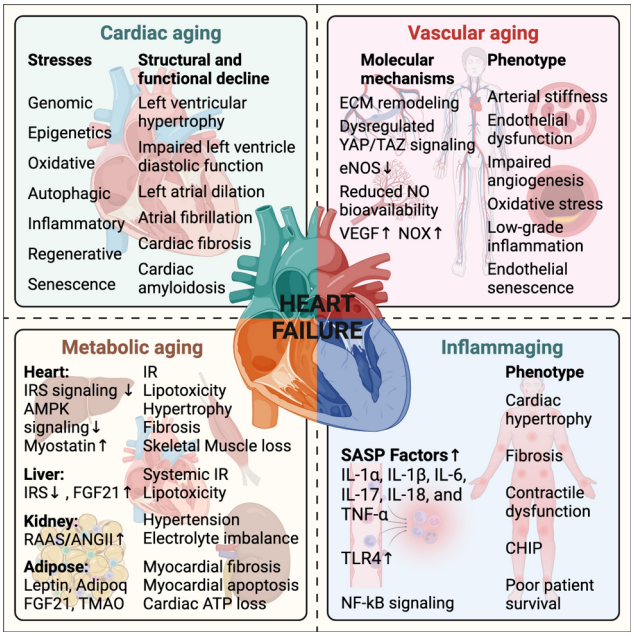
Cellular senescence, triggered by telomere attrition or other forms of cellular stress, results in permanent cell cycle arrest, functional decline and the acquisition of a pro-inflammatory phenotype.[114] Elevated expression of senescence markers like p53 and p16Ink4a is apparent in aging hearts and contributes to hypertrophy, mitochondrial dysfunction, increased cardiomyocyte death, decreased contractility and chronic HF.[115,116] Senescent cells progressively accumulate during life, exerting deleterious paracrine effects on neighbouring cells and systemic effects on other tissues and organs through SASP.[117] Growing evidence suggests that senescent cells contribute to cardiac remodelling and dysfunction during aging.[115,118] Beyond the classical pro-inflammatory SASP factors [IL-1α, IL-1β, IL-6 and tumour necrosis factor alpha (TNF-α)] promoting local and systemic inflammation, emerging research indicates a broader role for various secreted proteins or RNAs in the context of aging-related

diseases, including HF.[6] For instance, an age-related increase in secreted activin triggers smad ubiquitination regulatory factor 1 (Smurf1)-mediated ubiquitination and subsequent degradation of the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a (SERCA2a), an enzyme critical for heart contractility, whereas targeted inhibition of activin receptor type 2B (ActRIIb) signalling improves aging and failing hearts.[119] Angiopoietin-like protein 2 (ANGPTL2) is primarily secreted by cardiomyocytes and adipocytes. Aged animal hearts, as well as HF animal models and patients, exhibit elevated ANGPTL2 expression.[120,121] Cardiomyocytes may induce senescence in neighbouring cells through the secretion of non-traditional SASP signals, including endothelin 3 (Edn3), transforming growth factor beta 2 (Tgf-β2) and growth differentiation factor 15 (Gdf15), as identified in purified cardiomyocytes from old mice.[50] Hence, targeting senescence and SASP factors in the context of aging and chronic HF provides a promising therapeutic avenue.

Vascular aging and HF

Vascular aging, characterized by arterial and capillary stiffness, endothelial dysfunction, impaired angiogenesis capacity, oxidative stress, low-grade chronic inflammation and endothelial senescence, makes up the biggest pathological hallmark of many age-related CVDs, including HF (Figure 2).[7] Arterial stiffness places strain on the heart as it pumps blood against vessels that are less flexible, creating an environment conducive to the development of chronic HF.[122] Changes in the ECM composition due to imbalances in matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) lead to ECM remodelling, characterized by increased collagen deposition and elastin fragmentation.[123] Furthermore, dysregulated mechanosignalling transcriptional co-activators like yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) due to mechanical strain play a crucial role in arterial stiffness during vascular aging and its impact on HF.[124] Endothelial dysfunction is primarily characterized by impaired nitric oxide (NO) signalling, heightened oxidative stress and chronic inflammation. Diminished activity of endothelial NO synthase (eNOS) contributes to a reduction in NO bioavailability. This is exacerbated by elevated levels of ROS, particularly the superoxide anion that interacts with NO and forms peroxynitrite, diminishing the vasodilatory effects of NO on adjacent smooth muscle cells.[125] Consequently, disruption in NO turnover compromises the ability of blood vessels to properly dilate, impacting the regulation of blood flow.[125] Diminished NO levels may also reduce cardiomyocyte contractility, leading to reduced left ventricular diastolic compliance in a cyclic GMP-dependent protein kinase G (PKG)-dependent manner.[126] Moreover, endothelial dysfunction can lead to restricted nutrient and oxygen availability to cardiomyocytes, contributing to inadequate coronary perfusion and aggravating cardiac dysfunction leading to chronic HF.[127]

Figure 2 Systemic aging and heart failure (HF). Systemic aging fuels HF, with cardiac, vascular, metabolic and inflammaging as major contributors. HF-associated molecular mechanisms—cardiac, vascular, metabolic and inflammaging—are summarized along with observed phenotypes. ATP, adenosine triphosphate; CHIP, clonal haematopoiesis of indeterminate potential; IR, insulin resistance; IRS, insulin receptor substrate; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; TMAO, trimethylamine N-oxide; ↑, up-regulated; ↓, down-regulated.



Impaired angiogenesis impedes neovascularization and contributes to vascular aging. Diminished expression of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), hampers endothelial cell proliferation and vessel formation.[128] In chronic HF, inadequate angiogenesis curtails the heart's adaptability to changing demands, resulting in insufficient blood supply.[129] Furthermore, vascular aging instigates oxidative stress concomitant with persistent inflammation. Elevated expression of NOX, a principal ROS source, amplifies oxidative stress during vascular aging. This heightened oxidative milieu activates pro-inflammatory pathways, notably NF-κB.[130] The reciprocal interaction between oxidative stress and inflammation plays a pivotal role in myocardial damage, fibrosis and compromised contractility during HF.[131] Age-related senescence also introduces an inflammatory phenotype in both vascular and myocardial endothelial cells, as observed in the hearts of senescence-accelerated mice. These events exacerbate diastolic dysfunction and left ventricular hypertrophy, coinciding with HF.[132] Hence, targeting vascular aging mechanisms holds potential for developing interventions aimed at preserving vascular health in chronic HF.

Metabolic aging and HF

Metabolic aging is a dynamic process marked by cumulative cellular and molecular changes impacting organs, including the heart, liver, adipose tissue, kidney and skeletal muscles, affecting energy metabolism, hormonal regulation and overall homeostasis.[8] With aging, molecular events modulating metabolic processes in these tissues significantly contribute to chronic HF (Figure 2).[9] Age-related shifts in glucose and lipid metabolism play a pivotal role in HF pathogenesis.[133] Insulin resistance in the aging heart impairs glucose uptake (via compromising glucose transporters), prompting reliance on fatty acids for energy production. This metabolic inflexibility leads to mitochondrial dysfunction and increased ROS production.[134] Disruptions in the insulin receptor substrate (IRS) signalling cascade and AMPK pathway dysregulation are crucial components of this intricate signalling network.[135] Concurrently, insulin resistance raises circulating free fatty acids (FFAs), inducing lipid accumulation (lipotoxicity) within cardiomyocytes due to reduced lipid oxidation.[136,137] Age-related perturbations in the lipid metabolism-related peroxisome proliferator-activated receptors (PPARs) signalling pathway and mTOR pathway activation contribute to cardiac hypertrophy, fibrosis and impaired autophagy during chronic HF.[138]

The metabolic hub, the liver, undergoes age-related changes contributing to chronic HF. Liver insulin resistance heightens gluconeogenesis and elevates circulating FFAs, impacting glucose and lipid homeostasis.[139] Dysregulation of the insulin signalling pathway in the liver involves crosstalk via hepatokines, such as fibroblast growth factor 21 (FGF21), influencing systemic metabolic balance and potentially contributing to HF-related disturbances.[140] The liver–heart axis is bidirectional, with heightened cardiac sympathetic activity potentially stimulating the liver to release glucose into the bloodstream, contributing to systemic insulin resistance.[141] In the kidneys, age-related glomerular dysfunction, reduced renal blood flow and impaired sodium excretion contribute to hypertension—a significant HF risk factor.[142] Dysregulation of the renin-angiotensin-aldosterone system (RAAS) in aging kidneys increases angiotensin II (AngII) levels, promoting vasoconstriction, sodium retention, fluid overload and cardiac remodelling.[143] In HF, chronic activation of this system induces adverse cardiac remodelling, fibrosis and hypertrophy, exacerbating the condition. Metabolic aging in the kidneys is also associated with systemic inflammation, oxidative stress and electrolyte imbalances, all of which contribute to HF progression.[144]

The crosstalk between adipose tissue and cardiac cells involves adipokines like adiponectin, leptin, resistin and FGF21 release, influencing the cardiac metabolic milieu.[145] Age-related adipose tissue dysfunctions, especially in visceral adipose tissue, significantly impact HF pathophysiology. Elevated serum adiponectin levels correlate with HF severity and are associated with a poor prognosis.[146] Additionally, circulating resistin exacerbates myocardial fibrosis and apoptosis by inducing DNA damage, triggering a dysfunctional cardiac response that ultimately leads to chronic HF.[147] Age-related brown adipose tissue dysfunction elevates plasma trimethylamine N-oxide levels, inducing mitochondrial damage by inhibiting cytochrome c oxidase 1 (COX1), limiting ATP levels in cardiac tissue and contributing to HF.[148] Age-related metabolic changes in skeletal muscle aggravate HF. For instance, altered myokine secretion, including myostatin, contributes to the intricate landscape of metabolic and systemic aging.[149] Sarcopenia, characterized by a decline in muscle mass and function, involves dysregulation of the AMPK pathway and activation of the NF-κB pathway, contributing to impaired mitochondrial function, decreased energy production and systemic inflammation that fosters cardiac pathologies.[150] Reduced physical activity due to skeletal muscle dysfunction or sarcopenia can exacerbate metabolic imbalances, further impacting HF progression.[151] Notably, the heart's aberrant myostatin release in chronic HF may activate proteolysis in an ActIIB/Smad-dependent manner, promoting skeletal muscle loss.[152] In summary, bidirectional crosstalk between the heart and other organs emphasizes the need for a comprehensive understanding of inter-organ communications to develop targeted interventions for preserving cardiac function and mitigating HF progression in the aging population.

Inflammaging and HF

Age-related decline in organ function, attributed to the accumulation of senescent cells and the acquisition of chronic low-grade inflammation, contributes to systemic defects and the onset of diseases.[10] In the context of HF, both inflammation and autoimmunity play crucial roles in initiation and progression, as evidenced by increased inflammatory cell infiltration within the myocardium of chronic HF patients (Figure 2).[153,154] Chronic inflammation promotes the release of pro-inflammatory SASP factors. In turn, the activation of inflammatory pathways, such as NF-κB signalling, in the heart serves as a crucial molecular link between inflammaging and chronic HF. NF-κB directly induces the release of pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-17 and TNF-α), promoting cardiomyocyte hypertrophy, fibrosis and contractile dysfunction, hallmarks of HF.[155] Up-regulation of pro-inflammatory cytokines correlates with increased Toll-like receptor-4 (TLR-4) expression, a pattern observed in the aging process and evident in the myocardial tissue and circulating monocytes of chronic HF patients.[156] In ischaemic HF models, IL-1 increases rapidly within hours, correlating with the progressive nature of cardiac dysfunction.[157] Conversely, recombinant IL-1β administration induces myocardial

dysfunction in outbred CD-1 mice.[158] Elevated IL-6 and IL-18 levels are significantly associated with CVDs and HF in the elderly.[159] Cardiac IL-6 expression gradually increases with age in animal models, and IL-6 deficiency correlates with the mitigation of age-related cardiac dysfunction.[160] Terminally differentiated $CD4^+$ T lymphocytes are markers of myocardial inflammaging,[161] and circulating IL-6 levels are associated with accelerated aging of T lymphocytes, serving as predictors of survival in HF patients.[162] Notably, elevated circulating IL-6 is noted in elderly patients with concomitant HF and CHIP, particularly those with double somatic mutations of the DNMT3A and TET2 genes, suggesting that age-related clonal haematopoiesis may contribute to HF development.[163] This is supported by evidence that TET2 deficiency accelerates age-related cardiomyopathy, resulting in more pronounced cardiac hypertrophy and fibrosis.[164] TNF-α impairs contractility in the mammalian heart, exacerbating HF symptoms. Balancing TNF-α and IL-10 expression may play a pivotal role in mitigating chronic HF-related inflammation and oxidative stress.[165] Nevertheless, these observations provide valuable insights for developing targeted interventions to mitigate the impact of inflammaging on chronic HF.

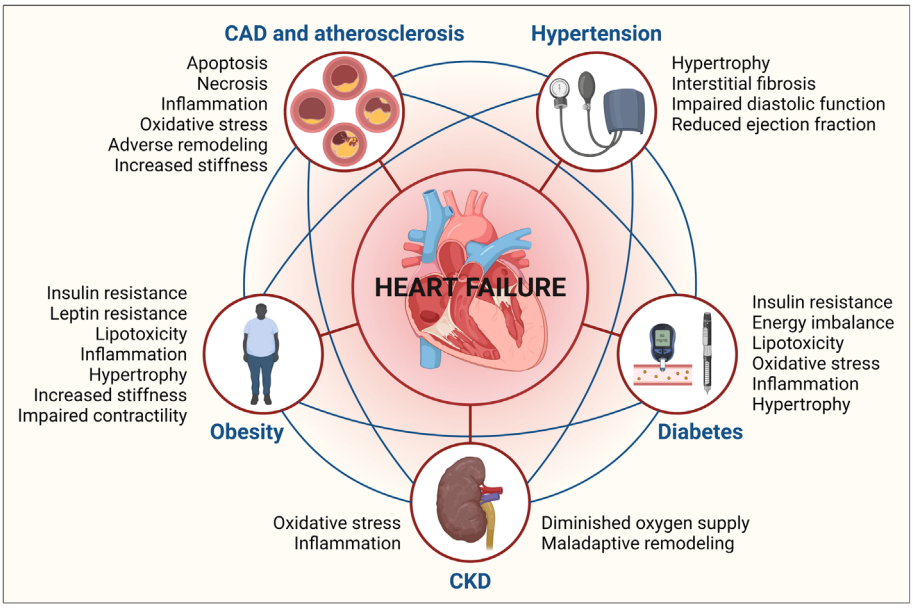
Diseased aging exacerbates HF

As individuals age, they encounter a range of diseases and health challenges, adding complexity to the management of overall well-being. Age-related comorbidities, including CAD, atherosclerosis, hypertension, obesity, diabetes and CKD, interact and collectively affect cardiovascular health, playing a substantial role in the initiation and advancement of cardiac dysfunction that leads to chronic HF.[11] In this section, we delve into the molecular underpinnings of specific aging-related comorbidities, unravelling the intricate connections between these conditions and HF in the aging population (Figure 3).

CAD and atherosclerosis

The onset of CAD initiates atherosclerotic plaque formation, characterized by the accumulation of low-density lipoproteins (LDLs) in the arterial intima. These LDL particles undergo oxidative modifications, resulting in oxidized LDL (ox-LDL), which instigates an inflammatory response. This cascade attracts immune cells, particularly monocytes, leading to their differentiation into foam cells and forming fatty streaks in early atherosclerotic lesions. As lesions progress, persistent inflammatory signalling involving cytokines, chemokines and MMPs contributes to plaque destabilization, elevating rupture risk. A ruptured plaque exposes thrombogenic material, activating platelets and causing thrombus formation, ultimately partially or completely occluding coronary arteries and inducing myocardial ischaemia, resulting in HF.[166,167] Ischaemia triggers molecular events, releasing ATP and potassium ions due to cellular stress, activating purinergic receptors and inducing inflammation. Concurrently, ischaemic myocardium releases damage-associated molecular patterns,

Figure 3 Diseased aging and heart failure (HF). Age-related comorbidities, especially coronary artery disease (CAD), atherosclerosis, hypertension, obesity, diabetes and chronic kidney disease (CKD), exacerbate HF. Cardiac dysfunction mechanisms, through which these comorbidities promote HF, are listed.



amplifying the inflammatory response.[168,169] Inflammatory and oxidative stress conditions play pivotal roles in HF progression, inducing cardiomyocyte apoptosis, necrosis and adverse cardiac remodelling via hypertrophic signalling pathways involving Akt and mTOR.[170,171] The fibrotic response, driven by TGF-β and collagen deposition, leads to increased myocardial stiffness. This chronic stress, coupled with maladaptive remodelling and cardiac dysfunction, collectively culminates in chronic HF.[172]

Hypertension

Hypertension, defined by persistently elevated blood pressure, is an age-related CVD. It induces stress on the heart and blood vessels, causing adverse structural and functional changes that pave the way for chronic HF.[173] Aging dysregulates the RAAS, a key hormonal network in blood pressure regulation. This dysregulation involves increased AngII production, a potent vasoconstrictor, leading to vascular smooth muscle cell hypertrophy, inflammation and oxidative stress. These molecular changes contribute to endothelial dysfunction and hypertension pathogenesis.[174] Hypertension instigates adverse cardiac remodelling through neurohormonal activation, especially via AngII and the sympathetic nervous system. This stimulation induces hypertrophic signalling cascades, including mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/Akt, p38-MAPK and c-Jun N-terminal kinase (JNK) signalling pathways, leading to cardiomyocyte hypertrophy and interstitial fibrosis.[175] Oxidative stress, a hallmark of both aging and hypertension, worsens endothelial dysfunction, perpetuating a vicious cycle of molecular events impacting cardiac function.[176] The transition from hypertension to HF entails impaired diastolic function, progressing to reduced ejection fraction, ultimately compromising cardiac output.[177]

Obesity

Obesity, a critical challenge to an aging population, contributes to HF pathogenesis through a complex molecular interplay involving multiple facets, including insulin resistance, dyslipidaemia, chronic inflammation and oxidative stress, collectively imposing a substantial burden on the cardiovascular system.[178] Insulin resistance disrupts glucose homeostasis, promoting hyperglycaemia and oxidative stress within cardiomyocytes.[179] Chronic inflammation in obesity, driven by pro-inflammatory cytokines such as TNF-α and IL-6, heightens the immune response and directly impacts cardiac health.[180] Dyslipidaemia, characterized by elevated circulating fatty acids and triglycerides, induces cardiac lipotoxicity and exacerbates inflammation.[181] Oxidative stress from mitochondrial dysfunction in obesity increases ROS production, leading to cellular damage and cardiac dysfunction.[182] Epigenetic modifications induced by obesity, such as alterations in DNA methylation and histone modifications, impact gene expression related to cardiac function, metabolism and inflammation.[183] Persistent inflammation and oxidative stress induce fibrosis, which promotes stiffness and impairs cardiac contractility.[184] Obesity-induced cardiac hypertrophy, an adaptive response to increased workload, further contributes to the events leading to chronic HF.[178] Moreover, RAAS activation in obesity, with elevated aldosterone levels, leads to sodium retention, fluid overload and increased blood pressure, placing extra strain on the heart.[174] Leptin resistance, along with dysregulation of other adipokines such as adiponectin, resistin and visfatin, further contributes to the molecular landscape driving chronic HF in the aging obese population.[185]

Diabetes

Diabetes, a prevalent aging-related comorbidity, profoundly affects cardiovascular health and contributes to HF progression. The molecular underpinnings of diabetes-related HF are rooted in insulin resistance, a hallmark of type 2 diabetes, which compromises glucose utilization and cardiomyocyte metabolism.[186] Hyperglycaemia, a defining characteristic of diabetes, triggers intricate molecular events, inducing oxidative stress through pathways involving protein kinase C (PKC) activation and advanced glycation end product formation. These cascades play a pivotal role in developing endothelial dysfunction, inflammation and fibrosis within the cardiovascular system.[187] Furthermore, diabetes-associated dyslipidaemia, marked by elevated triglycerides, LDL and cholesterol, significantly contributes to atherosclerotic processes and exacerbates cardiac dysfunction.[188] Central to this molecular landscape, mitochondrial dysfunction causes energy imbalance, impacting cardiomyocyte function.[189] Insulin resistance fosters an inflammatory milieu that exacerbates cardiovascular complications.[186] The complex molecular dialogue extends to RAAS activation in diabetes, contributing significantly to adverse cardiac remodelling, fibrosis and hypertrophy, ultimately leading to chronic HF in diabetic patients.[174]

CKD

CKD, an aging-related condition featuring a progressive decline in renal function with reduced glomerular filtration rate and impaired sodium handling, fosters a molecular environment conducive to HF progression.[190] Impaired sodium handling disrupts electrolyte balance, causing sodium retention and volume overload. This fluid imbalance activates the RAAS, releasing AngII and aldosterone. AngII induces

vasoconstriction, while aldosterone enhances sodium and water reabsorption, collectively increasing blood volume and systemic blood pressure and imposing an additional workload on the heart, contributing to chronic HF.[191] Uraemic toxins, arising from advanced CKD, contribute to HF by inducing systemic inflammation and oxidative stress. These toxins trigger endothelial dysfunction, impairing vasodilatory capacity and promoting a pro-inflammatory environment extending to the heart.[192] The CKD-associated chronic inflammatory state, marked by elevated cytokines like IL-1β, IL-6 and TNF-α, may contribute to adverse cardiac remodelling in HF.[193] CKD disrupts the erythropoietin production balance, resulting in anaemia. Reduced oxygen-carrying capacity may compromise cardiac function by diminishing myocardial oxygen supply. This anaemic state, combined with increased afterload due to CKD-induced endothelial dysfunction, compromises cardiac performance, leading to chronic HF.[194] Sympathetic nervous system overactivation, common in CKD, exacerbates HF progression by raising heart rate and myocardial workload, inducing maladaptive cardiac remodelling. The sympathetic surge, along with RAAS activation, creates a synergistic effect, intensifying the neurohormonal burden on the heart.[195]

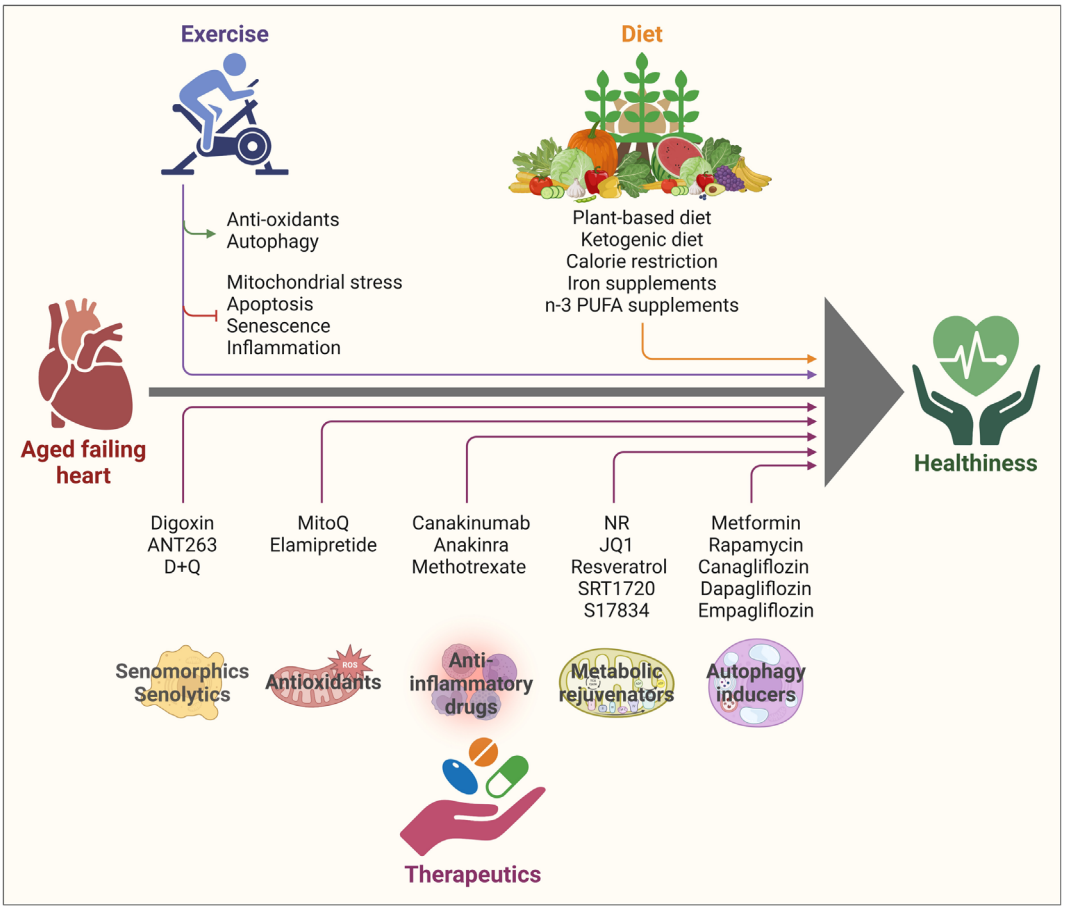
Lifestyle interventions mitigate systemic aging in HF

Living a healthy lifestyle not only slows the aging process but also keeps diseases at bay. In this section, we highlight exercise and dietary plans as key lifestyle interventions with the potential to mitigate systemic aging in HF (Figure 4).

Exercise

Exercise, renowned for its antioxidant effects, has the potential to partially reverse pathological cardiac remodelling in

Figure 4 Lifestyle interventions and aging-related therapeutic implications in heart failure (HF). Lifestyle interventions such as exercise and dietary plans are adaptive strategies to counteract systemic aging and improve the health status of HF patients. Furthermore, targeted therapeutics against systemic aging such as senomorphics, senolytics, antioxidants, anti-inflammatory drugs, metabolic rejuvenators and autophagy enhancers are being tested to alleviate HF.



the elderly by counteracting various pathological processes associated with age-related HF, including mitochondrial dysfunction, inflammation, senescence and declining cardiomyocyte regeneration.[14,196,197] Aerobic exercise training over 3–6 months demonstrates improved peak oxygen consumption and exercise efficiency in elderly subjects aged 65–79.[198] Additionally, progressive and vigorous endurance exercise training in previously inactive individuals over 65 leads to physiological left ventricular remodelling, increasing ventricular mass without affecting the mass-to-volume ratio.[199] Exercise stimulates mitochondrial biogenesis in the heart, improving bioenergetics and enhancing the antioxidant response in HF.[200] This antioxidant response to exercise goes beyond the heart, as evidenced by the increased activity of ROS-scavenging enzymes in the skeletal muscle of HF patients following a 6 month exercise training regimen.[201] Aged myostatin knockout mice display better preserved cardiac structure and function. Notably, myostatin levels in the skeletal muscle of chronic HF patients and rats decrease following exercise training,[202] emphasizing the potential benefits of exercise on age-related changes.

Exercise enhances cardiac autophagy, thereby stimulating mitochondrial biogenesis, mitigating local tissue inflammation and enhancing cardiac function.[200,203] Notably, endurance and strength exercises are associated with the activation of autophagy, whereas exhaustive exercise may lead to decreased autophagy in cardiac tissues.[204] Voluntary running in mice for 21 days induces telomerase activity and limits senescence in the heart, showcasing the geroprotective effects of physical activity.[205] Exercise also reduces cardiomyocyte apoptosis in aging animals and those subjected to ischaemia–reperfusion injury.[206] At the molecular level, exercise dynamically up-regulates SIRT3 in the aging heart to alleviate mitochondrial stress.[207] In addition, exercise promotes heart-specific insulin-like growth factor 1 (IGF-1) expression, which induces pro-angiogenic, anti-apoptotic and anti-fibrotic effects through PI3K/Akt signalling. This cascade leads to physiological hypertrophy and improved cardiac function in HF.[208] Notably, exercise-induced cell division cycle 42 (Cdc42) acts as a negative regulator of physiological hypertrophy, limiting excessive heart growth. This is evidenced by Cdc42 knockout animals experiencing more exercise-induced cardiac hypertrophy and subsequently developing HF.[209] Exercise counteracts apoptotic cell death by deactivating calcineurin/nuclear factor of activated T cells (NFAT) pathway-induced pathological hypertrophy and prevents adverse remodelling in HF.[210] Furthermore, moderate exercise alleviates myocardial apoptosis and promotes cardiac regeneration by inducing Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signalling, which is otherwise suppressed in HF.[206] Aerobic exercise and concurrent training interventions effectively suppress pro-inflammatory markers such as IL-6 and TNF-α and alleviate inflammaging in overweight HF patients.[211] Undoubtedly, exercise confers beneficial impacts on patients with HF, and experimental exercise models serve as valuable platforms for discovering novel therapeutic targets that can aid in alleviating cardiac distress.

Dietary plans

Aging and the onset of aging-related diseases are significantly influenced by nutritional patterns, underscoring the pivotal role of dietary interventions in addressing HF.[212] Adherence to a plant-based diet is inversely associated with HF risk.[213] Metabolomic and proteomic analyses in advanced HF patients and animal models suggest a shift in substrate utilization towards decreased fatty acid oxidation and increased reliance on ketones as fuel in HF.[214] Dietary interventions altering substrate availability, such as ketogenic diets, could potentially improve energy homeostasis in failing hearts.[61] In line with this, caloric restriction emerges as a pioneering therapy for overweight HF patients, as it enhances myocardial function by reducing body fat. However, a highly restricted diet may pose a significant risk factor associated with increased mortality in underweight HF patients.[215] Age-related micronutrient and macronutrient deficiencies may also contribute to the pathogenesis or outcome of HF. In particular, iron deficiency is linked to poor HF outcomes, and ongoing trials like FAIR-HF2 are exploring the impact of intravenous iron supplementation in HF patients.[216] Macronutrient supplementation, especially unsaturated fatty acids like omega-3 polyunsaturated fatty acids (n-3 PUFA), improves ejection fraction and limits HF-related hospitalizations,[217] though recent meta-analyses highlight potential risks of arterial fibrillation in patients with cardiovascular risk.[218] Hence, future studies are crucial to establishing the precise roles of dietary interventions in HF pathogenesis.

Aging-related therapeutic implications in HF

Leveraging anti-aging therapeutics in HF centres around suppression of senescence, oxidative stress and inflammation while promoting metabolic rejuvenation and autophagy. In this section, we discuss ongoing therapeutic advancements potentially targeting systemic aging mechanisms in HF (Figure 4).

Senomorphics and senolytics

Limiting senescence is cardioprotective, preventing age-related accumulation of senescent cardiomyocytes, averting cardiac dysfunction, diminishing chronic inflammation and preserving optimal cardiac performance.[219] Eliminating

p16Ink4a-expressing senescent cells not only halts aging phenotypes but also preserves cardioprotective channels, reduces hypertrophy and cardiac fibrosis, elevates cardiomyocyte proliferation and thereby extends lifespan,[220,221] highlighting the importance of developing senomorphics and senolytics for HF. Recently, owing to its senomorphic properties, such as altering the T cell pool to ameliorate SASP, digoxin has been suggested for repurposing as a geroprotector for patients with frailty and multimorbidity, including HF.[222] A short-term 2 week treatment with ABT263, a senolytic that inhibits BCL2, in 2-year-old mice before sacrifice cleared senescent cells and improved cardiac fibrosis and cardiomyocyte hypertrophy developed over 2 years of normal aging.[50] In an AngII infusion model, ABT263 treatment improves LVEF and prevents the accumulation of senescent cells, thereby limiting cardiac fibrosis, hypertrophy and inflammatory responses.[223] Dasatinib and quercetin (D + Q) combination exhibit senolytic properties. A single D + Q dose improves endothelial-dependent and -independent vasomotor function, reduces fibrosis and alleviates left ventricular systolic dysfunction in a 2-year-old mouse.[221,224] Quercetin alone may prevent cardiac fat accumulation and reduce high-fat diet (HFD)-induced cardiac fibrosis, systolic dysfunction, oxidative stress and hypertrophy,[225] the hallmarks of HF. Despite promising results, questions remain about the role of senescent cardiomyocytes within the myocardium, raising concerns about the potential impacts of senolytic-induced apoptosis on systolic function.[226] Therefore, long-term investigations are warranted to affirm sustained cardiac function improvements following senomorphic and senolytic treatment.

Antioxidants

Curtailing oxidative stress in CVDs is a promising approach; however, antioxidants like vitamin E have fallen short of expectations.[227] The limited efficacy may be due to ROS compartmentalization within mitochondria, a factor that predominantly influences the pathophysiology of HF and other cardiovascular disorders.[228] Consequently, there is a need for targeted approaches aimed specifically at mitigating mtROS. Mitoquinone (MitoQ), an antioxidant that selectively accumulates in the mitochondrial matrix to scavenge ROS, has demonstrated cardioprotective effects in animal models of pressure-overload-induced chronic HF.[229,230] While untested in HF patients, dietary supplementation with MitoQ improves endothelial function in healthy elderly individuals. Moreover, acute oral application benefits patients with peripheral artery disease by enhancing vasodilation and walking capacity.[231,232] Elamipretide, a peptide targeting mitochondrial cardiolipin, has improved cardiac function in rodent and canine models of chronic HF.[233,234] In humans, intravenous elamipretide in ST elevation myocardial infarction patients has demonstrated a lower new onset of congestive HF within 24 h after revascularization.[235] In a single-centre trial, a 4 h infusion of elamipretide to HF patients demonstrated a significant improvement in left ventricular function in a dose-dependent manner.[236] However, a subsequent multicentre trial with 4 weeks of subcutaneous elamipretide in stable HF patients has not displayed significant changes in left ventricular end-systolic volume or secondary outcomes.[237] Further clinical investigations are warranted to substantiate the use of MitoQ, elamipretide and other mitochondria-targeted therapies in HF patients.

Anti-inflammatory drugs

Restraining inflammation in chronic HF patients is a promising strategy; however, the development of targeted anti-inflammatory therapies in this context is still in its infancy. Preclinical data suggest that targeting IL-1β, a key pro-inflammatory cytokine, may exert cardioprotective effects by reducing inflammation and improving cardiac function in HF.[158] The CANTOS trial investigating canakinumab, an IL-1β inhibitor, in myocardial infarction patients with elevated C-reactive protein (CRP) has demonstrated a significant reduction in HF-related hospitalization and risk of mortality.[238] The DHART trial examining anakinra, an IL-1 blocker, in HF patients with elevated plasma CRP levels has illustrated a noteworthy reduction in the systemic inflammatory response and improved aerobic exercise capacity.[239] In contrast, the TNF-α receptor inhibitor etanercept has exhibited no discernible reduction in hospitalization or mortality among HF patients in the RENEWAL trial.[240] Furthermore, the TNF-α inhibitor infliximab has demonstrated an escalated risk of hospitalization and mortality in the ATTACH trial, particularly when administered at higher doses.[241] NF-κB regulates a multitude of genes downstream of TNF-α, which presents challenges in translating anti-TNF-α therapies into clinical benefits. Colchicine, an anti-inflammatory agent known for blocking NLRP3 inflammasome activation in gout, is now recognized as an anti-aging agent with potential cardiovascular benefits. Preclinical data suggest that colchicine improves exercise capacity and reduces cardiac diastolic dysfunction, oxidative stress and fibrosis in hypertensive HF mouse models.[242] However, a prospective, randomized study in stable chronic HF patients has showcased that colchicine treatment does not significantly impact functional status or the likelihood of death or hospitalization for HF, despite an effective reduction in inflammatory factors.[243] The ongoing COLpEF trial (NCT04857931) aims to investigate colchicine's efficacy in reducing inflammation and improving left ventricular diastolic function, functional status and symptoms in HF patients. Methotrexate, a key anti-rheumatic drug, exhibits cardiovascular benefits by limiting inflammation, atherosclerosis and vascular aging and is associated with lower HF risk in rheumatoid arthritis patients. It

alleviates endothelial dysfunction, arterial stiffness and hypertension,[244,245] suggesting repurposing for cardiovascular risk management in older adults.

Metabolic rejuvenators

Cellular NAD^+ is pivotal for regulating energy metabolism and managing oxidative stress. Age-related decline in NAD^+ is mirrored in failing human hearts.[246] As NAD^+ serves as a precursor for numerous enzymes, including SIRTs, which play integral roles in regulating cardiomyocyte survival and mitochondrial permeability through histone deacetylation, normalizing NAD^+ with nicotinamide riboside supplementation emerges as a promising approach to counteract cardiac aging and alleviate CVDs, including HF.[247] Administering 1000 mg of nicotinamide riboside twice daily to clinically stable HF patients is safe and well tolerated and approximately doubles the whole blood NAD^+ levels.[248] Notably, the HF-AF ENERGY trial is currently underway to explore the cardioprotective effects of nicotinamide riboside in HF patients.[249] In contrast to SIRTs, bromodomain and extraterminal domain (BET) proteins act as histone acetylation 'readers'. Selective inhibition of BETs by JQ1 reduces cardiac fibrosis, apoptosis and hypertrophy in a preclinical HF mouse model.[250] In principle, BET inhibition blocks NF-κB and TGF-β-mediated inflammatory and profibrotic gene networks,[251] suggesting a potential therapeutic avenue for protection against cardiac aging phenotypes and age-related chronic HF.

Resveratrol, a SIRT1 inducer, potentially alleviates oxidative and inflammatory stress, confers diverse anti-aging vascular effects, including reduced platelet aggregation and arterial stiffness, and provides protection against atherosclerosis, hypertension, ischaemia/reperfusion injury and chronic HF, ultimately contributing to an extended lifespan.[15] The beneficial effects of resveratrol in HF are attributed to eNOS and AMPK activation and endoplasmic reticulum calcium ATPase 2a expression.[252] Although resveratrol is well tolerated in humans, further investigations are required to affirm its cardioprotective effects in humans. SRT1720, a synthetic SIRT1 activator, improves endothelial function, reduces vascular oxidative stress and inflammation and inhibits atherogenic plaque formation, thereby exhibiting health and lifespan benefits in accelerated aging models.[253] Similarly, another SIRT1 regulator, S17834, demonstrates anti-inflammatory and anti-atherogenic effects in accelerated cardiovascular aging models,[254] warranting clinical evaluation of SIRT inducers in HF patients.

Autophagy enhancers

The age-related exhaustion of the autophagic response[81,82] suggests that interventions promoting autophagy could offer a promising avenue to counteract aging mechanisms in cardiac pathologies. Metformin, inducing autophagy through SIRT1 activation, reduces HF incidence and mortality in patients with CVDs.[255] Ongoing clinical trials (NCT05093959 for metformin and trial no. NCT04996719 for rapamycin) in HF patients will offer insights into the efficacy and safety of autophagy activation as a therapeutic strategy.[256] Furthermore, sodium-glucose cotransporter 2 (SGLT2) inhibitors, designed for diabetic glucose management, induce autophagy via AMPK/SIRT1 axis activation.[257] Earlier clinical trials with SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) in diabetic patients have demonstrated a reduced risk of cardiovascular mortality and HF-related hospitalization.[258–260] However, recent clinical trials suggest that SGLT2 inhibitors reduce the risk of CVDs, hospitalization for HF and cardiovascular and all-cause mortality in non-diabetic patients as well.[261,262] These findings underscore the potential of autophagy modulation and SIRT activation as a therapeutic strategy for age-related chronic HF.

Conclusion and perspectives

The rising global prevalence of HF in the aging population necessitates innovative therapeutic interventions. Systemic aging plays multifaceted roles in HF through cardiac, vascular, metabolic and inflammaging mechanisms, while age-related comorbidities exacerbate the scenario. Acknowledging this, lifestyle and dietary interventions emerge as crucial strategies to mitigate age-related processes. Exercise, in particular, holds promise for alleviating the aging burden on cardiac health and has unveiled potential targets.[263] As understanding of aging's role in chronic HF deepens, new candidates and therapeutic strategies are unveiled, anticipating clinical translation to modulate specific aging aspects in the HF population. Given the complexity of aging, a singular intervention may not entirely mitigate age-related cardiac phenotypes in HF. Investigating individual molecular signatures associated with cardiac aging may facilitate tailored therapies, promoting personalized and precision medicine.[264] In contrast to chronological age, the emerging concept of biological age, which is determined by assessing individual health status based on SASP and metabolite profile, could serve as a key factor in distinguishing between healthy and rapidly aging individuals, as well as identifying those with high CVD and HF risk.[265] Similarly, biomarker discovery may also help to identify high-risk individuals, optimizing therapeutic strategies based on molecular profiles.[266] Addressing age-related comorbidities and their contribution to HF onset and progression may also unveil shared targets, benefiting a broad population and reducing HF burden.[267] These strategies have the potential to alleviate age-related chronic HF features, ushering in a new era in HF management and extending to other CVDs.

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Conflict of interest statement

The authors declare no conflicts of interest.

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