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STATE OF THE ART REVIEW
Miscellaneous

Senescence-related myocardial dysfunction: keeping a young heart

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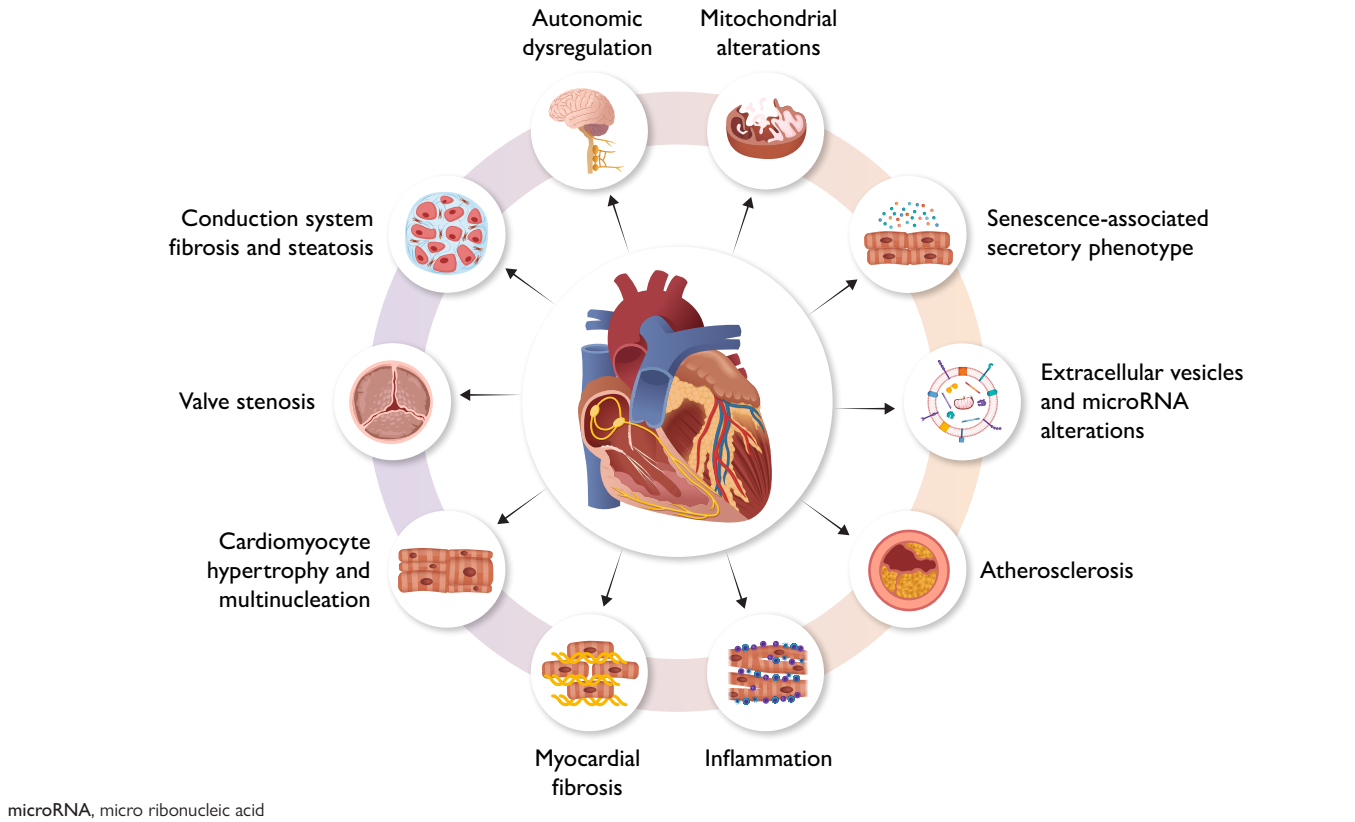
Graphical Abstract



microRNA, micro ribonucleic acid

Ajjan RA, *et al. European Heart Journal.*

The ageing heart undergoes progressive and substantial changes. Myocardial cells enter a senescence-associated secretory phenotype (SASP), associated with alterations in extracellular vesicles (EVs) containing microRNAs, creating an inflammatory environment. These molecular changes, combined with mitochondrial dysfunction, induce myocardial cell hypertrophy, multinucleation, and also result in altered responses to autonomic regulation. Alongside the stress of the continuous workload on the heart over a lifetime, there is a reduction in repair mechanisms, which coupled with fibrosis, steatosis, valve stenosis and compromised blood supply, due to atherosclerosis, ultimately lead to organ dysfunction, and myocardial ageing. Created in Biorender.

Abstract

The heart, a vital organ, works without interruption and constantly adjusts to the ever-changing demands on our body. It adapts to physiological and pathological changes, including exercise and emotional state, as well as metabolic, respiratory, and vascular abnormalities. The pumping action of the heart is determined by the health of the myocardium, which undergoes changes with ageing that are both under-investigated and incompletely understood, potentially impacting our approach to pathological conditions. Here, the alterations in cellular, tissue, and gross physiological function of the heart with age are discussed. At the molecular level, non-coding RNAs influence cellular senescence, and extracellular vesicles induce fibrosis through matrix remodelling. Mitochondrial dysfunction and altered fatty acid oxidation reduce cellular energetics, whilst accumulation of reactive oxygen species and steatosis, as well as telomere shortening coupled with reduced autophagy, limit the myocardium's regenerative capability. Loss of cardiomyocytes, combined with senescence, requires compensatory hypertrophy, inducing myocardial stiffness and altered muscle function. In addition to these direct alterations in myocardial characteristics with ageing, other factors that can affect the myocardium indirectly are addressed, including valve calcification, resulting in regurgitation and/or stenosis; vascular abnormalities, reducing compliance and exacerbating hypertension; fibrosis leading to cardiac arrhythmias; and autonomic dysregulation, reducing cardiac adaptability. Finally, potential modulation of cardiac ageing is discussed whilst also addressing which senescent modifications should be considered as

ageing-related physiological changes of the myocardium. A better understanding of myocardial ageing will differentiate physiological changes from early, preventable, and reversible pathological changes, consequently helping to optimize management of individuals with or at risk of myocardial disease by taking into account diverse trajectories of myocardial ageing.

Introduction

The adult human heart comprises 11 major cell types and contains 3–4 billion cells.[1] Over our lifetime, we generate ~3 billion heartbeats at a substantial energy requirement; turning over ~6 kg of ATP daily, 15–20-fold the heart's weight, supporting myofibrillar contraction, ion pumping, and other functional demands.[2]

The heart exhibits senescence as it ages. Cellular senescence is the irreversible arrest of the cell cycle and release of a senescence-associated secretory phenotype (SASP), including cytokines, proteases, and microRNAs (miRNAs), often associated with extracellular vesicles (EVs). Tissue senescence, defined as an ageing-related decline in the functional capacity or structure of a tissue,[3] follows cell loss and consequently results in morphological alterations, reduced regeneration, and fibrosis of the heart (*Graphical Abstract*); however, differentiating the effects of normal physiological ageing from co-existent pathology can be challenging. Ultimately, these processes may culminate in organ senescence, defined as an ageing-related decline in the functional capacity or structure of an organ.[3]

Health systems are encountering new challenges and opportunities in addressing the increasing prevalence of ageing-related cardiovascular conditions. Myocardial dysfunction is a critical contributor to morbidity and mortality in older populations, including both diastolic and systolic changes in cardiac function, valvular abnormalities, and alterations in the conduction system increasing the risk of arrhythmias.[3] Heart failure in individuals below 55 years is ~1%, increasing to >10% in those above 70 years,[4] with numbers rising as diagnostics improve. Ageing may lead to progressive cardiac dysfunction, but it may also imply increased susceptibility to pathological conditions as risk factors for cardiac dysfunction are more common with increasing age,[5] adding further complexity to understanding the effects of physiological age-related changes.

To improve clinical management of the older populations, there is a need for the systematic and comprehensive classification of ageing-related pathologies at metabolic, tissue, organ, and systemic levels.[6] To address this, the International Consortium to Classify Ageing-Related Pathologies (ICCARP) was established[7] and has recently defined the criteria for an ageing-related pathology[7] and reached an international consensus on senescence definitions.[8] A cardiovascular working group formed from ICCARP members, with broad expertise but a common cardiovascular interest, was formed to write this comprehensive review on age-related functional changes of the myocardium.

Ageing-related changes of cardiomyocytes, the cellular 'machines of contraction'

Morphological changes in cardiomyocytes. Cardiomyocytes constitute the majority of the atrial and ventricular volume but only comprise 30% and 50% of the cells in these tissues, respectively.[1] Catastrophic cardiomyocyte loss is associated with acute and chronic cardiac disease. However, the extent to which cardiomyocyte loss is a feature of normative ageing is relatively underexplored, partly related to the difficulties in separating ageing-related myocyte loss from the aggravated loss secondary to cardiac disease.[9] Left ventricular and septal mass decreases by ~0.5% per year, and given the exceptionally low cardiomyocyte loss with age, other changes must underpin the observed reduction in heart mass.[10,11] Even with extreme longevity, the number of human cardiomyocytes renewed over the life course is likely fewer than half of the perinatal population. Although this renewal rate decreases with age, cardiomyocyte numbers are largely constant across a CVD-free lifetime.[12] Whilst the mode of cardiomyocyte exchange in humans is not yet known, in mice new cardiomyocytes are generated predominantly by division of pre-existing cardiomyocytes[13] and not through transdifferentiation processes or *de novo* cardiomyocyte generation.[14] Following myocardial ischaemia, however, myocyte proliferation increases within and adjacent to the injury site in human and mouse hearts, and therefore the presence of pathology affects cardiomyocyte proliferation

A feature of human ageing is cardiomyocyte hypertrophy.[11] Senescent cardiomyocytes, with impaired contractile output, can accumulate in the ageing myocardium, and loss of 'functional cells' redistributes workload placing a greater contractile demand upon remaining cardiomyocytes, leading to hypertrophy.[15] Moreover, the long-term persistence of senescent cells disrupts tissue structure and function with deleterious paracrine, autocrine, and systemic effects in humans and animals,[16] remaining part of the tissue architecture but are functionally defunct.[17]

Human cardiomyocytes are normally polyploid, and increased polyploidization correlates with cardiomyocyte enlargement and variable cellular DNA content.[18] However, the relative proportions of mono and multinucleated cardiomyocytes can remain stable.[19] Whilst human ageing promotes cardiomyocyte hypertrophy, some pathological states associated with ageing have similar effects,[20] such as hypertension, making the distinction between physiological and pathological age-related changes challenging.

Importantly, time- and age-dependent changes in cardiomyocytes are often represented in linear relationship models. However, many studies lack adequate power to reveal complex non-linear behaviour, and age-linked dynamic processes are likely characterized by non-linear behaviour exhibiting thresholds or 'tipping points', which remains an area for active research.[21]

Molecular changes in cardiac ageing

DNA methylation is associated with cardiovascular ageing.[22] Cardiovascular risk factors, such as smoking and hyperhomocysteinaemia, interact with ageing, inducing dysregulated DNA methylation. The methylation status of CpG sites forms an epigenetic clock to measure human ageing rates. DNA methylation-based estimation correlates well with cardiovascular disease (CVD) incidence,[23] and dysregulation of epigenetic regulators in

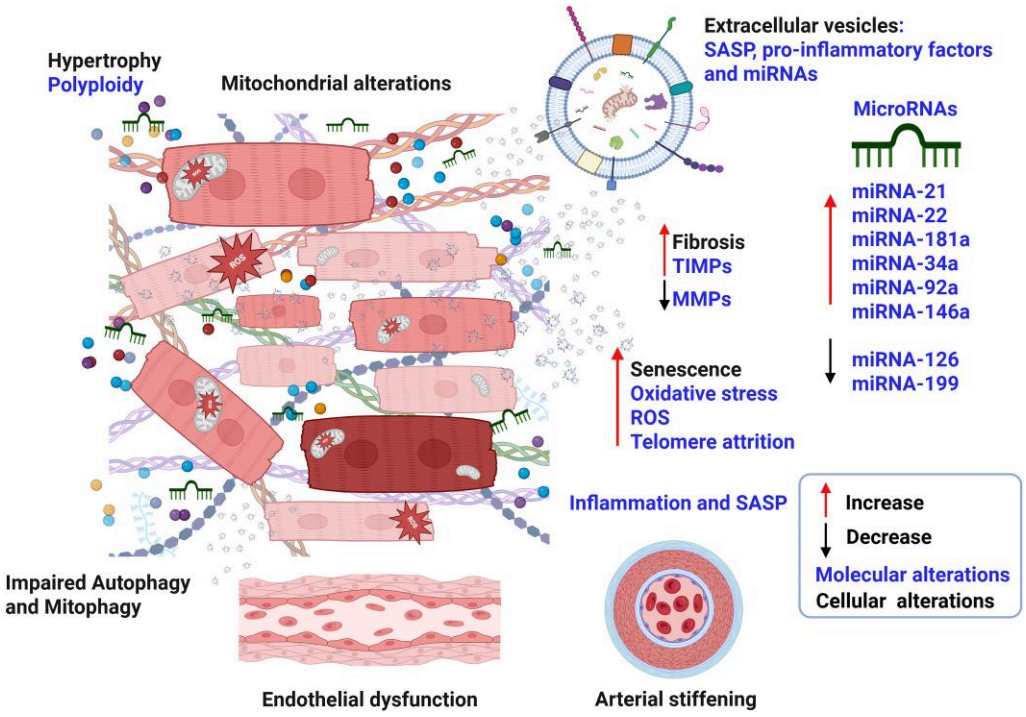


Figure 1 Ageing-related myocardial cellular and molecular alterations. Cellular changes occur with myocardial ageing, encompassing cardiomyocyte hypertrophy, cell senescence, mitochondrial alterations, impaired autophagy and mitophagy, increased fibrosis, and vascular alterations, including arterial stiffening and endothelial dysfunction. These cellular alterations are governed by molecular mechanisms involving increased senescence-associated secretory phenotype (SASP) and pro-inflammatory factors, up-regulation and down-regulation of different microRNAs, increased oxidative stress and reactive oxygen species (ROS), telomere attrition, polyploidy of cardiomyocytes, increased tissue inhibitors of metalloproteinases (TIMPs), and decreased matrix metalloproteinases (MMPs). Extracellular vesicles of myocardial cells release SASP and pro-inflammatory factors, and miRNAs. These molecular alterations directly and indirectly influence the cellular changes contributing to myocardial ageing. The up red and down black arrows indicate an increase or decrease, respectively. Created in Biorender.

histone modifications predisposes to cardiac ageing. Down-regulation of genes clustered in oxidative stress and gene transcription regulation is associated with epigenetic changes, including decreased H3K9ac, increased H3K9me3, and H3K27me3,[24] which are implicated in myocardial hypertrophy.

MicroRNAs are post-transcriptional regulators of gene expression that target specific mRNAs for promoting degradation or translational arrest, thus influencing inflammatory, fibrotic, and senescence pathways, with the first miRNA inhibitor currently trialled for heart failure.[25] Arterial stiffening, endothelial dysfunction, and increased oxidative stress are all pathological processes and part of normative ageing, controlled by miRNAs. For example, miR-21-5p, miRNA-22-3p, and miRNA-22-5p promote fibrosis and cardiovascular remodelling,[26,27] whilst miR-92a-3p, miR-146a-5p, and miR-126 are essential for maintaining endothelial integrity and function[28–30] and miRNA-34a regulates cardiac ageing and vascular senescence.[31,32] Cardiovascular-enriched miRNAs may act as minimally invasive biomarkers of age; e.g. circulating miR-146a-5p, miR-126-3p, miR-21-5p, and miR-181a-5p progressively increase with age, except in ultra-centenarians in whom levels are comparable to young individuals.[33]

The interaction of miRNAs with long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) adds further complexity to the regulation of cardiovascular ageing. CircRNAs sequester miRNAs, modulating their availability to target mRNAs. circRNA–miRNA–mRNA networks associated with ageing-related macular degeneration,[34] and lncRNA–miRNA–mRNA networks are also involved in age-associated CVD.[35] A summary of cardiomyocyte changes with ageing is provided in *Figure 1*.

Ageing-related alterations in myocardial energetics and metabolism

Myocardial energetics

In humans, myocardial energetic reserve declines with age,[36,37] through either a proportional depletion of both ATP and phosphocreatine (PCr) contents[36] or a fall in the phosphocreatine-to-ATP ratio (PCr/ATP).[37] The ageing-related decline in PCr/ATP occurs alongside reduced left ventricular mass and ejection fraction[37] and correlates with diastolic dysfunction. Lower PCr in the myocardium may result from impaired creatine kinase activity.[38]

Substrate metabolism

ATP requirements are met through oxidation of glucose, ketone bodies, lactate, and fatty acids.[39] Myocardial fatty acid oxidation

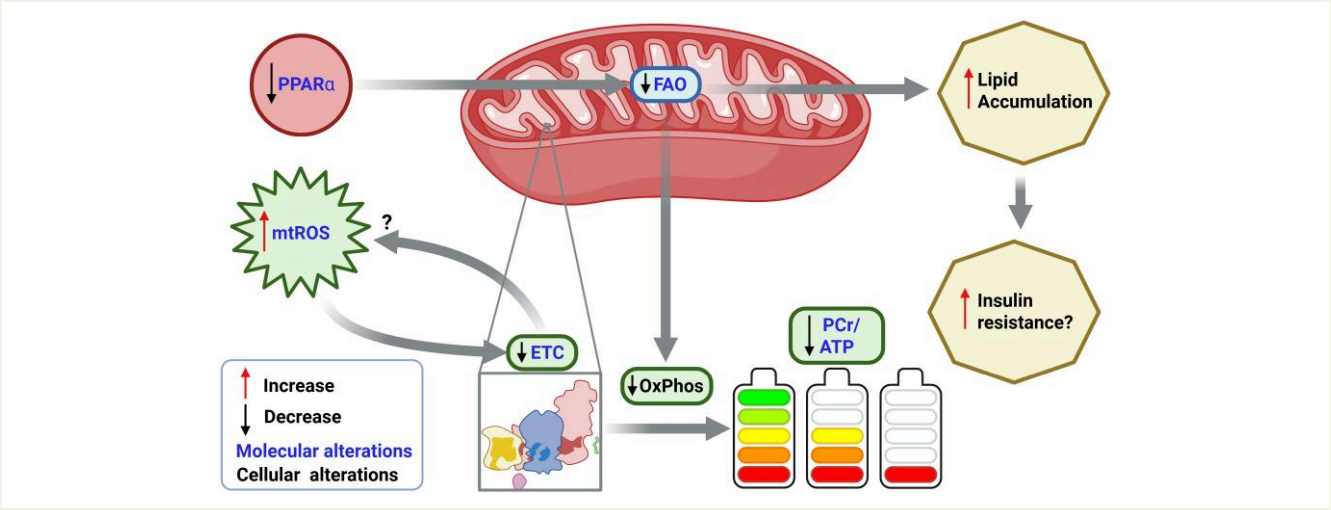


Figure 2 Mitochondrial and metabolic alterations in the ageing myocardium. Ageing is characterized by impaired myocardial energy reserve secondary to molecular alterations such as low phosphocreatine-to-ATP ratio (PCr/ATP) and suppressed electron transport chain (ETC) activity, as well as decreased capacity for fatty acid oxidation (FAO), leading to decreased oxidative phosphorylation (OxPhos). ETC impairments, including decreased supercomplex formation, may result from mitochondrial reactive oxygen species (mtROS) generation, whilst altered ETC function may further exacerbate mtROS generation. FAO capacity is suppressed downstream of peroxisome proliferator-activated receptor α (PPARα) expression, resulting in cellular changes such as myocardial lipid accumulation, which likely contributes to insulin resistance. The up red and down black arrows indicate an increase or decrease, respectively. Created in Biorender.

declines with age, suggesting increased reliance on glucose metabolism,[40] coupled with mitochondrial impairment.[41] Altered fatty acid oxidation may relate to ageing-related down-regulation of the fatty acid-activated transcription factor PPARα, and its downstream targets *Cpt1* and *HADH*, as well as lower HADH activity.[42] Mechanistically, cardiac-specific deletion of GCN5L1 (a mitochondrial acetyltransferase) restores fatty acid (and glucose) oxidation, consequently rescuing diastolic function.[43] Impaired fatty acid oxidation, increased circulating lipids, and myocardial fatty acid uptake can contribute to lipid accumulation in the aged myocardium.[44] This can cause metabolic and functional changes, including myocardial triacylglycerol accumulation, which correlates with ageing-related loss of diastolic function[45] and, in rodents, mitochondrial alterations.[46]

The plasma membrane fatty acid transporter CD36 is implicated in ageing-related steatosis[46] and myocardial lipotoxicity.[47] The accumulation of toxic lipid species may also occur with ageing[44] and is linked to altered nerve signalling[44] and increased myocardial insulin resistance.[48] In ageing populations, hearts exhibit impaired anaplerotic response to insulin stimulation,[41] and depletion of protein and mRNA of the insulin-responsive glucose transporter, GLUT-4[49] leads to impaired insulin-stimulated glucose uptake.[50] Insulin resistance and impaired myocardial glucose uptake provide additional challenges to cardiac substrate metabolism in later life, occurring secondary to and alongside suppressed fatty acid oxidation.[51]

Mitochondria

Ageing-associated mitochondrial impairments include lower tricarboxylate cycle enzyme activities,[52] diminished oxidative capacity,[53] and increased reactive oxygen species (ROS).[54] A population of cytochrome *c* oxidase [electron transport chain (ETC) complex IV]-deficient cardiomyocytes increases with advanced age.[55] Lower cellular respiration rates supported by substrates for Complexes III[56] and IV[57] are seen in the intermyofibrillar mitochondria (IFM) subpopulation, with the subsarcolemmal mitochondria (SSM) relatively unaffected.[57] Unexpectedly, enzyme activities of Complexes I, II, III, and IV are preserved in older human hearts,[58] highlighting that not all aspects of mitochondrial function decline with age. The discrepancy between these findings and reports of lower mitochondrial oxidative capacities can be explained by decreased assembly of mitochondrial supercomplexes in the aged heart,[59] compromising electron transfer, consequently resulting in functional impairment.

Role of oxidative stress

Markers of oxidative stress show age-dependent accumulation in the myocardium, including increased lipid peroxidation,[54,58] mitochondrial DNA (mtDNA) oxidation, and mutational load,[60] with increased mitochondrial biogenesis as a potential compensatory mechanism.[61] Whilst mitochondria are a source of ROS in the aged myocardium, they might also be susceptible to ROS-mediated dysfunction. Peroxidation of mitochondrial lipids can result in loss of cardiolipin,[62] a phospholipid important for mitochondrial dynamics.[63] This impairs the activity of cytochrome *c* oxidase,[62] whilst molecules that target cardiolipin enhance ETC respiratory function.[64] mtROS production might also increase the opening of the mitochondrial permeability transition pore (mtPTP) during ischaemia,[53] leading to mitochondrial swelling, functional impairment, and potentially apoptosis.

Increased mtPTP opening in response to Ca^{2+} overload can be mitigated by sirtuin-3 (SIRT3)-mediated deacetylation, preventing ageing-related cardiac hypertrophy,[65] suggesting that some ageing-related changes are reversible. A summary of myocardial energetics and metabolism changes is provided in *Figures 1 and 2*.

Loss of protection, inflammation, and cardiac ageing

Telomeres and cardiac ageing

Telomeres are repeated DNA sequences at the end of the chromosome, tasked with protecting DNA from degradation. Both premature and chronological ageing are associated with telomere shortening, which contributes to reduced regenerative capacity and heightened inflammation. Telomere shortening is associated with CVD pathology, making the independent contribution of ageing difficult to decouple. Importantly, interaction between different ageing-related changes can accelerate myocardial dysfunction; e.g. telomeric DNA sequences are more susceptible to DNA damage from oxidative stress, and thus ROS production augments telomere attrition.[66,67] In parallel, telomeric shortening induces mitochondrial reprogramming, resulting in functional alterations,[66] processes exacerbated by oxidative stress.[68]

Reduction in autophagy

The minimal replicative capacity of cardiomyocytes, coupled with a metabolically demanding redox-enriched intracellular environment, makes cardiomyocytes vulnerable to sustained damage. Autophagy, a cardioprotective mechanism, targets damaged proteins and organelles for lysosomal-mediated degradation, which is critical for maintaining myocardial baseline homeostasis and stress responses.[69] There is good evidence linking myocardial ageing with impaired autophagy and cardiomyocyte senescence,[69] including in progeria, a premature ageing syndrome.[70] In highly aerobic tissues like the heart, with its extensive mitochondrial networks, mitophagy (a specialized autophagy) preserves mitochondrial function and 'fitness',[71] although the exact role of mitophagy in ageing-related changes remains to be defined.

The role of immune cells

The immune system impacts cardiac development, composition, and function.[72] After myocardial injury, immune cells are recruited to remove dying heart tissue, scavenge pathogens, and promote healing.[72] However, immune cells can also cause irreversible damage, contributing to heart failure.[72] Ageing alters the relative proportions of cardiac leukocytes with increased monocyte-derived cardiac macrophages and CD8+ T cells.[73] Increased cardiac fibrosis with age can also be due to the modulation of macrophage fibrotic function (discussed below).

Haematopoietic stem cells can acquire mutations causing expansion of mutated clones (clonal haematopoiesis of indeterminate potential, CHIP), inducing inflammatory changes.[74] Such mutations predominantly occur in epigenetic regulators (such as DNMT3a or TET2) and adversely affect heart function.[74] Clonal haematopoiesis is enriched in patients with heart failure, increases with age, and predicts mortality.[75,76] This is partly due to the CHIP-induced inflammageing processes including up-regulation of pro-inflammatory genes, increasing cardiac leukocyte infiltration,[75] which contribute to cardiac dysfunction.[75,76]

Mice with heart failure and CHIP display enlarged hearts with increased fibrosis and reduced output.[75] In addition, CHIP contributes to atherosclerosis[75] and a thrombotic environment, [77] thus increasing coronary artery disease risk.[76] Ageing increases senescent cardiac progenitor cells producing pro-inflammatory SASP factors, which promote cellular senescence via paracrine mechanisms, reducing cardiac repair capability.[78] SASPs also recruit monocytes to the heart, which promotes further senescence in a vicious feed-forward loop.[79] Whilst the immune system changes with age, further studies are required to directly link inflammageing to cardiac ageing.

Extracellular vesicles and myocardial senescence

Exosomes are small EVs exocytosed from cells, surrounded by a lipid bilayer that facilitates intercellular communication by transferring bioactive molecules including RNA, DNA, and proteins. EVs are both mediators and markers of cellular dysfunction.[80] In mice and humans, senescent cardiomyocytes and endothelial cells release EVs enriched with pro-inflammatory and profibrotic factors, which contribute to myocardial remodelling, extracellular matrix (ECM) degradation, and propagation of senescence to neighbouring cells, exacerbating tissue dysfunction.[81]

EV-associated plasma miRNAs are linked to senescence and myocardial dysfunction and may be useful diagnostic markers. For example, patients with heart failure and preserved ejection fraction have EVs with specific miRNA signatures.[82] EVs from senescent endothelial cells, isolated from older human coronary arteries, carry calcification-promoting proteins and inflammatory mRNAs, contributing to vascular stiffness and ageing.[80,83]

EVs also hold promise as therapeutic agents given that progenitor cell-derived EVs demonstrate anti-inflammatory and anti-fibrotic effects *in vitro* and *ex vivo* on senescent human myocardial tissue.[84] Additionally, EV-based therapies to deliver anti-senescent molecules, such as siRNAs targeting SASP components, are under investigation. These strategies aim to mitigate the spread of senescence and restore cardiac function in ageing myocardium.

Cells within the myocardium and vasculature are intimately linked; in human and animal tissues, the release of EV by activated endothelial cells can affect myocardial function.[85] This opens a new avenue for managing cardiac dysfunction, an area under active investigation. *Figure 3* summarizes the potential role of EVs in cardiac ageing.

Additional factors contributing to cardiac ageing

Valvular and vascular abnormalities

Ageing is associated with valvular abnormalities, including stenosis and regurgitation.[86] For example, aortic stenosis affects 2%–7% of individuals >65 years of age[87] and predisposes to heart failure. Vascular abnormalities also increase with age due to reduced elastin, increased collagen and calcification,

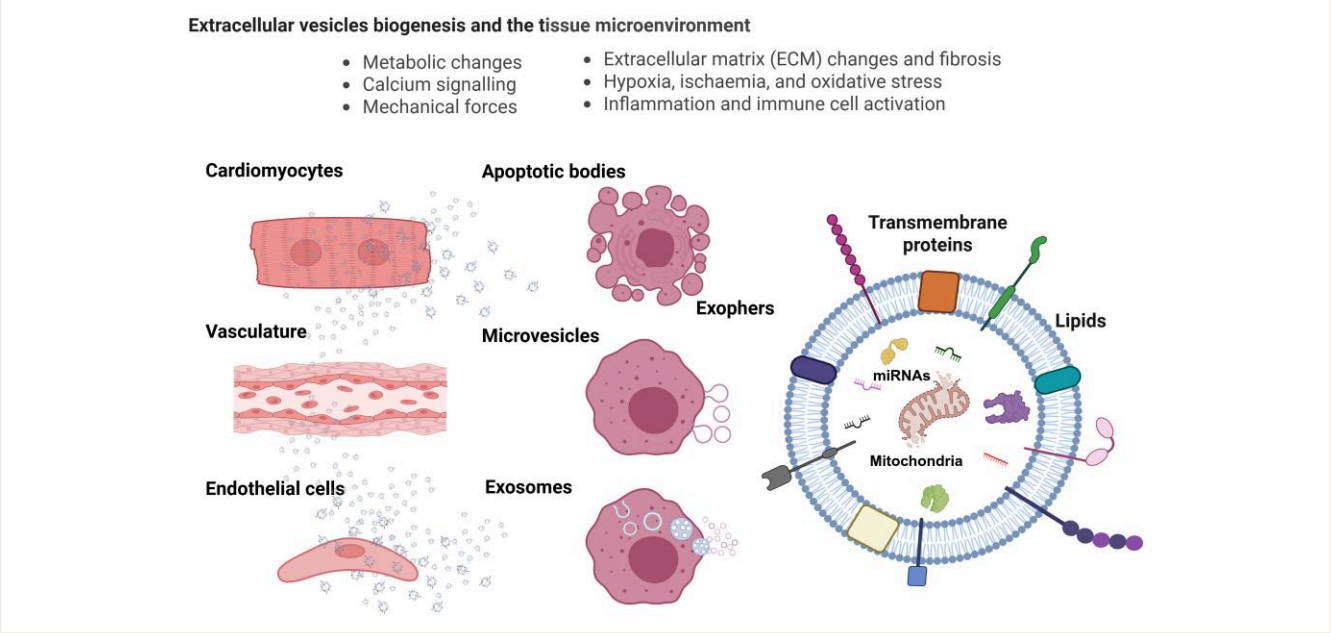


Figure 3 Extracellular vesicle (EV) biogenesis and its role in vascular and myocardial ageing. Cardiomyocytes, endothelial cells, and vascular cells release extracellular vesicles secondary to alterations in tissue microenvironment, including metabolic changes, mechanical forces, calcium signalling, extracellular matrix changes and fibrosis, hypoxia and ischaemia, inflammation and immune cell activation, and oxidative stress. EVs include exosomes, microvesicles, apoptotic bodies, exophers, and exomeres, which carry bioactive molecules such as transmembrane proteins, lipids, mitochondria, and non-coding RNAs (e.g. miRNAs). Created in Biorender.

thus narrowing the vessels and increasing stiffness,[88] consequently leading to hypertension and compromising cardiac function.[89]

Cardiac perfusion

Vascular changes with age reduce coronary blood flow,[90] increasing the risk of myocardial ischaemia.[91] Moreover, microvascular rarefaction contributes to reduced coronary flow through reduced angiogenesis, and increased apoptosis resulting in diminished nitric oxide bioavailability and increased inflammation.[92–95] Additionally, age-related decreases in vascular and platelet-derived growth factors reduce vascular repair and maturation of endothelial cells.[92,93,95] Senescent endothelial cells and pericytes contribute to apoptosis whilst inhibiting angiogenesis.[92,94] In addition, pericyte coverage is reduced, and the crosstalk with neighbouring cells is weakened in aged hearts, resulting in depressed pro-angiogenic activity, pro-fibrotic commitment, and loss of ribosome biogenesis.[96] These defects contribute to vascular fragility, loss of microvascular barrier integrity, and increased severity of ischaemic injury. Several pathways central to vessel formation, such as hypoxia-inducible factor (HIF)-1α, peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, and endothelial nitric oxide synthase (eNOS), interact with ageing-related mechanisms.[97] Nucleolar proteins play critical roles in lifespan extension and DNA repair, regulate cellular plasticity in cardiomyocytes, and protect against ischaemia-induced damage, explaining why rescuing nuclear proteins reactivates angiogenesis in the ageing heart.[96]

Cardiac fibrosis

In preclinical models of ageing, soluble collagen rises, whilst insoluble collagen falls,[98] increasing net intracardiac collagen.[99] In humans, endomysial and perimysial collagen types I and III increase in aged hearts.[100] Conversely, tissue inhibitors of metalloproteinases (TIMPs) are reduced,[99] whilst matrix metalloproteinases (MMPs), collagen type I and III, and Lylsyl oxidase are all up-regulated in cardiac remodelling.[101,102] SMAD2/3/4 [proteins involved in cardiac remodelling via extracellular matrix (ECM) gene expression] are altered with age.[102] Importantly, miRNA profiling shows miR-1468-3p is elevated in aged cardiac fibrosis patients,[103] which can result in arrhythmias,[104,105] whilst also predisposing to heart failure.[106] Late gadolinium-enhanced cardiac magnetic resonance imaging can be used to assess myocardial scarring and is a predictor of mortality, particularly in individuals with non-ischaemic dilated cardiomyopathy.[107] Cardiac fibroblast proliferation is dependent on extracellular matrix stiffness, which modulates NF-YA protein levels, altering the mechanosensitive transcription factors pathways,[108] whilst calcium handling plays an important role in fibroblast proliferation and myocardial fibrosis.[109] Finally, β-adrenergic receptors regulate fibroblast proliferation, suggesting a role for the autonomic nervous system in myocardial fibrosis.[110]

The conducting system and autonomic innervation

Cardiac innervation changes with age, with maximal heart rate the most significantly affected,[111] in contrast to mean heart rate which shows minor changes,[112] and resting pulse rate

that remains consistent.[113] Changes in maximal and mean heart rate were thought to be due to fibrosis and subsequent atrophy of the sinoatrial node (SAN).[114] Lipids begin infiltrating the SAN around age 30, collagen and elastic tissue equal muscle tissue by age 40, and the node is delineated by fat and elastic fibres at age 50.[115] By age 75, the remodelling of the node is so pronounced that the muscular distribution in the sinoatrial node shows almost no overlap with younger hearts.[116]

Similar changes are found throughout the conducting system, atrioventricular (AV) node, the bundle of His, and the beginning of the right and left branches,[117] without any ageing-related calcification or inflammation.[115] Diseases of conduction, such as AV block, are not usually associated with fibrosis of the conduction pathway unless myocardial ischaemia impacts the nodes. Normal sinus rhythm occurs even with most fibrotic sinoatrial nodes[118] and heart block is only seen in the most severe fibrotic lesions of the AV node.[118] It is now evident that fibrosis provides structural integrity by forming a scaffold, with fatty depositions and blood vessels, providing electrical insulation.[119] Therefore, fibrosis of the conducting system is not, as previously thought, a disease of ageing but instead is essential for normative ageing.

Autonomic innervation contributes to inotropic, dromotropic, and chronotropic properties of the heart. Parasympathetic (acetylcholinergic) and sympathetic (noradrenergic) neurons decrease with age,[120] accompanied by loss of dopamine-β-hydroxylase neurons, which support sympathetic activity.[120] Whilst sympathetic nerves are decreased, sympathetic nerve activity reciprocally increases with age.[121] The increased neurotransmitter release is met by ageing-related β-adrenergic desensitization.[122,123] Coupling increased noradrenaline release with age-associated reductions in its transporter density and activity,[124] causing a higher rate of noradrenaline spillover from the heart to the plasma,[125] although whether this is global or occurs in specific areas of the heart remains controversial.[126–128] Conversely, parasympathetic drive decreases with age,[129] reducing heart rate variability.[130] In animal models, ageing-associated cardiac denervation can be diminished by senolytic therapy, suggesting this is a reversible process.[131]

The aforementioned loss of parasympathetic tone, accompanied by increased sympathetic tone, contributes to age-related hypertension.[132–134] In conjunction, fibrosis of heart chamber walls and hypertrophy increase stiffness,[135] predisposing to ventricular and atrial arrhythmias.[136,137] The combination of the above processes predisposes to heart failure and cardiac arrhythmias, frequently encountered in the older population.[134,138] The effects of non-myocardial cell changes on cardiac ageing are summarized in *Figure 4*.

Biomarkers or cardiovascular ageing

N-terminal pro-B-type natriuretic peptide is released by the heart under excessive strain and is an established biomarker of myocardial health.[139] However, due to its large overall inter-individual variability with older age, it would not appear to be a useful marker of normative ageing.[140] As such, NT-proBNP appears to better signal the presence of cardiovascular disease, rather than changes seen in ageing *per se*.[141] This is a common feature of biomarkers of cardiac ageing, such as troponin, which

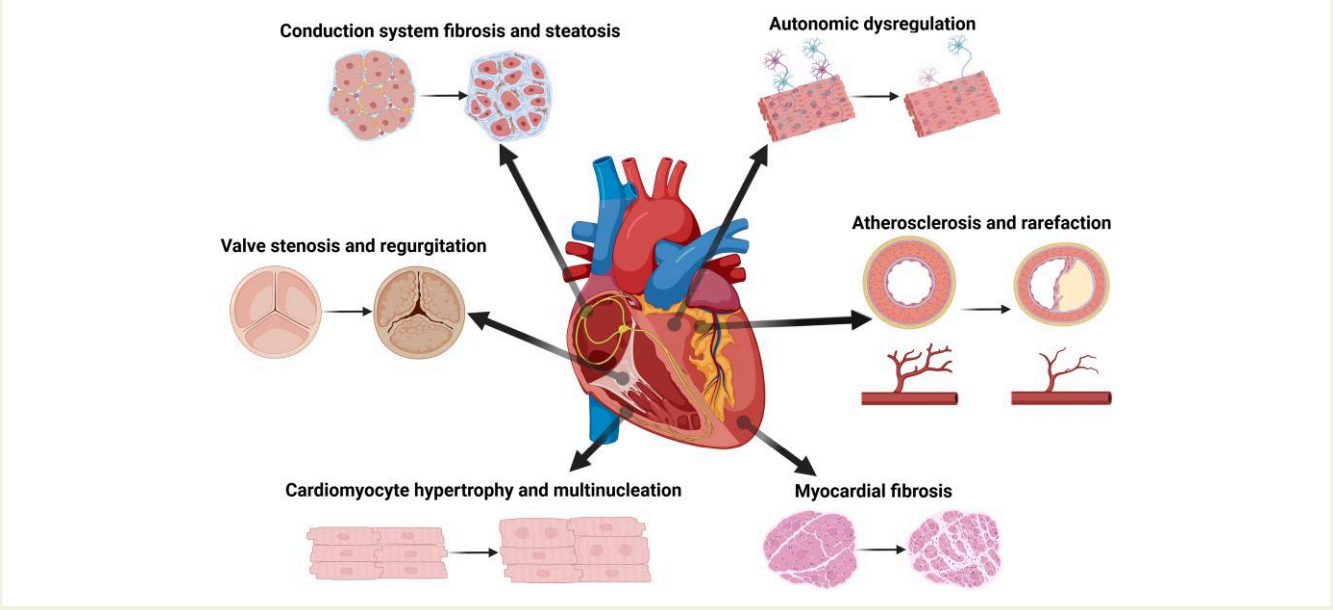


Figure 4 Physical changes within the myocardium and associated structures. The conducting tissue undergoes lipid infiltration and fibroblast activation, leading to fibrosis and steatosis. The alterations in the conducting system are accompanied by autonomic dysregulation, with a decrease in sympathetic and parasympathetic innervation accompanied by sympathetic overdrive that is compensated for by adrenergic desensitization. In contrast, parasympathetic drive decreases with age, which reduces heart rate variability and may contribute to cellular senescence. Altered collagen and elastin in coronary arteries, coupled with calcification, alter function and induce microvascular rarefaction. Similar mechanisms in the heart valves result in stenosis. Cellular loss and senescence are accompanied by compensatory hypertrophy and remodelling of the myocardium, including increased fibrosis. Created in Biorender.

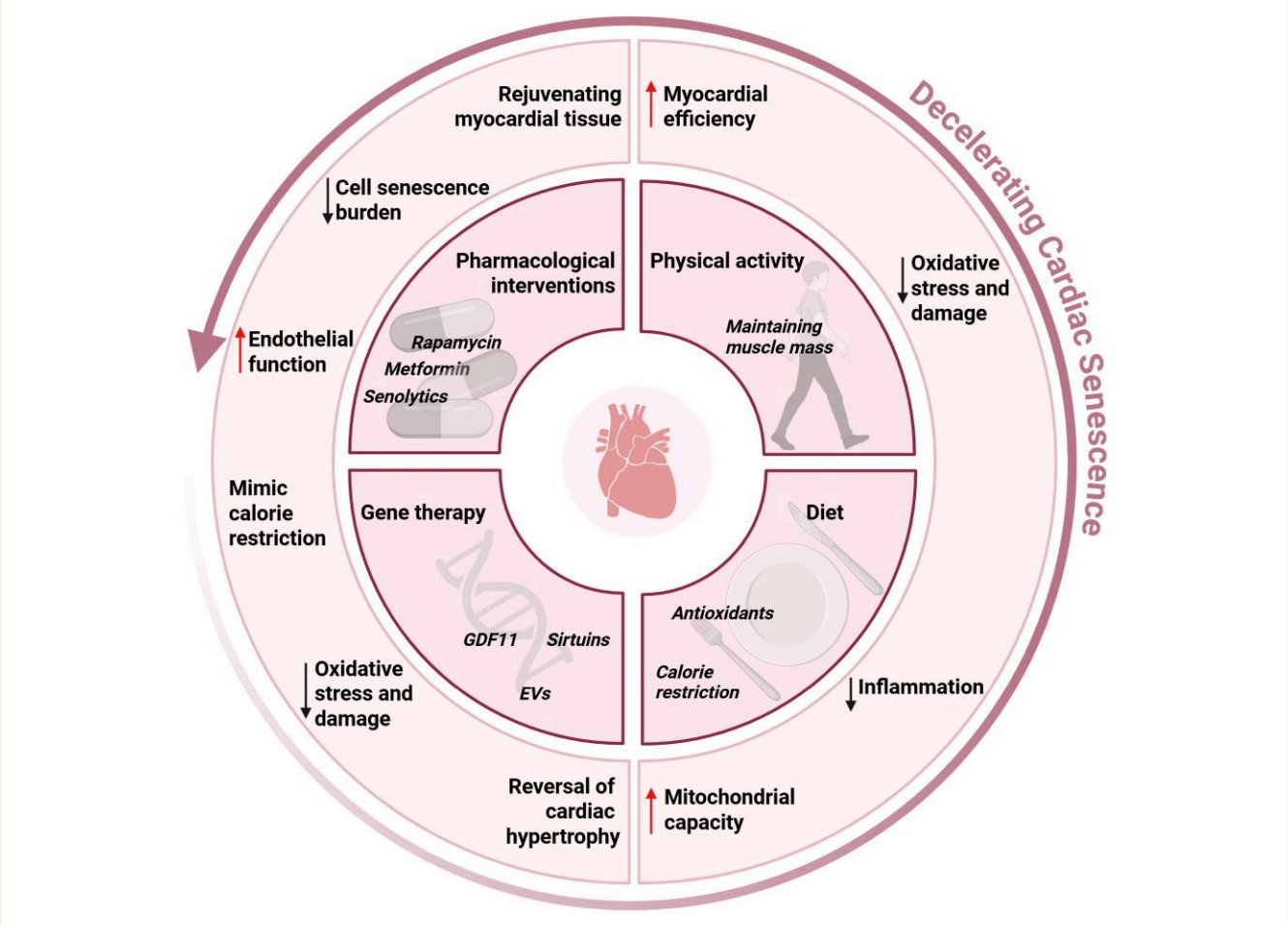


Figure 5 Prevention of ageing-related cardiac senescence. Regular moderate physical activity and a balanced diet, rich in antioxidants and low in calories, can mitigate oxidative stress and inflammation whilst improving mitochondrial capacity, myocardial efficiency, and muscle mass, thus promoting myocardial health. Pharmacological intervention strategies, such as rapamycin, metformin, and senolytics, as well as gene therapies [sirtuins, extracellular vesicles (EVs), and growth differentiation factor 11 (GDF11)], have demonstrated early effectiveness in reducing cell senescence and oxidative damage. These therapies are also associated with improved endothelial function, restoring myocardial tissue, and aiding the reversal of cardiac hypertrophy. The up and down arrows indicate an increase or decrease, respectively. Created in Biorender.

also increase with age but are mainly related to the association with myocardial pathology.[141]

A gene expression-based age monitoring clock (GamC) has been created for cardiovascular health, comprising three key genes (*ABLIM1*, *CCR7*, and *LEF1*) involved in muscle contraction, immune function, cardiac repair, and response to injury.[142] GamC shows a positive correlation with chronological age, with variation decreasing as age increases, but fails to correlate with markers of autonomic function, casting doubts over its relevance as a reliable measure of biological ageing.[142]

Prevention of ageing-related changes

Regular physical activity and a balanced diet mitigate ageing-related cardiac decline and support cardiovascular health by improving myocardial metabolism[42] and reducing oxidative stress.[143] A diet rich in antioxidants and anti-inflammatory components may further support cardiac function by combating oxidative damage and inflammation.[144] Calorie restriction (CR), defined as a sustained reduction in caloric intake without malnutrition, may attenuate age-associated structural and functional changes in the myocardium by enhancing mitochondrial function, reducing oxidative stress, and modulating metabolic pathways.[145,146] However, hard evidence that such a dietary approach improves myocardial health or increases longevity is lacking.

Gene therapy offers innovative approaches to counteract myocardial ageing. For instance, overexpression of the gene encoding growth differentiation factor 11 reverses ageing-related cardiac hypertrophy and improves cardiac function in animal models.[147] Intravenous injection of small EVs from young mice mitigates cardiac ageing by reducing cellular senescence.[148] Furthermore, therapies that enhance the expression of sirtuins, a family of proteins involved in cellular regulation, are under exploration for their potential to mimic the effects of calorie restriction.[149]

Myosin heavy chain (MHC) proteins in cardiomyocytes are differentially modulated during ageing.[150,151] Although the adult heart primarily contains the β-MHC isoform, a significant amount of α-MHC, which is more efficient, is present in neonatal hearts and can be reactivated by antiaging gene therapy.[96,152] Administration of a polymorphic gene variant associated with extreme longevity or its encoded protein improves capillary density and perfusion, reduces fibrosis, and reverses diastolic dysfunction associated with ageing.[153,154] Potential strategies to prevent cardiac ageing are summarized in *Figure 5*.

Effects of senolytics on cardiac disorders

Navitoclax

In aged mice, navitoclax ameliorates left ventricular mass loss by decreasing myocyte hypertrophy and senescence whilst reducing cardiac fibrosis, consequently improving cardiac function.[155–157] Moreover, this agent rejuvenates the vasculature by reducing stiffness and improving endothelial dysfunction.[157,158] Navitoclax reduces mortality by improving ejection fraction following myocardial infarction in aged mice but not in ageing alone.[156,158,159] Whilst navitoclax reduces senescence markers in primates and is well tolerated,[160] clinical uses may be limited as it increases endothelial-to-mesenchymal transition in advanced atherosclerotic lesions and raises mortality in some animal studies.[155]

Dasatinib and quercetin (D + Q)

Quercetin monotherapy is unable to improve cardiac function or longevity in aged mice but can reduce mortality following hypoxic cardiac damage.[161,162] In rodents, this agent is useful as a preventative measure where cardiovascular risk is high, such as sepsis and diabetes.[161,162] Quercetin is often used intermittently in conjunction with dasatinib; monotherapy with the latter agent is avoided due to adverse effects in heart failure patients.[160,162] D + Q induces apoptosis in senescent cells, decreasing SASP, whilst promoting cardiomyocyte production from progenitor cells, enhancing cardiac regenerative capacity and reversing ageing.[78,160,162] Concurrently, D + Q reduces fibrosis, recovering cardiac function and preserving electrical stability, consequently improving survival in aged rodents.[155,157,160,162] In high cardiovascular risk animals, such as obese mice, D + Q reduces senescent cells, improves insulin sensitivity, and enhances cardiac function.[158] Even a single dose of D + Q improves cardiovascular function, boosts health, and increases rodent survival.[162,163] Their positive effects in cell line models of human age-related cardiomyopathy, including organoid models, promise future clinical potential.[158,162,164]

Other senylotics and senomorphics

Hesperidin and hesperetin display senomorphic effects diminishing SASP levels and enhancing antioxidant enzymes to protect aged rat hearts.[161] In models of ischaemia–reperfusion injury, kaempferol, apigenin, baicalin, fisetin, naringenin, and luteolin all protected cardiomyocytes by ameliorating mitochondrial dysfunction and ROS production, attenuating myocardial apoptosis and fibrosis, thus restoring cardiac function.[161] Spermidine induces autophagy in hearts and vessels, delaying cardiac and vascular ageing and extending lifespan in mice, whilst also improving function in animal models with different cardiovascular pathologies.[157] In elderly people, spermidine may lower the risk of cardiovascular disease and mortality,[157] although definitive trials are needed. Canagliflozin and dapagliflozin counteract myocyte senescence in a model of diabetic cardiomyopathy,[160] which may underlie their beneficial effects in heart failure.

In aged mice, senolytic and senomorphic agents acting on endothelial cells (anthocyanins), vascular smooth muscle cells (rutin)[161] or both (fiestin, naringenin, apigen) have been tested.[155,157,160,161] Fisetin ameliorates atherosclerosis in murine models of the disease, as does rutin in diabetic mice.[161] Luteolin decreases vascular inflammation in mice and in human cell lines[161] but human *in vivo* studies are lacking.

mTOR inhibitors

Rapamycin and its analogues demonstrate cardiac benefits in aged rodents with and without cardiomyopathies.[155,160] However, these benefits are not necessarily translatable to humans,[161] and therefore results from animal studies should be interpreted with caution.[160] Metformin, a widely used agent clinically, suppresses SASP expression, vascular inflammation, and mitochondrial ROS generation in preclinical models of ageing[155] and ameliorates endothelial dysfunction, arterial stiffness, and left ventricular hypertrophy.[155] Whilst observational studies suggest a cardiovascular benefit for metformin,[155,160,165] robust data from randomized controlled trials are lacking.

Cardiovascular inflammageing

Inflammageing is age-related persistent low-grade inflammation that adversely impacts ageing, morbidity, and mortality. Immune ageing impedes the resolution of inflammatory processes, perpetuating inflammation.[166] At the organ level, inflammageing is more complex, consisting of three interrelated processes: chronic inflammation, cellular senescence, and maladaptive tissue remodelling.[167]

Chronic inflammation, including various pro-inflammatory mediators, drives cellular senescence, tissue damage, and irreversible remodelling.[166,167] In the heart, macrophage-mediated signalling and altered ECM degradation promote fibrosis through up-regulation of MMPs, NF-κB, and activation of the NLRP3 inflammasome.[167] Oxidative stress and subsequent mitochondrial dysfunction promote the release of mtDNA, stimulating damage-associated molecular pattern secretion, further activating the NLRP3 inflammasome.[166,167] Inflammation drives oxidative stress and mitochondrial dysfunction,[166] promoting cellular senescence. Interestingly, deficiency in mitochondrial transcription factor A in T cells alone replicates inflammageing and accelerates senescence.[139] SASP cells modify the local tissue environment by secreting pro-inflammatory cytokines, impairing stem cells through activin A secretion, and exacerbating fibrosis through fibroblast activation.[167] Maladaptive tissue remodelling increases cellular senescence by suppressing p53, Rb1, and Meis2 and initiating inflammatory processes through matrikines, further driving fibrosis and reducing contractility. In the coronary vasculature, these processes induce atherosclerosis and in heart valves can result in fibrosis and calcification.[166,167] Age-related decline in 5′ AMP-activated protein kinase and sirtuins (which

ameliorate inflammatory gene expression, DNA damage, and mitochondrial dysfunction) further potentiates inflammageing.[167]

The myocardium, where pathology meets physiology

Whilst one would predict that any form of ageing-related senescence in an organ would be classified as an ageing-related pathology, in the heart, the process is more complicated and nuanced. The loss or cell arrest of cardiomyocytes and hypertrophy of valvular cells are classical examples of ageing-related pathologies that fulfil the three criteria defined by the ICCARP,[7] as they (i) develop and progress with increasing chronological age; (ii) are associated with, and contribute to, functional decline and an increased susceptibility to functional decline; and (iii) are evidenced by studies in humans.

Whilst some ageing-related alterations may cause concerns, some of these changes are not necessarily detrimental. For example, cardiomyocyte hypertrophy may be regarded as problematic, but cardiomyocyte loss, or senescence, without reciprocal hypertrophy would lead to a significant reduction in heart volume and loss of structural integrity, compromising pump function. Therefore, hypertrophy can be a compensatory protective mechanism that does not comply with the second criterion above. Cardiac fibrosis and steatosis must also be considered carefully, as they are not always inherently detrimental. We recognize that myocardial fibrosis and lipid infiltration may contribute to a decline in cardiac function and risk of arrhythmias. However, in the absence of overt disease or injury, fibrosis and steatosis of the conduction pathway are required to ensure appropriate pacing of the adult heart by providing increased insulation and structural stability to this tissue.

The understanding that certain changes within the myocardium, which have always been seen as pathological (e.g. hypertrophy and fibrosis), may constitute, under specific circumstances, protective mechanisms or be required for normal function in the heart has only just begun to emerge. This new discovery has significant implications for future myocardial disease treatment, where apparently similar processes are both pathological and pseudophysiological.

Conclusion: clinical implications of cardiac ageing

Disentangling physiological myocardial ageing processes from pathology, encountered in older populations, is key to understanding the impact of age on heart health. It can be argued that changes associated with cardiac ageing, which negatively impact function, do not practically differ from pathological dysfunction as both impact a patient's capacity to perform daily tasks. Furthermore, cardiac ageing may compromise the ability of the organ to adapt to pathological conditions, worsening symptom severity, and adding another dimension to the adverse role of cardiac ageing.

To simplify a rather complicated area, one option is to classify myocardial changes with ageing into those that are adaptive and have neutral/protective effects on cardiac function and those that negatively impact the function of the myocardium, regardless of whether there is an associated pathological condition. Examples of adaptive changes include compensatory hypertrophy of myocytes, which can be regarded as protective as it helps to maintain cardiac volume in response to myocyte loss and gradual atrophy. However, pathological conditions commonly occurring in the elderly, such as hypertension, can cause myocyte hypertrophy, which is usually associated with cardiac enlargement. Another example is the age-related fibrotic changes around the conducting system, which preserve function and prevent arrhythmias. In contrast, fibrosis in the cardiac chambers can result in impaired myocardial relaxation/contraction and can predispose to arrhythmias. Therefore, it is not only the type of change but also the site and context that decide whether age-related alterations result in unwanted functional symptoms. These compensatory changes represent potentially important clinical challenges: e.g. could treating the valvular hypertrophy that underlies stenosis worsen cardiac function if it also removes the myocardial hypertrophy that acts to lessen the effect of myocardial cell loss? Likewise, treating myocardial fibrosis to prevent arrhythmias from re-entry loops could lead to even more inappropriate pacing of the heart if it disrupts the essential fibrosis of the conducting system.

A better understanding of myocardial changes with ageing has the potential to help with the clinical management of older people at a number of levels. First, elucidating the exact relationships between age-related changes and cardiac function will ensure appropriate management strategies for older people by avoiding the start of therapies when structural changes are detected that are protective or have no functional effects. Second, understanding the mechanisms for cardiac ageing, particularly those that cause functional myocardial decline, can help devise early and simple preventative strategies, thus improving longer-term outcomes. Third, elucidating the additive, or even synergistic, effects of myocardial ageing on an existing cardiac pathology will ensure that treatment modalities are both personalized and optimized. Finally, developing a new generation of therapies that specifically target cardiac ageing, such as senolytic therapies, will help to normalize myocardial function with ageing, thus improving the general well-being of older people and increasing productivity of the society.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

Nothing to declare.

Although they have nothing to declare with regard to this review, for transparency, A.A.S.T. declares submission of two patent applications (PCT/EP2019/066546 and PG450503GB/YR), one of which is currently being explored with Life Molecular Imaging. A.A.S.T. has an active collaboration with Unilever. A.J.M. declares a paid consultancy role with Rivus Pharmaceuticals. J.B. received honoraria for lectures/consulting from Novartis, Abbott, Bayer, Pfizer, Boehringer Ingelheim, AstraZeneca, Cardior, CVRx, BMS, Amgen, Edwards, Roche,

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Data Availability

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