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Pharmacy and Exercise as Complimentary Partners for Successful Cardiovascular Ageing

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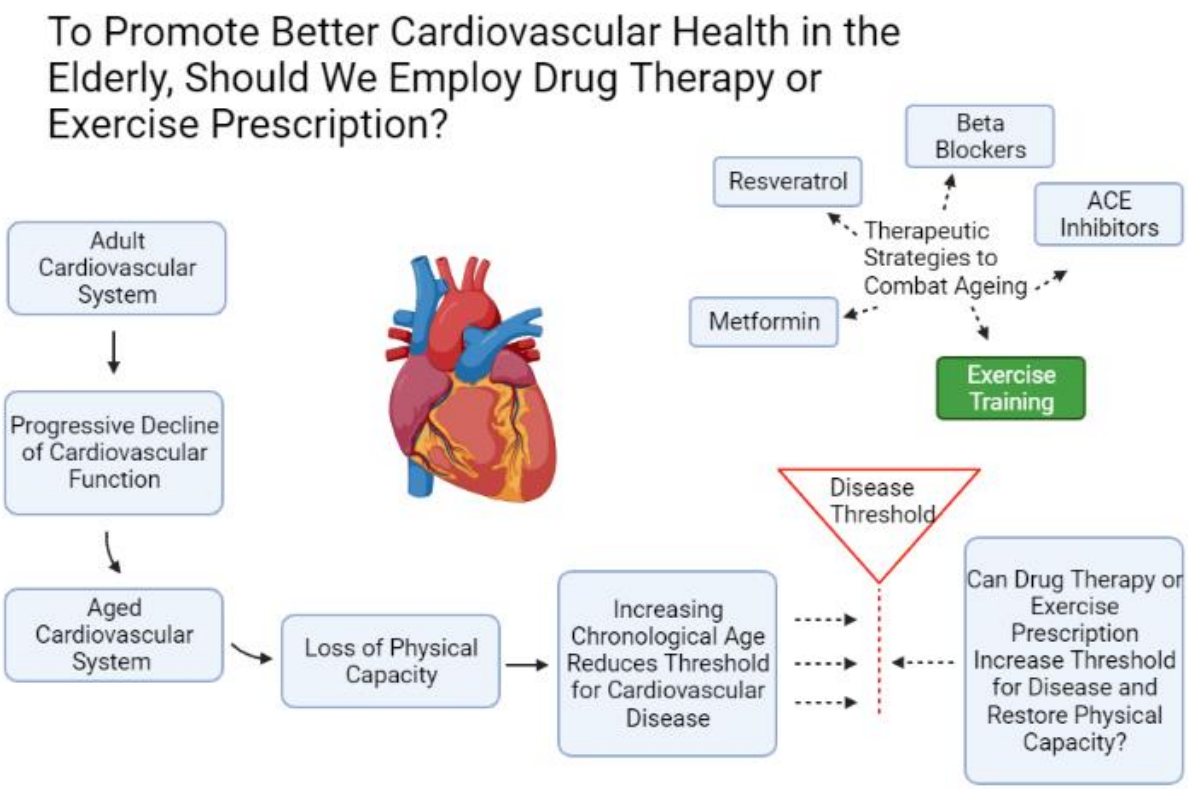
Graphical Abstract



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Abstract

Diseases of the cardiovascular system have been the biggest cause of mortality for the majority of the last century, currently contributing to almost a third of deaths every year globally. Ageing associates with changes to the structure and function of the heart and vascular system that progressively increase the incidence of abnormalities, morbidity, and cardiovascular disease. The burden of ageing and its relationship to cardiovascular disease risk highlights the need for more research into the underlying mechanisms involved and how they may be treated and/or prevented. Factors influencing adrenergic dysfunction may explain a significant part of the age-related deterioration in health and responsiveness of the cardiovascular system. Increased sympathetic activity in old age overstimulates adrenergic receptors and causes detrimental changes within the associated signalling mechanisms including a reduction in receptor number and downstream effector efficiency. Pharmacological agents such as metformin, resveratrol, beta-blockers, and angiotensin converting enzyme (ACE) inhibitors have been identified as potential anti-ageing therapies with cardiovascular effects, which may be beneficial in treating the decline in cardiovascular function with old age. Regular exercise has also shown promise in the prevention and treatment of harmful age-related effects on the cardiovascular system. This review will investigate age-associated vascular and cardiac remodelling, and the link between adrenergic dysfunction and vascular and cardiac control. This review will also consider whether pharmacological or non-pharmacological therapies are most effective, or indeed complimentary to potentially optimise ageing of the cardiovascular system and improve quality of life in the elderly.

Keywords

Ageing, Anti-Ageing, Adrenergic Receptor Signalling, Cardiovascular Remodelling, Vascular Health, Exercise Training.

Article Highlights

- Progressive reductions in vascular and cardiac function are observed during ageing.
- Adrenergic dysfunction in the control of both the heart and vasculature in old age is a key mechanism in the age-related loss of physical capacity.
- To reduce the detrimental effects of an aged cardiovascular system, potential anti-ageing pharmacological therapies are compared with exercise training.
- Exercise training may reverse detrimental age-related remodelling, particularly in the context of adrenergic control, and may be complimentary or superior to pharmacological therapies.

Abbreviations

αAR: Alpha Adrenergic Receptor

α_1AR: Alpha-1 Adrenergic Receptor

α_2AR: Alpha-2 Adrenergic Receptor

AC: Adenylyl Cyclase

ACE: Angiotensin Converting Enzyme

ADP: Adenosine Di-Phosphate

AMPK: 5’ Adenosine Monophosphate Activated Protein Kinase

ANS: Autonomic Nervous System

AP: Action Potential

ATP: Adenosine Tri-Phosphate

β: Beta

βAR: Beta Adrenergic Receptor

β_1AR: Beta-1 Adrenergic Receptor

β_2AR: Beta-2 Adrenergic Receptor

BP: Blood Pressure

Ca^{2+}: Calcium

CAD: Coronary Artery Disease

CaMK: Ca^{2+}/Calmodulin-Dependent Protein Kinase

cAMP: Cyclic Adenosine ‘3, ‘5 Monophosphate

CO: Cardiac Output

CVD: Cardiovascular Disease

DNA: Deoxyribonucleic Acid

E:A: Early-to-Late-Filling Ratio

ECM: Extracellular Matrix

EDV: End-Diastolic Volume

EF: Ejection Fraction

ESV: End-Systolic Volume

FAD(H): Flavin Adenine Dinucleotide

FBP1 = Fructose-1,6-Bisphosphatase-1

GRK: G-Protein Receptor Kinase

HCN: Hyperpolarisation-Activated Cyclic Nucleotide-Gated Cation Channels

HF: Heart Failure

HFpEF: Heart Failure with Preserved Ejection Fraction

HR: Heart Rate

I_f: Funny Current

IL: Interleukin

IP_3: Inositol Triphosphate

K^+: Potassium

mGP_{DH}: Mitochondrial Glycerophosphate Dehydrogenase

NAD(H): Nicotinamide Adenine Dinucleotide

NCD: Non-Communicable Disease

ND3: NADH Dehydrogenase 3

NFAT: Nuclear Factor of Activated T-Cells

NO: Nitric Oxide

OCT1: Organic Cation Transporter 1

P_i: Inorganic Phosphate

PKA: Protein Kinase A

PKC: Protein Kinase C

PLC: Phospholipase-C

PLN: Phospholamban

PNS: Parasympathetic Nervous System

RAAS: Renin Angiotensin Aldosterone System

ROS: Reactive Oxygen Species

RyR2: Ryanodine Type 2 Receptor

SAN: Sinoatrial Node

SERCA2a: Sarco/endoplasmic Reticulum Ca^{2+}-ATPase

SGLT2: Sodium-Glucose Co-Transporter-2

SIRT: Sirtuin

SNS: Sympathetic Nervous System

SR: Sarcoplasmic Reticulum

TNF-α: Tumour Necrosis Factor-Alpha

1.0 Introduction

An “ageing crisis” due to the expansion of the population that is over 65 years old is a current and prospective concern for many countries. Off the back of improvements in science, availability of medicine, improved nutrition, and access to information over the past 2 centuries, society has enjoyed a predominantly upward trajectory in life expectancy, with life expectancy in the 21st century almost twice that of the 19th century [3-6]. While ever increasing longevity should be considered a great achievement, this has simultaneously led to the realisation of the need to match growth in lifespan with growth in health span. Currently, there is some suggestion of a limit to lifespan for humans of approximately 120-150 years [7], though this remains a topic of some controversy. Absolute lifespan is not necessarily a key goal though since with advancing age comes an increasing risk of morbidity and poor health. For example, in the UK in 2016, data show that if one lived to the age of average life expectancy (81 years), any individual would expect to spend approximately 20-23% of their life in poor health [8, 9]. Disparity in lifespan:health span could mean the general population spends a greater portion of their lives in poor health [3, 4, 10]. In the absence of therapeutic strategies that can delay specific biological processes contributing to age-associated degradation of physiological systems, attention must be concomitantly directed to alternative strategies to prevent further disparity in the lifespan: health span ratio and ensure individuals arrive at old age (>65 years) healthier [11-15] and can preserve this health for longer. An increasing elderly population will present a greater demand on already strained healthcare resources, which is very costly and may ultimately lead to a decline in the quality of care received. Most importantly, this could lead to a reduction in the quality of life of this growing elderly population.

Typically, as an individual ages, a plethora of adaptations occur normally resulting in the poorer and less efficient function of several physiological systems which culminate in increased vulnerability and likelihood of disease and abnormality [3, 16-19]. Age-

related physiological changes tend to go unnoticed by individuals as cellular remodelling is continuous after biological maturity is reached and often delivers only very gradual change [3, 18, 19]. Notably, elderly individuals are susceptible to neurodegeneration, altered catecholamine regulation, chronic inflammation, reduced ability for repair, immunosenescence, and reduced ability to respond to stress [16, 20-22]. There are many theories to explain these age-related changes as well as the general ageing process [23-26].

Age is the greatest single independent risk factor for the development of cardiovascular diseases (CVDs) [16]. CVD is the leading killer globally, with data suggesting CVD-related deaths are responsible for almost a third of all deaths each year [5, 6]. Despite a gradual decline in prevalence in recent years, CVD rates are still very high and some have predicted a future surge as a result of high rates of obesity, drug use, inactivity, and poor diet in young adults currently [27, 28]. Added to this, with advancing age being the single greatest risk factor for CVD and the increase of the aged population, attempting to ameliorate the age-related increase in CVD becomes an important clinical and societal issue. The question remains though just how modifiable as a risk factor for CVD is the ageing process?

2.0 Age-Related Remodelling in the Heart and Vasculature

Age-related remodelling of the heart and vascular system associates with a broad range of changes [4]. Identifying the key ones and dealing with the marked heterogeneity that can be seen in terms of ageing both between individuals and organs presents a significant challenge to developing therapeutic targets and solutions.

2.1 Hypertrophy

Age-related cardiac hypertrophy is characterised at the cellular level by a loss in myocyte number and an increase in myocyte size (figure 1) [29, 30]. Different signalling pathways exist instigating these morphological changes, yet the main triggers are mechanical stress or neurohormonal activation. Changes in the vascular system with age lead to increases in systolic blood pressure (BP) (approximately 0.9 to 9 mmHg per decade) [31, 32] subsequently triggering cardiac hypertrophy [33, 34].

Increased involvement of calcium/calmodulin-dependent protein kinase (CAMKII) due to catecholamine overstimulation and reduced efficiency of intracellular calcium (Ca^{2+}) handling in old age is also associated with hypertrophy through activation of the renin angiotensin aldosterone system (RAAS) pathway [35, 36]. Activation of CaMKII through downstream beta-adrenergic receptor (βAR) stimulatory signalling coupled with a direct increase in stimulation of the RAAS, augments this hypertrophy [3, 37, 38]. Catecholamine overstimulation can also contribute to hypertrophy through the phospholipase-C (PLC)/calcineurin/Nuclear factor of activated T-cells (NFAT) pathway. In the calcineurin/NFAT pathway, βAR are stimulated by both catecholamines and angiotensin 2, activating PLC, leading to the activation of calcineurin and Ca^{2+} release, culminating in the dephosphorylation of NFAT [38-40]. The hypertrophy (48-89% increase in left ventricular mass; 12-47% increase in wall thickness) [41-44] linked with advancing age (>65 years) may contribute to the reduction of cardiac reserve and exercise capacity due to the association with impaired diastolic and contractile function.

2.2 Prolonged Contraction

A prolongation in myocardial contraction with increasing age occurs as a compensatory measure for the development of diastolic dysfunction generated through remodelling of the vascular system, cardiac tissue and ventricular ion channels [45-47]. Age-associated cardiac hypertrophy also associates with slowed Ca^{2+} kinetics and a prolonged ventricular action potential (AP). Slowed relaxation kinetics can also limit ventricular filling, especially at higher heart rates (HR) [47]. At the cellular level, the elderly heart demonstrates a pattern of reduced sarcoplasmic reticulum (SR) Ca^{2+} release magnitude (of around 5%) coupled with reduced Ca^{2+} transient duration (by ~6%) and increased frequency (91%) of spontaneous SR release, reflective of the known age-related increase in ryanodine type 2 receptor (RyR2) leak [47, 48]. An age-related decline in SR loading (of ~30-50%) as a result, in part, of unfavourable alterations in the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA2a): phospholamban (PLN) ratio contributes to slowed Ca^{2+} kinetics and a reduced calcium transient amplitude with ultimately a reduced contractile response in myocytes [47-50]. This age-related impairment in Ca^{2+} cycling, combined with the dysfunction in factors contributing to efficient excitation such as the slowed kinetics of

AP (figure 1), repolarisation driven by sustained Ca^{2+} entry and reduced repolarising potassium (K^+) channel function as well as an increase in fibrosis poses a problem for maintaining efficient cardiac function during high HR such as under stress or during physical activity [45, 51-56]. Indeed, the age-associated reduction in maximum HR may actually be required to cope with the reduced ability of the heart to work efficiently at high HRs in advanced age.

Similarly, in the vascular system, changes in Ca^{2+} handling are involved in the age-related impairment of vascular contractility [57]. A reduction in Ca^{2+} entry due to a reduction in L-type Ca^{2+} channel expression and associated current density in smooth muscle in old age, contributes to the decline in contractility and overall efficient functioning of the vascular system, compounded by vessel stiffening and deterioration of sympathoadrenal signalling, impacting the control of BP and blood flow as well as potentiating a mismatch in arterial and ventricular load [57, 58]. In addition, endothelial dysfunction has been associated with old age [59] characterised by the loss of endothelial-dependent vasodilation, which has been shown to reduce by approximately 0.21% per year in the brachial artery of humans >40 years old [60]. Other work has even reported much greater differences in vasodilatory response to agonist stimulation (acetylcholine), where old humans (>60 years) displayed a 4.5-fold reduction compared with young adults (<30 years old) [61]. The age-related reduction in endothelial function is largely a result of a reduction in nitric oxide (NO) synthase and an increase in oxidative stress [59, 62]. Together, these changes harm the ability to cope with modulations in cardiorespiratory demand, increase vascular inflammation, and elevate CVD risk.

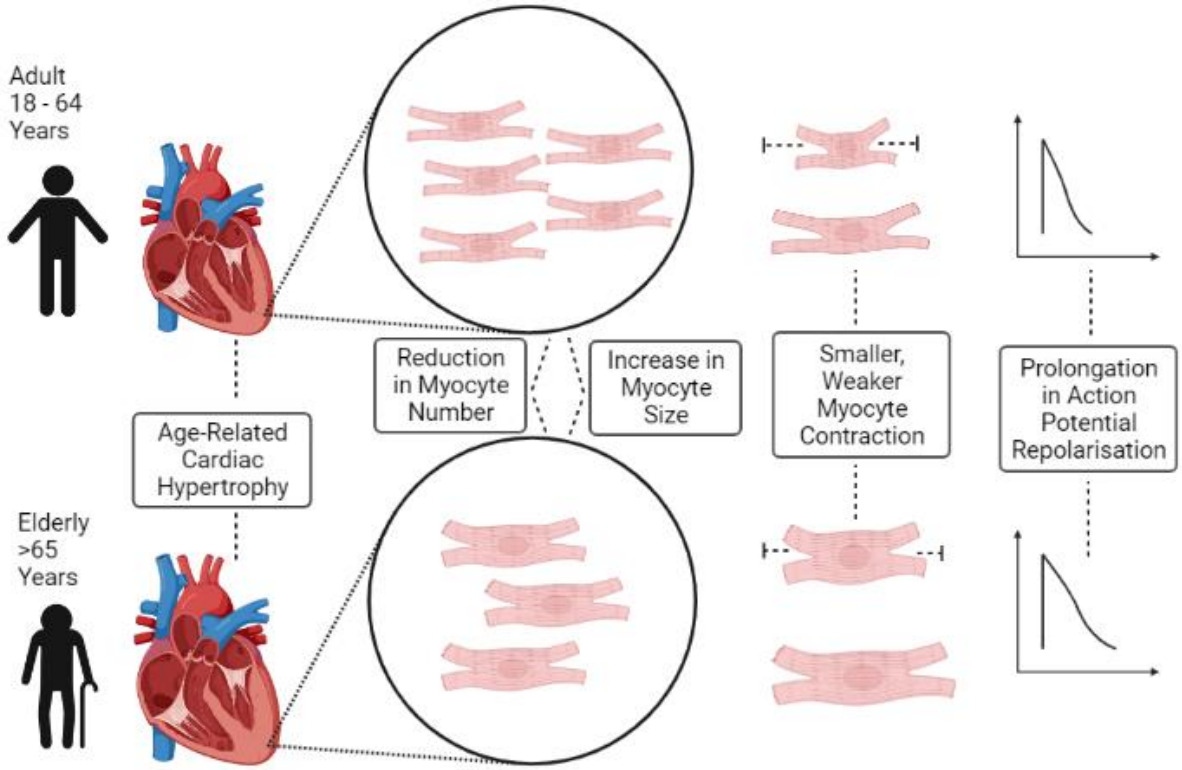

Figure 1. Depiction of some adaptations observed in age-related cardiac remodelling. Image created with BioRender.

2.3 Diastolic Dysfunction

Diastolic dysfunction is one of the most prominent age-related changes and has acquired attention due to the similarity to heart failure with preserved ejection fraction (HFpEF), a debilitating condition with currently few effective treatment options [63]. Diastolic dysfunction in the aged heart is contributed to by changes in ventricular wall thickness as well as fibrosis and is characterised by poorer diastolic filling efficiency, where filling pressure is increased without concomitant increases in filling volume alongside a requirement for greater functional involvement of the atria [45, 64]. Early diastolic filling is typically greatly reduced (approximately 60% in humans >70 years *vs* 20-29 years) [45], and the heart becomes reliant on increased late diastolic filling, reducing the early-to-late-filling (E:A) ratio [45, 64]. These changes are supported by maintained or improved end-diastolic volume (EDV) and end-systolic volume (ESV) and contribute to prolonged contractions [45, 64].

2.4 Reduced Automaticity

Age-related impairments in automaticity result from a reduction in intrinsic HR control and a shift in autonomic nervous system (ANS) modulation and reactivity of the sympathetic and parasympathetic nervous systems (SNS; PNS), whereby PNS control during basal conditions declines and SNS control compensates, contributing to the reduction in maximum attainable HR [65, 66]. The shift in ANS control may contribute to the deterioration of the ability to function at high HR alongside changes in adrenergic signalling efficiency. The declining function of the sinoatrial node with old age is characterised by losses in sinoatrial node (SAN) cell number, hyperpolarisation-activated cyclic nucleotide-gated cation channel (HCN) expression (underlying the funny current (I_f)) and RyR2, L-type Ca^{2+} channel and SERCA2a expression, all contributing to a reduction in intrinsic pacemaker function [51, 67-70]. Losses in SAN cell number, coupled with changes in the extracellular matrix (ECM) and overall cardiac hypertrophy also collectively impede electrical connectivity with the rest of the heart, impairing impulse propagation, increasing pacemaker instability and subsequently increasing arrhythmia risk as well as potentially limiting maximal rate of operation [68, 71, 72].

2.5 Increased Fibrosis

The fibrotic changes identified with advancing age widely impact on overall myocardial efficiency [73, 74]. An increase in fibrosis has been observed in almost all tissues and is a prominent factor in ageing. The changes that occur with fibrosis in the heart are known to manifest as alterations in ECM, elastin breakdown and collagen deposition [1, 73]. Fibrotic processes are required to maintain adequate myocardial structure for correct cardiac functioning and for repair and rejuvenation after injury or insult as well as supporting efficient electrical conduction and ventricular loading [73]. Ageing can stimulate pathological (interstitial) fibrotic processes leading to an increased remodelling of ECM and accumulation of fibroblasts [73, 74]. This results in structural changes that can impair function and damage the ability to efficiently perform reparative processes as well as the overall mechanical and electrical function of the heart [73, 75]. Increased deposition of type 1 collagen and the remodelling of gap junctions impede impulse transduction and propagation, leading to an increased risk of arrhythmias and the blunting of contraction magnitude [71, 76]. Meanwhile, the

overall loss of elasticity and increase in stiffening negatively influences the chamber filling and contraction efficiency [73, 75]. Together, these changes influence the generation of cardiac output (CO) and the narrowing of cardiac reserve, reducing the ability of the elderly heart to cope with increases in demand.

In old age, the arterial stiffening caused by similarly increased fibrosis (figure 2) is further compounded by elevated levels of inflammation, through the upregulation of atherosclerotic deposits and loss of efficiency in the electron transport chain [46, 77]. Together, this creates an environment whereby reactive oxygen species (ROS) production and subsequent oxidative activity become more prevalent, triggering the accumulation of pro-inflammatory cytokines [46]. Over a chronic period, the associated chronic inflammation leads to endothelial dysfunction (figure 2) and can impede blood flow via suppression of NO availability [46, 78, 79]. Sustained exposure to low-level inflammation, such as in old age, has been repeatedly implicated in the increased risk of disease development and further fibrosis and stiffening [78, 79].

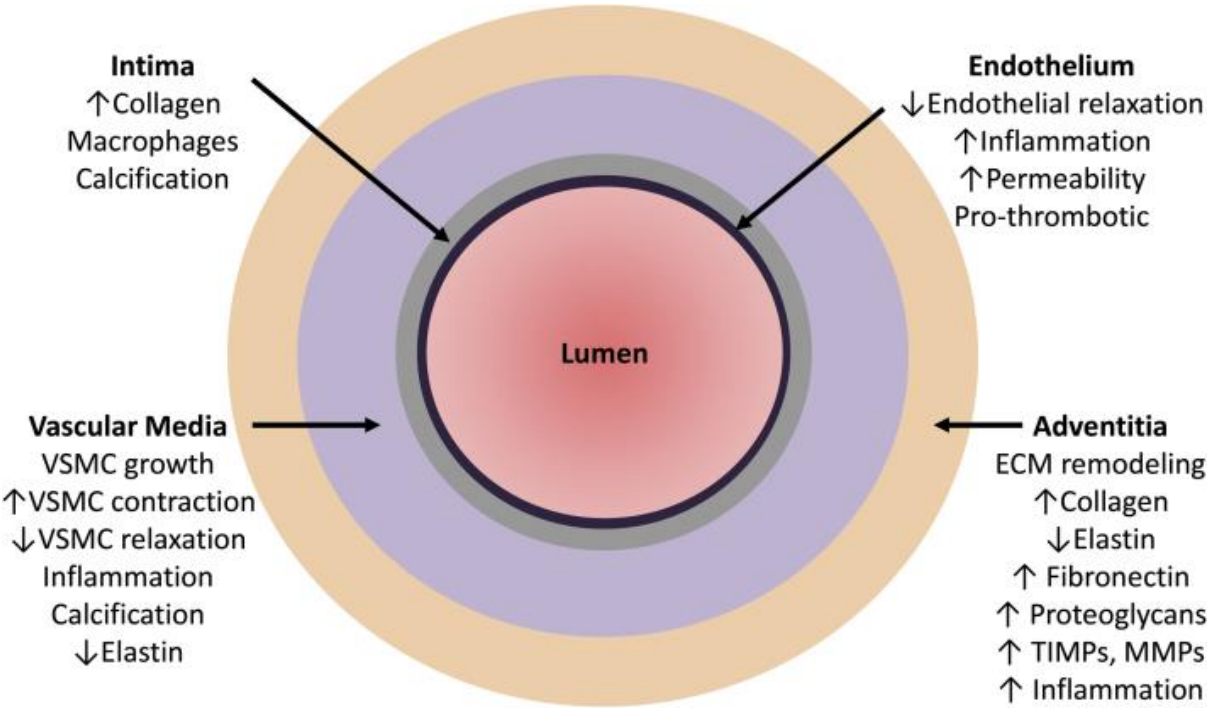

Figure 2. *The vascular phenotype in aging and hypertension. With aging and during the development of hypertension, the endothelium, vascular wall, and adventitia undergo functional and structural changes. Endothelial function is impaired, and the vascular media is thickened. The adventitial extracellular matrix undergoes remodelling, with increased collagen deposition, reduced elastin content, and increased proinflammatory cells. These processes contribute to vascular fibrosis and stiffening.*

ECM, extracellular matrix; MMP, matrix metalloproteinases; TIMPs, tissue inhibitory metalloproteinases; VSMC, vascular smooth muscle cell [1]. Figure reprinted from "Vascular Fibrosis in Aging and Hypertension: Molecular Mechanisms and Clinical Implications" by A. Harvey, A. Montezano, R.A. Lopes, F. Rios and R.M. Touyz. (2016). *Canadian Journal of Cardiology,* 32, (5), p. 659-68 [1].

2.6 Arterial and Ventricular load

Increased collagen deposition and the breakdown of elastin by elastase facilitates age-related arterial stiffening, which is further exacerbated by hypertrophy of the intimal vessel wall which increases the risk of CVD-related events such as stroke or myocardial infarction [46, 80, 81]. An increase in arterial stiffness causes increased arterial systolic and pulse pressure [46, 81]. Reductions in arterial compliance of 40-43%, increase in stiffness index of 111-132%, and increase in pulse wave velocity of 50-58% have been reported in old (60-74 years) compared with young adults (18-29 years) [82]. This leads to greater pressure exerted on the ventricles and cardiac work [83]. Continued higher wall tension fuels a perpetual cycle of increased pressure and hypertrophy of both the heart and the vasculature, along with a deterioration in diastolic function [33, 84]. Greater wall thickness in the ventricles and vasculature facilitates the normalisation of wall stress or tension, preventing a deleterious effect on CO generation by preserving the ejection fraction (EF) and enlarging atrial cavities, advancing atrial filling and increasing EDV [80, 85, 86]. However, preserving EF is at the expense of early diastolic filling rate, as a prolongation of contraction time occurs [86] reducing contraction velocity and efficiency. Such remodelling creates a mismatch in arterial and ventricular load, which becomes problematic during exercise as arterial and ventricular loads become unbalanced, contributing to poorer exercise tolerance and cardiac reserve in old age [83, 87, 88]. During the performance of exercise in old age, there is a blunting of the normal reduction in cardiac afterload observed in young adults, which contributes to poorer cardiac performance during physical activity and a narrowing of cardiac reserve [83, 89]. A continuous increase in arterial stiffening increases afterload resistance to cardiac function as well as higher wall pressure in the vasculature, further increasing vulnerability to CVD or CVD-related injury. This remodelling in aged populations may explain in part, the associated loss of physical capacity and increasing risk of CVD [85].

2.7 Impeded Response to Physical Exertion

Age-related reduction of the response to physical activity and reduced cardiac reserve are also considered a result of a loss in adrenergic signalling efficiency [3, 80]. Reduction in β-1 adrenergic receptor (β_1AR) expression and activity alongside further detrimental remodelling of early and downstream signalling components and effectors,

caused by chronic catecholamine overstimulation, significantly impairs the response in cardiac rate and contractility at the onset of physical activity [72, 90-99]. A cascade of associated components accumulate to significantly limit cardiac reserve and physical capacity in old age, impairing the ability to perform activities of daily living that require physical exertion and the upregulation of cardiovascular function [72].

3.0 Adrenergic Dysfunction with Age as a Key Problem

The age-related development of adrenergic dysfunction is a prominent factor contributing to some of the most important detriments to quality of life, through diminishing physical capacity leading to increased morbidity and ultimately mortality. The age-related degradation of the adrenergic response in the heart primarily concerns changes in the β_1AR signalling pathway. Key age-related alterations of this pathway have been previously described [3, 18, 45, 70, 72, 86, 100]. However, in the vasculature, alterations in the adrenergic response through alpha 1, alpha 2 and beta 2 adrenergic receptors (α_1AR; α_2AR; β_2AR) signalling alterations as well as baroreceptor control have been comparatively less studied [33, 101]. The remodelling of adrenergic control in the vascular system with ageing and its subsequent impact on the ageing heart is important due to the intertwining nature of cardiovascular function physical capacity, and CVD risk. Increased sympathetic activity associated with ageing causes sustained elevated stimulation of both αAR and βAR, though overstimulation of β_1AR appears to be the most prominent and detrimental to cardiovascular function [20, 21, 35]. Interestingly, a link between hypertension, a common comorbidity during the ageing process, and chronic overstimulation of adrenergic receptors has also been suggested as a result of the associated increase in sympathetic tone, whereby the onset of hypertension may amplify age-related degradation in processes related to the adrenergic response [35, 101]. This could mean that anti-ageing treatments or preventive strategies may benefit from treating or preventing high BP initially if the end goal is to correct the overstimulation of adrenergic receptors and progressive age-related deterioration in cardiovascular function.

Alpha 1 adrenergic receptors are prominent in the smooth muscle of the vascular system and utilise the PLC/inositol triphosphate (IP_3)/protein kinase C (PKC) signalling

pathway to mediate vasoconstriction [102]. Alpha 1 receptors also have a role in myocardial contractility and hypertrophy [103, 104]. Increases in catecholamine circulation stimulate α_1AR which then activates the PLC/IP_3/PKC pathway [105]. Activation of this pathway triggers increased intracellular Ca^{2+} entry through phosphorylation of Ca^{2+} channels by PKC alongside concomitant SR Ca^{2+} release, triggering vasoconstriction and in turn increasing peripheral resistance and raised BP [105]. During exercise, the action of α_1AR stimulation enables the redirection of blood flow away from the digestive system and areas with low aerobic demands, facilitating an increase in blood flow within active tissues, supporting efficient cardiovascular function [106].

In the heart and associated vasculature, a maintenance or increase in α_1AR signalling occurs with ageing, as a compensatory mechanism for declining β_1AR signalling [57, 101, 106-108]. A key potential role of α_1AR signalling in the aged heart may be to offer cardioprotection as well as facilitate physiological hypertrophy [109]. However, a blunting of the α_1AR signalling-induced contractile response (of ~50%) has been reported alongside reductions in PKC activity and associated anchoring proteins in old aged rat hearts [110]. It should be noted that α_1AR signalling modulates contractility in the human heart to a lesser extent than in rodents [106]. An age-related increase (or maintenance) in α_1AR response, when combined with the known loss of arterial baroreceptor control, may explain, at least in part, the exaggerated BP response to exercise reported in old individuals, as the vasoconstrictive impact of the described α_1AR hyperactivity is not modulated and subsequently blunted to the same extent as in youth [33, 57, 101, 111].

Alpha 2 receptors are primarily located on postganglionic sympathetic neurons and smooth muscle and are responsible for modulating the influence of catecholamines through inhibition of adenylyl cyclase (AC) also moderating HR and BP [112]. Alpha 2 stimulation inhibits AC and in turn cyclic adenosine ‘3 ‘5 monophosphate (cAMP) and causes alterations in outward K^+ and inward Ca^{2+} currents inhibiting neuronal firing [112]. This generates a cycle that blunts catecholamine release and subsequent adrenergic signalling, and offers protection from excess catecholamine overstimulation [112]. Alpha 2 stimulation causes a reduction in vascular resistance, BP, HR and CO [112].

The response to α_2AR signalling may become altered or impaired with age [101, 113]. Although relatively little evidence exists in the context of cardiovascular function and the data shows a mixed response to ageing, though this is possibly due to the broad range of conditions and samples investigated thus far [101]. A poorer response to α_2AR stimulation/signalling would reduce catecholamine control and may have a role in age-related overstimulation of adrenergic receptors contributing to the age-related alterations in BP response to stress through the previously mentioned remodelling of α_1AR and baroreceptor sensitivity [33, 57, 101, 111].

Beta 2 receptors are situated in the heart and smooth muscle and have a relationship with both stimulatory and inhibitory G proteins unlike the other adrenergic receptors [3, 114]. Beta 2 receptors utilise AC/cAMP/protein kinase A (PKA) pathway to aid smooth muscle relaxation, cell survival, and cardiac contractility [3, 115, 116].

With ageing, β_2ARs become less sensitive in the cardiovascular system [17, 33, 101, 107, 117]. The balance of effects of adrenergic receptors alters since the reduced β_1AR response reduces contractile chronotropic effects on the heart, while vascular effects promote increased afterload and BP elevation. An age-related reduction in β_2AR response impacts the efficiency of BP control and cardiovascular function as the vasodilatory response is weakened against the competing vasoconstriction brought on by αAR stimulation during adrenergic signalling [17, 107]. A link between β_2AR downregulation and hypertension and further inflammation exists, which may exacerbate the decline in overall cardiovascular function [17].

4.0 Therapeutic Strategies Combatting the Age-Related Decline

Interest in combatting the debilitating effects of ageing has led to the identification and implementation of an array of therapeutic strategies which may help restore cardiovascular function or at least blunt the age-related degradation of the cardiovascular system [118]. The overwhelming majority of strategies are pharmacological using agents such as metformin, resveratrol, angiotensin-converting-enzyme (ACE) inhibitors and beta(β)-blockers [118].

4.1 Metformin

Metformin is used for the treatment of type 2 diabetes and facilitates greater utilisation of glucose and a reduction in its production (figure 3) [119, 120]. Metformin reduces glucose production in the liver through pathways involving alterations in AMP-activated protein kinase (AMPK), cAMP production, the electron transport chain, and lactate metabolism (figure 3) [119, 120]. The mechanism of increased glucose utilisation in the gut with metformin is currently unclear [119].

The beneficial effects of metformin on ageing are likely related to the associated reductions in non-communicable disease (NCD) risk [120]. Metformin has been associated with reduced risk of CVD, cancer, obesity, and neurodegenerative diseases [120]. Given age is a vital risk factor in the majority of these NCDs, metformin has been implicated as a potential anti-ageing treatment [120, 121]. Studies in mice and Caenorhabditis elegans (C**.** elegans) support this and have reported extensions in average lifespan of between 4 and 40% [120, 122-124]. Greater blood glucose control and an improved blood lipid profile as a result of metformin ingestion could help facilitate a reduction in the age-related increment of ROS production alongside subsequent oxidative damage, inflammation and vascular decline which would help ameliorate ageing-associated effects on vascular function, BP, and cardiac function [120]. This is supported by evidence of metformin induced reductions in cardiac hypertrophy (6% reduction in left ventricular mass index), BP (3-4% reduction in systolic BP) and oxidative stress (9-11% reduction in measured lipid peroxidation products) in old individuals with coronary artery disease (CAD) [125]. Metformin has also been found to reduce overall mortality and cardiovascular events in humans [126]. In addition, metformin treatment has been shown to slow the progression of HF in rats by increasing EF (~35%) and end-diastolic diameter (6%) and end-systolic diameter (7%) and was associated with increases in AMPK and endothelial NO synthase phosphorylation [127]. However, a recent study in mice reported that metformin did not provide the expected improvements in life expectancy and cardiac function [128]. Human trials of anti-ageing and preventive effects of metformin are in progress.

Another drug class used in the treatment of type 2 diabetes, sodium-glucose co-transporter-2 (SGLT2) inhibitors have also been suggested as a potential therapeutic strategy for restoring or slowing the age-related degradation of cardiovascular function [129]. The increasing interest in SGLT2 inhibitors as a potential anti-ageing strategy is a result of findings demonstrating the attenuation of inflammation and oxidative

stress, as well as the prevention of age-related endothelial dysfunction [129]. Though more research is required to assess the long-term consequences of use in healthy individuals.

Finerenone, a drug used in the treatment of kidney disease and type 2 diabetes, has also been suggested to be of value in acting against age-related dysfunction [130]. Finerenone has been shown to reduce the incidence of cardiovascular events and death in patients with kidney disease and type 2 diabetes [131]. A key mechanism of action is reduction of myocardial fibrosis which is a key hallmark of cardiac ageing [132]. This would be expected to potentially improve vascular and cardiac compliance perhaps reversing the normal trend of age-related reduction in this key parameter. In addition, finerenone can improve ventricular contractility during chronic adrenergic (over)stimulation [130-132]. As such there is good potential for this agent but more research is required to validate and assess the magnitude of beneficial effects in the absence of complicating pathophysiology.

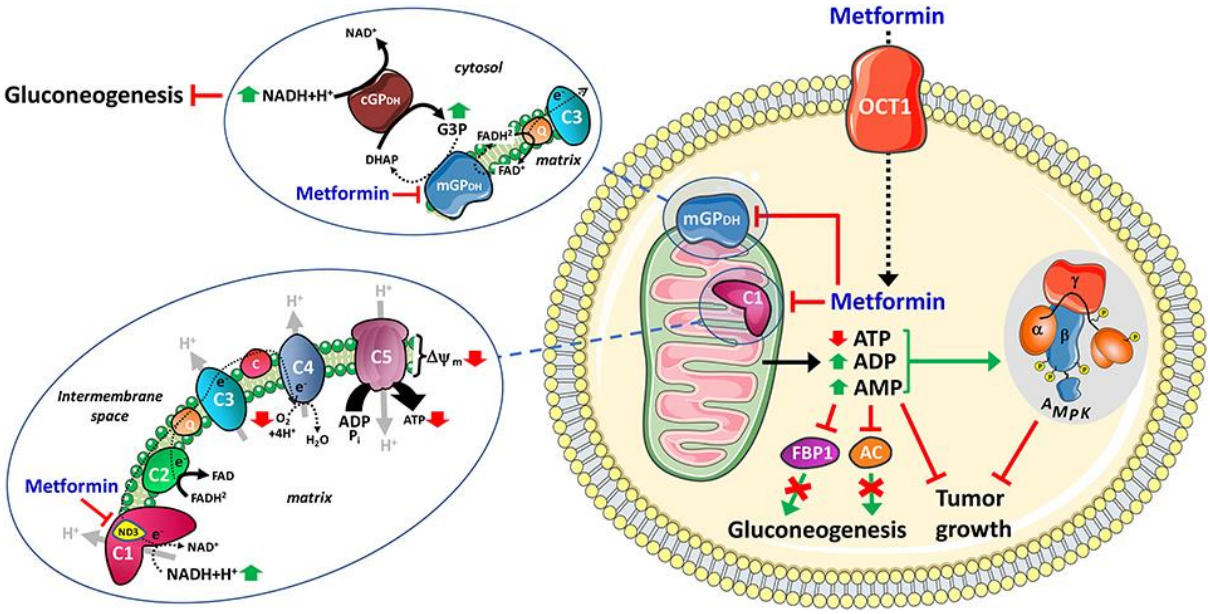

Figure 3. *Mitochondrial mechanisms of action of metformin. After cellular uptake, mainly through organic cation transporter 1 (OCT1) in hepatocytes, the mitochondria is the primary target of metformin which exerts specific inhibition on the respiratory-chain complex 1, presumably through direct interaction with the NADH dehydrogenase 3 (ND3) core subunit, and on mitochondrial glycerophosphate dehydrogenase (mGP$_{DH}$). The inhibition of complex 1 decreases* nicotinamide adenine dinucleotide *(NADH) oxidation, proton pumping across the inner mitochondrial membrane and oxygen consumption rate, resulting in lower proton gradient (Δψ) and reduction of proton-driven adenosine tri-phosphate (ATP) synthesis from adenosine di-phosphate (ADP) and inorganic phosphate (Pi). The inhibition of mGP$_{DH}$ modulates cytosolic and mitochondrial redox state resulting in increased cytosolic NADH. (FBP1 = fructose-1,6-bisphosphatase-1; AC = adenylate cyclase; FADH = flavin adenine dinucleotide; AMPK =* 5' adenosine monophosphate-activated protein kinase).

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4.2 Resveratrol

Resveratrol is a polyphenol found in plants and common foods [133]. Resveratrol has been suggested to have potential anti-ageing benefits through associated increased reparative capacity, reduced inflammation, and increased mitochondrial biogenesis [134]. In fact, studies have shown resveratrol increases the lifespan of C elegans, fruit flies and bees by 10-~40% [134-138]. In rats, resveratrol has been shown to improve vascular function and aerobic capacity [134, 139]. The benefits of resveratrol have been found to be mediated primarily through changes in pathways involving sirtuins [133] which are believed to be involved in both the normal ageing process and response to physical activity as well as the development of pathological age-related changes which in turn negatively impact responses to physical activity [140-142]. Sirtuin's (SIRT's) are a family of proteins that depend on nicotinamide adenine dinucleotide (NAD) and are specifically activated by high NAD levels as found in low energy states [100]. Sirtuin's 1, 3, 6, and 7 are the most prominent when investigating cardiac function and are responsible for a role in signalling related to cell mortality and metabolically associated ROS synthesis [143]. $SIRT_1$, when activated by increased NAD levels or resveratrol, increases mitochondrial activity, cell survival or death, apoptosis, atrophy, DNA repair, and ROS synthesis through a number of molecular reactions involving the stimulation of transcription factors and inhibition of the Akt pathway [100, 133]. $Sirtuin_3$ also has a role in the modulation of hypertrophic myocardial remodelling following a similar signalling pathway, however, concluding in the activation of different proteins and protein kinases [100]. Much like βAR's, SIRT's decline in activity and expression during the ageing process and play a role in age-associated cardiomyocyte hypertrophy. In aged rats, $SIRT_1$ has been reported to downregulate and translocate/compartmentalise [140]. However, when subject to pressure overload, the associated transient alterations in $SIRT_1$ are controversial, with some studies showing increases in activity while others do not [140]. Age-related reductions in $SIRT_1$ expression and activity have been suggested to increase endothelial senescence and atherosclerosis as a result of its impaired function and associated increases in endothelial inflammation [141, 142]. Such modifications to $SIRT_1$ function with age, which increase senescence in particular, may also contribute to premature ageing through associated increases in vascular fibrosis, contractile dysfunction, oxidative damage, and decreases in NO synthesis [140, 144].

Clinical trials have shown that resveratrol treatment (3 months) improves endothelial function in patients with metabolic syndrome (4-5% increase in flow-mediated dilation); improves glycaemic control and reduces systolic BP (by ~4%) and arterial stiffness (5% reduction in cardio-ankle vascular index) in type 2 diabetes [145-147]. Shorter treatment periods (4-6 weeks) have also been shown to improve endothelial function (23% increase in endothelial-dependent dilation) as well as glucose control (4% reduction in blood glucose concentration) and systolic BP (-4%) in obese patients [148, 149]. Longer term resveratrol treatment (1 year) has been found to reduce inflammation, through a reduction in proinflammatory cytokines (9 and 13% reductions in tumour necrosis factor-α and interleukin-6) in patients with CAD and type 2 diabetes[150]. Despite the wide range of benefits reported to occur from resveratrol treatment such as: improved diastolic function in HF, reduced arterial stiffness, systolic BP, pro-inflammatory cytokines and improved endothelial-dependent dilation and blood lipid regulation in CAD and improved blood glucose control in diabetes, some contradicting clinical studies exist due to variations in study methodology [151-156]. Future studies are required to better understand the benefits of resveratrol in clinical and healthy control groups.

4.3 ACE inhibitors

ACE inhibitors are commonly used for patients with HF or hypertension [157]. By inhibiting the production of angiotensin 2 and bradykinin, they facilitate significant reductions in BP as well as CO [157]. Studies in rodents have shown that ACE inhibitors have potential anti-ageing benefits, increasing lifespan by 9-30% [158-161]. The anti-ageing benefits of ACE inhibitors have been shown to reduce the risk of CVD and may have a protective effect on the ageing cardiovascular system by reducing vasoconstriction, BP and cardiac hypertrophy [158]. Reducing vasoconstriction and hypertrophy in the ageing heart and vasculature reduces the risk of vascular insults such as stroke [162] and blunts the age-related alterations in mitochondria and vascular wall thickness [163]. This may facilitate a reduction in cardiac stress and alleviate the development of diastolic dysfunction in old age. In hypertensive rats treatment with an ACE inhibitor has been shown to prevent the deterioration of diastolic function into HF and blunt the progression of myocardial fibrosis and hypertrophy [164]. In humans, ACE inhibition (38 weeks) improved diastolic function

in patients with hypertension and existing diastolic dysfunction, evidenced by improved myocardial relaxation (6% reduction in isovolumetric relaxation time), reduced septal wall thickness (2%) and left ventricular mass (6%), and reduced EDV (2%) and ESV (5%), with a concomitant improvement in EF (2%) [165]. This improvement in cardiac function was interpreted to be, at least in part, a result of the improved BP (8-9% reduction in diastolic and systolic BP, respectively) control under ACE inhibition [165]. Long term ACE inhibitor treatment has also been found to reduce the occurrence of myocardial insult and mortality in HF and patients with diastolic dysfunction [166]. However, RAAS inhibition has been associated with renal impairment and may lead to a worse prognosis in patients particularly with HFpEF [167]. Moreover, in HFpEF patients, ACE inhibitors may improve EF and in turn systolic function but not measures of diastolic function [168]. Though it was speculated that improvements in systolic function may have resulted from associated reductions in BP and thus afterload along with the vasodilatory effects from RAAS inhibition [168]. Further research into the use of ACE inhibitors or RAAS inhibition during ageing of the heart and in the elderly is required.

4.4 Beta-blockers

Beta-blockers are a common medication used to treat hypertension and cardiac arrhythmias [18] by blocking receptor – catecholamine binding or through the re-sensitisation of the β_1AR signalling mechanism [18]. Beta-blockers cause a reduction in HR, contractility, and BP [169] and indirectly protect diastolic filling, cardiac efficiency and reduce hypertrophy and susceptibility to arrhythmia [169]. Studies have shown the use of β-blocker treatment in cases of acute coronary syndrome yields lower mortality [170]. Similarly, patients receiving percutaneous coronary intervention after myocardial infarction have been suggested to display reduced mortality with β-blocker treatment [171]. Such findings of reduced mortality with β-blocker treatment post myocardial infarction and for those with HF have been well documented in clinical studies [172-174]. Though, β-blocker treatment after myocardial infarction in patients without HF or systolic dysfunction or those with HFpEF has been shown to yield no reduction in mortality [174, 175]. The decreased mortality afforded by β-blocker administration during HF as well as normal ageing (increased median lifespan in mice and Drosophila is 10 and 23%, respectively) alongside some evidence of the blunting

of the development of HF in young rats after aortic constriction, has generated interest in β-blockers as a potential therapy for the age-related degradation of the heart and vasculature [118, 176-178]. The blunting of the development of HF with β-blocker treatment has been proposed to be a direct result of reducing cardiac hypertrophy and upregulation of NO production [118, 176]. One study in middle-aged hypertensive men (39-55 years) recorded reductions in HR (16%), systolic BP (6-7%), and diastolic BP (10-11%) and elevations in EF (6%) and stroke volume (11%) with β-blocker treatment for just 3 weeks [179]. Such an approach applied to an elderly population may be beneficial in combatting age-related decrements in cardiovascular function. However, conclusive evidence of such potential benefits is lacking currently in humans, although one study has reported the use of β-blockers in old subjects lead to some restoration of cardiac reserve through restoration of β_1AR signalling [3, 180].

4.5 Exercise Training

Comparatively, participation in exercise training might prove more favourable for long-term adherence than pharmacological strategies due to the accessibility, lower cost, and limited potential for side effects [72, 181]. Despite the existence of clearly promising potential pharmacological interventions that may eventually be used to treat age-related organ decline, it should be debated whether drug therapy treatment is the most effective way forward. The use of non-drug-related therapies, such as exercise training, may provide equal or greater promise in treating or even preventing the diminishing influence of old age, particularly when concerning cardiovascular function. Although the preferred direction of such anti-ageing or preventive therapies to protect cardiovascular function may be more intricate and depend on the patient's current quality of life. For example, where quality of life has already been considerably impacted or where prescriptive exercise is not possible, drug therapy may be the preferred option.

It has been suggested that exercise type and intensity may be particularly important to make exercise training a therapeutic strategy countering negative impacts of ageing [182]. Low intensity exercise is likely not enough to stimulate desired adaptations, whilst very high intensity may generate levels of inflammation and oxidative stress not conducive for beneficial adaptation [182]. Moderate intensity aerobic-based exercise appears to be associated with the most beneficial adaptations and subsequent

improvement in cardiovascular health, although a role for strength straining also exists due to individual and complimentary beneficial effects on BP and overall cardiovascular function [182].

Exercise training is well documented to lower the risk of CVD and has been suggested to potentially suppress the rate of decline with ageing or attenuate some age-associated decrements [183-187]. Existing literature focusing on the use of moderate to vigorous exercise training to restore the adrenergic response in old age has focused predominantly on attempting to rejuvenate components of the β_1AR signalling mechanisms [70, 72, 188-191]. Exercise training has been demonstrated to lead to maintenance or improvement in the overall adrenergic response, cardiac diastolic function and contractility by improving or maintaining β_1AR and SERCA2a expression as well as improving AC and cAMP responses, whilst effector components further downstream are either yet to be investigated or demonstrate apparently weak potential for adrenergic signalling restoration [70, 72, 189, 191-197].

Benefits of exercise training on adrenergic control of the vasculature have received comparatively far less attention. Exercise training is widely acknowledged to improve overall vascular health through improved BP control and thus cardiac load [198], improved arterial compliance [186, 199, 200], NO bioavailability [182, 201], control of vasoconstriction and vasorelaxation modulation [182, 202, 203] and endothelial function [182, 202, 203], decreasing overall disease risk in old age. Exercise training has been demonstrated in the elderly to lead to a decrease in diastolic BP, without changes in systolic BP, although some studies have shown systolic changes [198, 204, 205]. Cross-sectional studies have shown that trained populations exhibit greater arterial compliance than non-trained counterparts [186, 199]. In fact, research has indicated that committing to even just mild physical activity such as regular walking exercise (brisk walking, 25-45 min, 3-6 days/week) is enough to facilitate the restoration of arterial compliance impaired with advancing age countering the apparent impact of increased sympathetic activity [199, 200, 206].

Exercise training in the long term has been shown to be associated with the amelioration of the decline in endothelial function induced by ageing, however, much of the information available has been generated through cross-sectional studies as opposed to interventional studies [207]. This has led some to suggest that there is

currently not enough evidence to unequivocally state that exercise training enhances endothelial vascular function in old untrained subjects [207]. However, some studies have reported that exercise training reduces endothelin-1 vasoconstrictor tone, which is normally increased with advancing age [182, 202, 203]. While others show increased endothelial dependent relaxation in trained populations related to an increase in gene expression for proteins involved in NO production [186, 208-210]. Exercise trained old populations have also been shown to exhibit reduced benefits with anti-inflammatory interventions (such as vitamin C), which may be indicative of an existing reduction in oxidative stress [186, 211, 212]. Despite the demonstration of functional vascular changes with exercise training, evidence of structural benefits is lacking, with some suggesting that exercise training does not lead to the reversal of age-related vascular remodelling. Despite this, the overall changes in response to exercise provided by regular training are enough to give vital benefits to overall cardiovascular health and physical capacity [186, 213, 214].

Exercise training has also been found to counter the age-related increase in vasoconstriction by ameliorating the increase in αAR signalling activity [215]. This reduction of enhanced endothelial vasoconstriction occurs through increasing NO synthesis through αAR signalling pathways [215]. However, some research also suggests that exercise training can actually increase the vasoconstrictor response to αAR stimulation in old age, evidenced through an elevated systolic BP response to alpha agonists [216]. Exercise training has also been shown to reduce baroreflex sensitivity. It has been suggested that the potential adverse effects associated with this, such as a heightened risk of syncope – which is also an age-related issue of BP control - may be compensated for by the identified increase in vasoconstrictor response [216]. Contrasting data for exercise training-induced changes in αAR sensitivity perhaps reflects the specific tissues tested and the variability of the age-related remodelling of sensitivity of all other adrenergic receptor types and responses to exercise training.

Data is more unanimous regarding the age-related and exercise-induced remodelling of β_2AR [217]. Exercise training increases β_2AR mediated relaxation in old populations giving an improved vasodilatory response in part facilitated by a reduction in G-protein receptor kinase-2 (GRK2) activity which has an important pathogenic role in age-

related βAR remodelling in the vasculature, but not so much in cardiac settings [17, 185, 215, 218].

4.6 Combined Exercise Training and Drug Therapy

Due to the benefits described above in relation to both drug and non-drug (exercise training) therapies on the reduction of mortality, improvement in overall health, and condition management, there is an interest in investigating the effects of combined therapeutic approaches in terms of polypharmacy but of increasing interest the co-influencing impact of exercise training.

A study in insulin-resistant humans found that combined exercise training and metformin treatment improved left ventricular function (yielding a 68% increase in global longitudinal strain and 42% improvement in longitudinal strain rate) [219]. While another study in a similar population found exercise training and combined exercise training and metformin treatment (12 weeks) improved exercise capacity (18 *vs* 12% increase in oxygen uptake (VO_2) and 10-19% increase in maximum work completed during a cardiopulmonary exercise test), yet metformin treatment alone actually had a negative impact on exercise capacity (6% reduction in VO_2 with a 4% reduction in maximum work completed during a cardiopulmonary exercise test) indicating exercise training when receiving metformin treatment may be recommended to combat a negative impact on physical capacity [220]. A further study in humans with prediabetes, however, found metformin and combined metformin and exercise training therapy improved insulin clearance (24 *vs* 21%), while exercise training alone (12 weeks) had no effect [221].

In contrast, a study in rats with type 2 diabetes found exercise training had a greater beneficial impact on glycaemic control than metformin treatment, and found when combined, metformin may even impair beneficial exercise training-induced remodelling of mitochondrial components in the liver [222]. Similarly, a study in humans with impaired glucose tolerance found despite the benefits of metformin and exercise training on cardiovascular function and CVD risk factors when performed separately (6-7% reduction in systolic BP; 4-8% reduction in diastolic BP; 2-7% reduction in low-density-lipoprotein cholesterol; 8-13% increase in high-density-lipoprotein cholesterol; 20-27% reduction in C-reactive protein), combined therapy

provided no additive benefits [223]. In elderly humans (62 years), one study found combined metformin and exercise training therapy in fact ameliorated the benefits of exercise training only on insulin sensitivity (~0 *vs* ~20-30% improvement in whole-body insulin sensitivity) and exercise capacity (~50% reduction in exercise training-induced increase in VO_2) [224]. Similar findings were reported elsewhere which additionally suggests that combined metformin and exercise training treatment blunts reductions in markers of inflammation and cardiometabolic disease risk as well as improvements in insulin sensitivity [225].

Considering interactions with resveratrol use in aged humans (>65 years), a study found that combined resveratrol and exercise training blunted the improvements in cardiovascular function observed with exercise training alone (8 weeks) [226]. This study reported combined therapy reduced improvements provided by exercise training alone in VO_2max (13 *vs* 19% increase), MAP (3 *vs* 5% reduction), resting HR (3 *vs* 8% reduction) and low-density-lipoprotein cholesterol (6 *vs* 9%) [226]. This is supported by further work which has found resveratrol treatment combined with exercise training does not provide additive improvement to exercise-induced increases in cardiovascular function and may even result in impairment in aged humans [227]. The potentially negative impact of combined therapy compared with exercise in old humans (60-72 years) is also supported by a study which reported a reduction in exercise training-induced metabolic and anti-inflammatory benefits with additive resveratrol treatment compared with exercise training alone [153]. Combined therapy may also limit exercise-induced (8 weeks exercise training) muscular angiogenesis in old humans (>65 years) [228]. Although some argue, the extent of potential negative effects of combined therapy may not be clinically relevant [229, 230]. In contrast, a study in rats found resveratrol provided additive cardiovascular benefits when combined with exercise training (12 weeks) compared with exercise training alone (18 *vs* 9% increase in fractional shortening; 4-fold *vs* 3-fold increase in time to exhaustion during exercise testing; 18-58% greater increase in leg skeletal muscle strength; ~17 *vs* ~5% increase in EF; ~55 *vs* ~30% increase in E:A ratio) [231]. A study in middle-aged mice (16 months) supports the above findings and similarly reported an additive benefit with combined therapy compared with exercise training alone in muscle strength and aerobic exercise performance [232]. Such more positive results for combined approaches are not unique to animal models though. Combined

therapy of resveratrol and exercise training has also been shown to yield greater increases in the density of mitochondria volume, peak muscle power, and endurance compared to exercise training alone (12 weeks) in old humans (65-80 years) [233]. Combined therapy is has been shown to activate cellular protective pathways (PI_3K-Akt / FOXO3) combatting potential damage from oxidative stress [234]. A study in old mice (18 months) also reported anti-ageing benefits of combined resveratrol and exercise training therapy through the restoration of exercise capacity (2.5 fold increase in time to exhaustion during exercise testing) and components associated with mitochondrial biogenesis in skeletal muscle (3-fold increase in PGC-1α expression) [235].

Combined ACE inhibitor and exercise training therapy has been shown to provide greater improvements in left ventricular function than those exhibited by individual ACE inhibitor or exercise training therapy (10 weeks) in young rats (3 months) [236]. In addition, greater reductions in insulin concentration (54-56%), insulin resistance, and BP (9-11% reduction in systolic BP; 8-9% reduction in diastolic BP) have been reported with combined ACE inhibitor and exercise training therapy compared with the use of ACE inhibitors alone (34% reduction in insulin concentration; 7% reduction in systolic BP; 5% reduction in diastolic BP) and exercise training (43% reduction in insulin concentration; 4% reduction in systolic BP; 2% reduction in diastolic BP) in hypertensive humans [237]. In rats, combined therapy has also been shown to improve exercise-induced myocardial angiogenesis compared with individual therapies (65% increase in capillary surface area density in combined therapy *vs* 26% and 38% in ACE inhibitor and exercise training, respectively) [238]. Combined therapy also improves to a greater extent, glucose tolerance and insulin action in obese rats and better preserves cardiac function in rats post myocardial infarction [239, 240]. However, some contradicting studies have found that combined ACE inhibitor and exercise training therapy stimulates no additive benefits over exercise training alone in old humans (>65 years) and little to no additive effects on exercise capacity or exercise-induced skeletal muscle remodelling in rats [241, 242].

Lastly, studies investigating combined β-blocker and exercise training suggest improvements in exercise capacity in humans with HF or post myocardial infarction [243, 244]. In mice with HF, combined beta-blocker and exercise training therapy (4 weeks) provided additive improvements to cardiovascular function compared with

individual therapy through reduced HR (17 *vs* 16 *vs* 7%), increased stroke volume (71 *vs* 25 *vs* 34%) and increased EF (41 *vs* 34 *vs* 13%) in combined *vs* beta-blocker only *vs* exercise training only, respectively [245]. In support, another study in mice (5-7 months) with HF found combined therapy improved exercise tolerance, reduced mortality, and improved ventricular contractility [246]. Meanwhile, in hypertensive rats, a study found combined beta-blocker and exercise training therapy provided similar improvements in baroreflex function and reductions in HR compared with each treatment individually [247].

5.0 Summary and Conclusion

The heart and associated vasculature undergo wide-scale remodelling with advancing age. This age-related remodelling contributes to the loss of physical capacity and an increased risk for disease with progressive deterioration of physiological function. So far, a single factor or adaptation has not been demonstrated to trigger this cascade, instead the degradation of the ageing cardiovascular system is a result of diverse remodelling of several systems and signalling cascades. However, a key component of the age-related loss of cardiac reserve and in turn physical capacity is a loss of adrenergic signalling efficiency and sensitivity. Age-related losses in β_1AR signalling have dominated interest and mounting evidence supports a link between this and the age-related loss of cardiac reserve. Research interest, thus far, has predominantly focused on cardiac-specific changes, however, vascular remodelling plays an important role in the changes in overall cardiovascular function, also heavily influenced by changing adrenergic control with advancing age. A decline in adrenergic control of both the heart and vasculature increases disease risk as well as impacting CO and BP responses to physical activity.

There is no shortage of potential therapeutic strategies and the benefits of non-pharmacological strategies such as exercise training or combined exercise training and drug therapy should be seriously considered. Combined therapies display evidence of effectiveness for improving the management of CVD and age-associated degradation of the cardiovascular system, although evidence is more mixed regarding effects on exercise capacity, despite displaying some promise in aged subjects.

Exercise training has been shown to facilitate a level of restoration of adrenergic signalling as well as other age-related decrements leading to some apparent rejuvenation of cardiac and vascular function. More investigation is required to fully elucidate the range of benefits in terms of specific signalling and influence on the overall efficiency of adrenergic function and integrated control in its entirety, although evidence so far is positive for the reduction of disease risk and the improvement in the control of HR, contractility, and BP.

In conclusion, an ageing population triggers considerable issues for modern society and endangers quality of life for the large fraction of the population projected to be >65 years in the future. Due to the association with increased CVD risk, one of the biggest global killers and causes of morbidity, as well as the ramifications on quality of life, tackling factors influencing the deteriorating cardiovascular function in the elderly an effective strategy and therapeutic approach is required for preserving and improving quality of life. The normal focus on pharmacological therapy may be more effective when combined with the complimentary effects of exercise training.

Consent for Publication

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Conflict of Interest

No conflict of interest/competing interest for this study.

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6.0 References

[1] Harvey A, Montezano AC, Lopes RA, Rios F, Touyz RM. Vascular fibrosis in aging and hypertension: molecular mechanisms and clinical implications. Canadian Journal of Cardiology, 2016; 32: 659-668.

[2] Vial G, Detaille D, Guigas B. Role of mitochondria in the mechanism (s) of action of metformin. Frontiers in endocrinology, 2019; 10: 294.

[3] Ferrara N, Komici K, Corbi G, Pagano G, Furgi G, Rengo C, Femminella GD, Leosco D, Bonaduce D. β-adrenergic receptor responsiveness in aging heart and clinical implications. Frontiers in physiology, 2014; 4: 396.

[4] Mathers CD, Stevens GA, Boerma T, White RA, Tobias MI. Causes of international increases in older age life expectancy. The Lancet, 2015; 385: 540-548.

[5] Roser M, Ritchie H, Ortiz-Ospina E. World population growth. Our world in data, 2013.

[6] Organization WH. World health statistics 2019: monitoring health for the SDGs, sustainable development goals. 2019.

[7] Pyrkov TV, Avchaciov K, Tarkhov AE, Menshikov LI, Gudkov AV, Fedichev PO. Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts human lifespan limit. Nature communications, 2021; 12: 1-10.

[8] Raleigh V. What is happening to life expectancy in the UK. England The King's Fund, 2019.

[9] Marmot M. Health equity in England: the Marmot review 10 years on. BMJ, 2020; 368.

[10] Randall M. Overview of the UK population: July 2017. UK Office for National Statistics (July 2017), 2017.

[11] de Beer J, Bardoutsos A, Janssen F. Maximum human lifespan may increase to 125 years. Nature, 2017; 546: E16-E17.

[12] Rozing MP, Kirkwood TB, Westendorp RG. Is there evidence for a limit to human lifespan? Nature, 2017; 546: E11-E12.

[13] Lenart A, Vaupel JW. Questionable evidence for a limit to human lifespan. Nature, 2017; 546: E13-E14.

[14] Dong X, Milholland B, Vijg J. Evidence for a limit to human lifespan. Nature, 2016; 538: 257-259.

[15] Crimmins EM. Lifespan and healthspan: past, present, and promise. The Gerontologist, 2015; 55: 901-911.

[16] Niccoli T, Partridge L. Ageing as a risk factor for disease. Current biology, 2012; 22: R741-R752.

[17] Santulli G, Iaccarino G. Pinpointing beta adrenergic receptor in ageing pathophysiology: victim or executioner? Evidence from crime scenes. Immunity & Ageing, 2013; 10: 10.

[18] De Lucia C, Eguchi A, Koch WJ. New insights in cardiac β-adrenergic signaling during heart failure and aging. Frontiers in pharmacology, 2018; 9: 904.

[19] Maron BJ, Pelliccia A. The heart of trained athletes: cardiac remodeling and the risks of sports, including sudden death. Circulation, 2006; 114: 1633-1644.

[20] BARNES RF, RASKIND M, GUMBRECHT G, HALTER JB. The effects of age on the plasma catecholamine response to mental stress in man. The Journal of Clinical Endocrinology & Metabolism, 1982; 54: 64-69.

[21] Fleg JL, Tzankoff SP, Lakatta EG. Age-related augmentation of plasma catecholamines during dynamic exercise in healthy males. Journal of Applied Physiology, 1985; 59: 1033-1039.

[22] Aalami OO, Fang TD, Song HM, Nacamuli RP. Physiological features of aging persons. Archives of Surgery, 2003; 138: 1068-1076.

[23] Nagaratnam N. Ageing and Longevity. In: ed.^eds., Advanced Age Geriatric Care. Springer, 2019; pp. 3-9.

[24] Jin K. Modern biological theories of aging. Aging and disease, 2010; 1: 72.

[25] Hayflick L. Theories of biological aging. Experimental gerontology, 1985; 20: 145-159.

[26] Bwiza CP, Son JM, Lee C. Integrated Theories of Biological Aging. In: ed.^eds., Oxford Research Encyclopedia of Psychology, 2019.

[27] Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. Nature Reviews Cardiology, 2018; 15: 230.

[28] Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R, Rayner M, Townsend N. European cardiovascular disease statistics 2017. 2017.

[29] Olivetti G, Melissari M, Capasso J, Anversa P. Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. Circulation research, 1991; 68: 1560-1568.

[30] Sheydina A, Riordon DR, Boheler KR. Molecular mechanisms of cardiomyocyte aging. Clinical Science, 2011; 121: 315-329.

[31] Gurven M, Blackwell AD, Rodríguez DE, Stieglitz J, Kaplan H. Does blood pressure inevitably rise with age? Longitudinal evidence among forager-horticulturalists. Hypertension, 2012; 60: 25-33.

[32] Pearson JD, Morrell CH, Brant LJ, Landis PK, Fleg JL. Age-associated changes in blood pressure in a longitudinal study of healthy men and women. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 1997; 52: M177-M183.

[33] Ferrari AU, Radaelli A, Centola M. Invited review: aging and the cardiovascular system. Journal of Applied Physiology, 2003; 95: 2591-2597.

[34] Dai D-F, Chen T, Johnson SC, Szeto H, Rabinovitch PS. Cardiac aging: from molecular mechanisms to significance in human health and disease. Antioxidants & redox signaling, 2012; 16: 1492-1526.

[35] Shin E, Ko KS, Rhee BD, Han J, Kim N. Different effects of prolonged β-adrenergic stimulation on heart and cerebral artery. Integrative medicine research, 2014; 3: 204-210.

[36] Shimizu I, Minamino T. Physiological and pathological cardiac hypertrophy. Journal of molecular and cellular cardiology, 2016; 97: 245-262.

[37] Backs J, Song K, Bezprozvannaya S, Chang S, Olson EN. CaM kinase II selectively signals to histone deacetylase 4 during cardiomyocyte hypertrophy. The Journal of clinical investigation, 2006; 116: 1853-1864.

[38] Nakamura M, Sadoshima J. Mechanisms of physiological and pathological cardiac hypertrophy. Nature Reviews Cardiology, 2018; 15: 387-407.

[39] Wilkins BJ, Molkentin JD. Calcium–calcineurin signaling in the regulation of cardiac hypertrophy. Biochemical and biophysical research communications, 2004; 322: 1178-1191.

[40] Chacar S, Hajal J, Saliba Y, Bois P, Louka N, Maroun RG, Faivre JF, Fares N. Long-term intake of phenolic compounds attenuates age-related cardiac remodeling. Aging Cell, 2019; 18: e12894.

[41] Anversa P, Hiler B, Ricci R, Guideri G, Olivetti G. Myocyte cell loss and myocyte hypertrophy in the aging rat heart. Journal of the American College of Cardiology, 1986; 8: 1441-1448.

[42] Manne N, Kakarla S, Arvapalli R, Rice K, Blough E. Molecular mechanisms of age-related cardiac hypertrophy in the F344XBN rat model. J Clin Exp Cardiolog, 2014; 5: 2.

[43] Gerdts E, Roman M, Palmieri V, Wachtell K, Smith G, Nieminen MS, Dahlöf B, Devereux RB. Impact of age on left ventricular hypertrophy regression during antihypertensive treatment with losartan or atenolol (the LIFE study). Journal of human hypertension, 2004; 18: 417-422.

[44] Lindsey ML, Goshorn DK, Squires CE, Escobar GP, Hendrick JW, Mingoia JT, Sweterlitsch SE, Spinale FG. Age-dependent changes in myocardial matrix metalloproteinase/tissue inhibitor of metalloproteinase profiles and fibroblast function. Cardiovascular research, 2005; 66: 410-419.

[45] Strait JB, Lakatta EG. Aging-associated cardiovascular changes and their relationship to heart failure. Heart failure clinics, 2012; 8: 143-164.

[46] Ungvari Z, Tarantini S, Donato AJ, Galvan V, Csiszar A. Mechanisms of vascular aging. Circulation research, 2018; 123: 849-867.

[47] Fares E, Howlett SE. Effect of age on cardiac excitation–contraction coupling. Clinical and Experimental Pharmacology and Physiology, 2010; 37: 1-7.

[48] Zhu X, Altschafl BA, Hajjar RJ, Valdivia HH, Schmidt U. Altered Ca2+ sparks and gating properties of ryanodine receptors in aging cardiomyocytes. Cell Calcium, 2005; 37: 583-591.

[49] Jiang M-t, Narayanan N. Effects of aging on phospholamban phosphorylation and calcium transport in rat cardiac sarcoplasmic reticulum. Mechanisms of ageing and development, 1990; 54: 87-101.

[50] Lim CC, Liao R, Varma N, Apstein CS. Impaired lusitropy-frequency in the aging mouse: role of Ca2+-handling proteins and effects of isoproterenol. American Journal of Physiology-Heart and Circulatory Physiology, 1999; 277: H2083-H2090.

[51] Liu J, Sirenko S, Juhaszova M, Sollott SJ, Shukla S, Yaniv Y, Lakatta EG. Age-associated abnormalities of intrinsic automaticity of sinoatrial nodal cells are linked to deficient cAMP-PKA-Ca2+ signaling. American Journal of Physiology-Heart and Circulatory Physiology, 2014; 306: H1385-H1397.

[52] Liu SJ, Wyeth RP, Melchert RB, Kennedy RH. Aging-associated changes in whole cell K+ and L-type Ca2+ currents in rat ventricular myocytes. American Journal of Physiology-Heart and Circulatory Physiology, 2000; 279: H889-H900.

[53] Walker K, Lakatta E, Houser S. Age associated changes in membrane currents in rat ventricular myocytes. Cardiovascular research, 1993; 27: 1968-1977.

[54] Feridooni HA, Dibb KM, Howlett SE. How cardiomyocyte excitation, calcium release and contraction become altered with age. Journal of molecular and cellular cardiology, 2015; 83: 62-72.

[55] Josephson IR, Guia A, Stern MD, Lakatta EG. Alterations in properties of L-type Ca channels in aging rat heart. Journal of molecular and cellular cardiology, 2002; 34: 297-308.

[56] Ocorr K, Reeves NL, Wessells RJ, Fink M, Chen H-SV, Akasaka T, Yasuda S, Metzger JM, Giles W, Posakony JW. KCNQ potassium channel mutations cause cardiac arrhythmias in Drosophila that mimic the effects of aging. Proceedings of the National Academy of Sciences, 2007; 104: 3943-3948.

[57] Harvey A, Montezano AC, Touyz RM. Vascular biology of ageing—Implications in hypertension. Journal of molecular and cellular cardiology, 2015; 83: 112-121.

[58] Albarwani SA, Mansour F, Khan AA, Al-Lawati I, Al-Kaabi A, Al-Busaidi A-M, Al-Hadhrami S, Al-Husseini I, Al-Siyabi S, Tanira MO. Aging reduces L-type calcium channel current and the vasodilatory response of small mesenteric arteries to calcium channel blockers. Frontiers in physiology, 2016; 7: 171.

[59] Taddei S, Virdis A, Ghiadoni L, Salvetti G, Bernini G, Magagna A, Salvetti A. Age-related reduction of NO availability and oxidative stress in humans. Hypertension, 2001; 38: 274-279.

[60] Celermajer DS, Sorensen KE, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Deanfield JE. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. Journal of the American College of Cardiology, 1994; 24: 471-476.

[61] Taddei S, Virdis A, Mattei P, Ghiadoni L, Gennari A, Fasolo CB, Sudano I, Salvetti A. Aging and endothelial function in normotensive subjects and patients with essential hypertension. Circulation, 1995; 91: 1981-1987.

[62] Donato AJ, Eskurza I, Silver AE, Levy AS, Pierce GL, Gates PE, Seals DR. Direct evidence of endothelial oxidative stress with aging in humans: relation to impaired endothelium-dependent dilation and upregulation of nuclear factor-κB. Circulation research, 2007; 100: 1659-1666.

[63] Upadhya B, Taffet GE, Cheng CP, Kitzman DW. Heart failure with preserved ejection fraction in the elderly: scope of the problem. Journal of molecular and cellular cardiology, 2015; 83: 73-87.

[64] Nakou E, Parthenakis F, Kallergis E, Marketou M, Nakos K, Vardas P. Healthy aging and myocardium: A complicated process with various effects in cardiac structure and physiology. International journal of cardiology, 2016; 209: 167-175.

[65] Christou DD, Seals DR. Decreased maximal heart rate with aging is related to reduced β-adrenergic responsiveness but is largely explained by a reduction in intrinsic heart rate. Journal of applied physiology, 2008; 105: 24-29.

[66] Stratton JR, Levy WC, Caldwell JH, Jacobson A, May J, Dale Matsuoka C, Madden K. Effects of Aging on Cardiovascular Responses to Parasympathetic Withdrawal. age, 2003; 41: 2077-83.

[67] Huang X, Yang P, Du Y, Zhang J, Ma A. Age-related down-regulation of HCN channels in rat sinoatrial node. Basic research in cardiology, 2007; 102: 429-435.

[68] Larson ED, Clair JRS, Sumner WA, Bannister RA, Proenza C. Depressed pacemaker activity of sinoatrial node myocytes contributes to the age-dependent decline in maximum heart rate. Proceedings of the National Academy of Sciences, 2013; 110: 18011-18016.

[69] Jones SA, Boyett MR, Lancaster MK. Declining into failure: the age-dependent loss of the L-type calcium channel within the sinoatrial node. Circulation, 2007; 115: 1183-1190.

[70] Roh J, Rhee J, Chaudhari V, Rosenzweig A. The Role of Exercise in Cardiac Aging: From Physiology to Molecular Mechanisms. Circulation research, 2016; 118: 279-295.

[71] Jones SA, Lancaster MK, Boyett MR. Ageing-related changes of connexins and conduction within the sinoatrial node. The Journal of physiology, 2004; 560: 429-437.

[72] Howlett LA, Lancaster MK. Reduced cardiac response to the adrenergic system is a key limiting factor for physical capacity in old age. Experimental Gerontology, 2021: 111339.

[73] Travers JG, Kamal FA, Robbins J, Yutzey KE, Blaxall BC. Cardiac fibrosis: the fibroblast awakens. Circulation research, 2016; 118: 1021-1040.

[74] Liu T, Song D, Dong J, Zhu P, Liu J, Liu W, Ma X, Zhao L, Ling S. Current understanding of the pathophysiology of myocardial fibrosis and its quantitative assessment in heart failure. Frontiers in physiology, 2017; 8: 238.

[75] Trial J, Cieslik KA. Changes in cardiac resident fibroblast physiology and phenotype in aging. American Journal of Physiology-Heart and Circulatory Physiology, 2018.

[76] Steenman M, Lande G. Cardiac aging and heart disease in humans. Biophysical reviews, 2017; 9: 131-137.

[77] Chaudhary KR, El-Sikhry H, Seubert JM. Mitochondria and the aging heart. Journal of geriatric cardiology: JGC, 2011; 8: 159.

[78] Trott DW, Fadel PJ. Inflammation as a mediator of arterial ageing. Experimental physiology, 2019; 104: 1455-1471.

[79] Wu J, Xia S, Kalionis B, Wan W, Sun T. The role of oxidative stress and inflammation in cardiovascular aging. BioMed research international, 2014; 2014.

[80] Lakatta EG. Age-associated cardiovascular changes in health: impact on cardiovascular disease in older persons. Heart failure reviews, 2002; 7: 29-49.

[81] Fleg JL, Strait J. Age-associated changes in cardiovascular structure and function: a fertile milieu for future disease. Heart failure reviews, 2012; 17: 545-554.

[82] Uejima T, Dunstan FD, Arbustini E, Łoboz-Grudzień K, Hughes AD, Carerj S, Favalli V, Antonini-Canterin F, Vriz O, Vinereanu D. Age-specific reference values for carotid arterial stiffness estimated by ultrasonic wall tracking. Journal of human hypertension, 2020; 34: 214-222.

[83] Chantler PD, Lakatta E. Arterial–ventricular coupling with aging and disease. Frontiers in physiology, 2012; 3: 90.

[84] Grossman W, Jones D, McLaurin L. Wall stress and patterns of hypertrophy in the human left ventricle. The Journal of clinical investigation, 1975; 56: 56-64.

[85] Houghton D, Jones TW, Cassidy S, Siervo M, MacGowan GA, Trenell MI, Jakovljevic DG. The effect of age on the relationship between cardiac and vascular function. Mechanisms of ageing and development, 2016; 153: 1-6.

[86] Lakatta EG, Sollott SJ. Perspectives on mammalian cardiovascular aging: humans to molecules. Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology, 2002; 132: 699-721.

[87] Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and ventricular systolic stiffening in hypertensive heart disease: insights into the pathogenesis of heart failure with preserved ejection fraction. Journal of the American College of Cardiology, 2009; 54: 410-418.

[88] Sonaglioni A, Baravelli M, Lombardo M, Sommese C, Anzà C, Kirk JA, Padeletti L. Ventricular-arterial coupling in centenarians without cardiovascular diseases. Aging clinical and experimental research, 2018; 30: 367-373.

[89] Najjar SS, Schulman SP, Gerstenblith G, Fleg JL, Kass DA, O'Connor F, Becker LC, Lakatta EG. Age and gender affect ventricular-vascular coupling during aerobic exercise. Journal of the American College of Cardiology, 2004; 44: 611-617.

[90] Tellez JO, Mączewski M, Yanni J, Sutyagin P, Mackiewicz U, Atkinson A, Inada S, Beresewicz A, Billeter R, Dobrzynski H. Ageing-dependent remodelling of ion channel and Ca2+ clock genes underlying sino-atrial node pacemaking. Experimental physiology, 2011; 96: 1163-1178.

[91] Davies C, Ferrara N, Harding S. β-Adrenoceptor function changes with age of subject in myocytes from non-failing human ventricle. Cardiovascular research, 1996; 31: 152-156.

[92] Najafi A, Sequeira V, Kuster DW, van der Velden J. β-adrenergic receptor signalling and its functional consequences in the diseased heart. European journal of clinical investigation, 2016; 46: 362-374.

[93] Narayanan N, Derby J-A. Alterations in the properties of β-adrenergic receptors of myocardial membranes in aging: Impairments in agonist—receptor interactions and guanine nucleotide regulation accompany diminished

catecholamine-responsiveness of adenylated cyclase. Mechanisms of ageing and development, 1982; 19: 127-139.

[94] White M, Roden R, Minobe W, Khan M, Larrabee P, Wollmering M, Port J, Anderson F, Campbell D, Feldman A. Age-related changes in beta-adrenergic neuroeffector systems in the human heart. Circulation, 1994; 90: 1225-1238.

[95] Ungerer M, Böhm M, Elce J, Erdmann E, Lohse M. Altered expression of beta-adrenergic receptor kinase and beta 1-adrenergic receptors in the failing human heart. Circulation, 1993; 87: 454-463.

[96] Xiao R-P, Spurgeon HA, O'connor F, Lakatta EG. Age-associated changes in beta-adrenergic modulation on rat cardiac excitation-contraction coupling. The Journal of clinical investigation, 1994; 94: 2051-2059.

[97] Farrell SR, Howlett SE. The age-related decrease in catecholamine sensitivity is mediated by ß1-adrenergic receptors linked to a decrease in adenylate cyclase activity in ventricular myocytes from male Fischer 344 rats. Mechanisms of ageing and development, 2008; 129: 735-744.

[98] Scarpace PJ, Turner N, Mader SL. β-Adrenergic function in aging. Drugs & aging, 1991; 1: 116-129.

[99] Tobise K, Ishikawa Y, Holmer SR, Im M-J, Newell JB, Yoshie H, Fujita M, Susannie EE, Homcy CJ. Changes in type VI adenylyl cyclase isoform expression correlate with a decreased capacity for cAMP generation in the aging ventricle. Circulation research, 1994; 74: 596-603.

[100] Spadari RC, Cavadas C, de Carvalho AETS, Ortolani D, de Moura AL, Vassalo PF. Role of beta-adrenergic receptors and sirtuin signaling in the heart during aging, heart failure, and adaptation to stress. Cellular and molecular neurobiology, 2018: 1-12.

[101] Marín J. Age-related changes in vascular responses: a review. Mechanisms of ageing and development, 1995; 79: 71-114.

[102] Jensen BC, O'Connell TD, Simpson PC. Alpha-1-adrenergic receptors: targets for agonist drugs to treat heart failure. Journal of molecular and cellular cardiology, 2011; 51: 518-528.

[103] O'Connell TD, Jensen BC, Baker AJ, Simpson PC. Cardiac alpha1-adrenergic receptors: novel aspects of expression, signaling mechanisms, physiologic function, and clinical importance. Pharmacological reviews, 2014; 66: 308-333.

[104] Garcia MI, Boehning D. Cardiac inositol 1, 4, 5-trisphosphate receptors. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 2017; 1864: 907-914.

[105] Graham RM, Perez DM, Hwa J, Piascik MT. α1-Adrenergic receptor subtypes: molecular structure, function, and signaling. Circulation research, 1996; 78: 737-749.

[106] Michelotti GA, Price DT, Schwinn DA. α1-Adrenergic receptor regulation: basic science and clinical implications. Pharmacology & therapeutics, 2000; 88: 281-309.

[107] Cupitra NI, Calderón JC, Narvaez-Sanchez R. Influence of ageing on vascular reactivity and receptor expression in rabbit aorta: a complement to elastocalcinosis and smooth muscle mechanisms. Clinical interventions in aging, 2020; 15: 537.

[108] Su N, Narayanan N. Age related alteration in cholinergic but not α adrenergic response of rat coronary vasculature. Cardiovascular research, 1993; 27: 284-290.

[109] Zhang J, Simpson PC, Jensen BC. Cardiac α1A-adrenergic receptors: emerging protective roles in cardiovascular diseases. American Journal of Physiology-Heart and Circulatory Physiology, 2021; 320: H725-H733.

[110] Korzick D, Holiman D, Boluyt M, Laughlin M, Lakatta E. Diminished α1-adrenergic-mediated contraction and translocation of PKC in senescent rat heart. American Journal of Physiology-Heart and Circulatory Physiology, 2001; 281: H581-H589.

[111] White M, Fourney A, Mikes E, Leenen FH. Effects of age and hypertension on cardiac responses to the α1-agonist phenylephrine in humans. American journal of hypertension, 1999; 12: 151-158.

[112] Giovannitti Jr JA, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. Anesthesia progress, 2015; 62: 31-38.

[113] Smith EG, Voyles WF, Kirby BS, Markwald RR, Dinenno FA. Ageing and leg postjunctional α-adrenergic vasoconstrictor responsiveness in healthy men. The Journal of physiology, 2007; 582: 63-71.

[114] Madamanchi A. β-Adrenergic receptor signaling in cardiac function and heart failure. McGill Journal of Medicine: MJM, 2007; 10: 99.

[115] Johnson M. Beta2-adrenoceptors: mechanisms of action of beta2-agonists. Paediatric respiratory reviews, 2001; 2: 57-62.

[116] Billington CK, Penn RB, Hall IP. β 2 Agonists. Pharmacology and Therapeutics of Asthma and COPD, 2016: 23-40.

[117] Xiao R-P, Tomhave ED, Wang D-J, Ji X, Boluyt MO, Cheng H, Lakatta EG, Koch WJ. Age-associated reductions in cardiac beta1-and beta2-adrenergic responses without changes in inhibitory G proteins or receptor kinases. The Journal of clinical investigation, 1998; 101: 1273-1282.

[118] Alfaras I, Di Germanio C, Bernier M, Csiszar A, Ungvari Z, Lakatta EG, De Cabo R. Pharmacological strategies to retard cardiovascular aging. Circulation research, 2016; 118: 1626-1642.

[119] Song R. Mechanism of metformin: a tale of two sites. Diabetes care, 2016; 39: 187-189.

[120] Lv Z, Guo Y. Metformin and its benefits for various diseases. Frontiers in Endocrinology, 2020; 11: 191.

[121] Valencia WM, Palacio A, Tamariz L, Florez H. Metformin and ageing: improving ageing outcomes beyond glycaemic control. Diabetologia, 2017; 60: 1630-1638.

[122] Anisimov VN, Berstein LM, Egormin PA, Piskunova TS, Popovich IG, Zabezhinski MA, Tyndyk ML, Yurova MV, Kovalenko IG, Poroshina TE. Metformin slows down aging and extends life span of female SHR mice. Cell cycle, 2008; 7: 2769-2773.

[123] Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, Gomes AP, Ward TM, Minor RK, Blouin M-J. Metformin improves healthspan and lifespan in mice. Nature communications, 2013; 4: 1-9.

[124] Chen J, Ou Y, Li Y, Hu S, Shao L-W, Liu Y. Metformin extends C. elegans lifespan through lysosomal pathway. Elife, 2017; 6: e31268.

[125] Mohan M, Al-Talabany S, McKinnie A, Mordi IR, Singh JS, Gandy SJ, Baig F, Hussain MS, Bhalraam U, Khan F. A randomized controlled trial of metformin on left ventricular hypertrophy in patients with coronary artery disease without diabetes: the MET-REMODEL trial. European heart journal, 2019; 40: 3409-3417.

[126] Han Y, Xie H, Liu Y, Gao P, Yang X, Shen Z. Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a

systematic review and an updated meta-analysis. Cardiovascular diabetology, 2019; 18: 1-16.

[127] Wang XF, Zhang JY, Li L, Zhao XY, Tao HL, Zhang L. Metformin improves cardiac function in rats via activation of AMP-activated protein kinase. Clinical and Experimental Pharmacology and Physiology, 2011; 38: 94-101.

[128] Zhu X, Shen W, Liu Z, Sheng S, Xiong W, He R, Zhang X, Ma L, Ju Z. Effect of metformin on cardiac metabolism and longevity in aged female mice. Frontiers in Cell and Developmental Biology, 2021; 8: 1739.

[129] Le Liu Y-QN, Zhan J-K, Liu Y-S. The Role of SGLT2 Inhibitors in Vascular Aging. Aging and disease, 2021; 12: 1323.

[130] Gorini S, Kim SK, Infante M, Mammi C, La Vignera S, Fabbri A, Jaffe IZ, Caprio M. Role of aldosterone and mineralocorticoid receptor in cardiovascular aging. Frontiers in endocrinology, 2019; 10: 584.

[131] Filippatos G, Anker SD, Agarwal R, Pitt B, Ruilope LM, Rossing P, Kolkhof P, Schloemer P, Tornus I, Joseph A. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. Circulation, 2021; 143: 540-552.

[132] Grune J, Beyhoff N, Smeir E, Chudek R, Blumrich A, Ban Z, Brix S, Betz IR, Schupp M, Foryst-Ludwig A. Selective mineralocorticoid receptor cofactor modulation as molecular basis for finerenone's antifibrotic activity. Hypertension, 2018; 71: 599-608.

[133] Li J, Zhang C-X, Liu Y-M, Chen K-L, Chen G. A comparative study of anti-aging properties and mechanism: resveratrol and caloric restriction. Oncotarget, 2017; 8: 65717.

[134] Bhullar KS, Hubbard BP. Lifespan and healthspan extension by resveratrol. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 2015; 1852: 1209-1218.

[135] Wood JG, Rogina B, Lavu S, Howitz K, Helfand SL, Tatar M, Sinclair D. Sirtuin activators mimic caloric restriction and delay ageing in metazoans. Nature, 2004; 430: 686-689.

[136] Viswanathan M, Kim SK, Berdichevsky A, Guarente L. A role for SIR-2.1 regulation of ER stress response genes in determining C. elegans life span. Developmental cell, 2005; 9: 605-615.

[137] Wang C, Wheeler CT, Alberico T, Sun X, Seeberger J, Laslo M, Spangler E, Kern B, De Cabo R, Zou S. The effect of resveratrol on lifespan depends on both gender and dietary nutrient composition in Drosophila melanogaster. Age, 2013; 35: 69-81.

[138] Rascón B, Hubbard BP, Sinclair DA, Amdam GV. The lifespan extension effects of resveratrol are conserved in the honey bee and may be driven by a mechanism related to caloric restriction. Aging (Albany NY), 2012; 4: 499.

[139] da Luz PL, Tanaka L, Brum PC, Dourado PMM, Favarato D, Krieger JE, Laurindo FRM. Red wine and equivalent oral pharmacological doses of resveratrol delay vascular aging but do not extend life span in rats. Atherosclerosis, 2012; 224: 136-142.

[140] Cencioni C, Spallotta F, Mai A, Martelli F, Farsetti A, Zeiher AM, Gaetano C. Sirtuin function in aging heart and vessels. Journal of molecular and cellular cardiology, 2015; 83: 55-61.

[141] Bai B, Vanhoutte PM, Wang Y. Loss-of-SIRT1 function during vascular ageing: hyperphosphorylation mediated by cyclin-dependent kinase 5. Trends in cardiovascular medicine, 2014; 24: 81-84.

[142] Bai B, Liang Y, Xu C, Lee MY, Xu A, Wu D, Vanhoutte PM, Wang Y. Cyclin-dependent kinase 5–mediated hyperphosphorylation of sirtuin-1 contributes to the development of endothelial senescence and atherosclerosis. Circulation, 2012; 126: 729-740.

[143] Tanno M, Kuno A, Horio Y, Miura T. Emerging beneficial roles of sirtuins in heart failure. Basic research in cardiology, 2012; 107: 273.

[144] Hsu Y-J, Hsu S-C, Hsu C-P, Chen Y-H, Chang Y-L, Sadoshima J, Huang S-M, Tsai C-S, Lin C-Y. Sirtuin 1 protects the aging heart from contractile dysfunction mediated through the inhibition of endoplasmic reticulum stress-mediated apoptosis in cardiac-specific Sirtuin 1 knockout mouse model. International journal of cardiology, 2017; 228: 543-552.

[145] Fujitaka K, Otani H, Jo F, Jo H, Nomura E, Iwasaki M, Nishikawa M, Iwasaka T, Das DK. Modified resveratrol Longevinex improves endothelial function in adults with metabolic syndrome receiving standard treatment. Nutrition research, 2011; 31: 842-847.

[146] Bhatt JK, Thomas S, Nanjan MJ. Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. Nutrition research, 2012; 32: 537-541.

[147] Imamura H, Yamaguchi T, Nagayama D, Saiki A, Shirai K, Tatsuno I. Resveratrol ameliorates arterial stiffness assessed by cardio-ankle vascular index in patients with type 2 diabetes mellitus. International heart journal, 2017; 58: 577-583.

[148] Wong RH, Berry NM, Coates AM, Buckley JD, Bryan J, Kunz I, Howe PR. Chronic resveratrol consumption improves brachial flow-mediated dilatation in healthy obese adults. Journal of hypertension, 2013; 31: 1819-1827.

[149] Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, Goossens GH, Hoeks J, van der Krieken S, Ryu D, Kersten S. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell metabolism, 2011; 14: 612-622.

[150] Tomé-Carneiro J, Larrosa M, Yáñez-Gascón MJ, Dávalos A, Gil-Zamorano J, Gonzálvez M, García-Almagro FJ, Ros JAR, Tomás-Barberán FA, Espín JC. One-year supplementation with a grape extract containing resveratrol modulates inflammatory-related microRNAs and cytokines expression in peripheral blood mononuclear cells of type 2 diabetes and hypertensive patients with coronary artery disease. Pharmacological research, 2013; 72: 69-82.

[151] Dyck GJ, Raj P, Zieroth S, Dyck JR, Ezekowitz JA. The effects of resveratrol in patients with cardiovascular disease and heart failure: a narrative review. International journal of molecular sciences, 2019; 20: 904.

[152] Huang H, Chen G, Liao D, Zhu Y, Pu R, Xue X. The effects of resveratrol intervention on risk markers of cardiovascular health in overweight and obese subjects: a pooled analysis of randomized controlled trials. Obesity reviews, 2016; 17: 1329-1340.

[153] Olesen J, Gliemann L, Biensø R, Schmidt J, Hellsten Y, Pilegaard H. Exercise training, but not resveratrol, improves metabolic and inflammatory status in skeletal muscle of aged men. The Journal of physiology, 2014; 592: 1873-1886.

[154] Bo S, Ponzo V, Ciccone G, Evangelista A, Saba F, Goitre I, Procopio M, Pagano GF, Cassader M, Gambino R. Six months of resveratrol supplementation has no measurable effect in type 2 diabetic patients. A

randomized, double blind, placebo-controlled trial. Pharmacological research, 2016; 111: 896-905.

[155] van der Made SM, Plat J, Mensink RP. Resveratrol does not influence metabolic risk markers related to cardiovascular health in overweight and slightly obese subjects: a randomized, placebo-controlled crossover trial. PLoS one, 2015; 10: e0118393.

[156] Yoshino J, Conte C, Fontana L, Mittendorfer B, Imai S-i, Schechtman KB, Gu C, Kunz I, Fanelli FR, Patterson BW. Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance. Cell metabolism, 2012; 16: 658-664.

[157] Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. Circulation, 1998; 97: 1411-1420.

[158] Blagosklonny MV. Disease or not, aging is easily treatable. Aging (Albany NY), 2018; 10: 3067.

[159] Santos EL, de Picoli Souza K, da Silva ED, Batista EC, Martins PJF, D'Almeida V, Pesquero JB. Long term treatment with ACE inhibitor enalapril decreases body weight gain and increases life span in rats. Biochemical pharmacology, 2009; 78: 951-958.

[160] Spindler SR, Mote PL, Flegal JM. Combined statin and angiotensin-converting enzyme (ACE) inhibitor treatment increases the lifespan of long-lived F1 male mice. Age, 2016; 38: 379-391.

[161] Basso N, Cini R, Pietrelli A, Ferder L, Terragno NA, Inserra F. Protective effect of long-term angiotensin II inhibition. American Journal of Physiology-Heart and Circulatory Physiology, 2007; 293: H1351-H1358.

[162] Gianni M, Bosch J, Pogue J, Probstfield J, Dagenais G, Yusuf S, Lonn E. Effect of long-term ACE-inhibitor therapy in elderly vascular disease patients. European heart journal, 2007; 28: 1382-1388.

[163] Inserra F, Romano L, Ercole L, de Cavanagh EM, Ferder Ln. Cardiovascular changes by long-term inhibition of the renin-angiotensin system in aging. Hypertension, 1995; 25: 437-442.

[164] Sakata Y, Yamamoto K, Mano T, Nishikawa N, Yoshida J, Miwa T, Hori M, Masuyama T. Temocapril prevents transition to diastolic heart failure in rats even if initiated after appearance of LV hypertrophy and diastolic dysfunction. Cardiovascular research, 2003; 57: 757-765.

[165] Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, Lacourcière Y, Hippler SE, Fields H, Naqvi TZ. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. The Lancet, 2007; 369: 2079-2087.

[166] Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moyé L. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. The Lancet, 2000; 355: 1575-1581.

[167] Beldhuis IE, Streng KW, Ter Maaten JM, Voors AA, van der Meer P, Rossignol P, McMurray JJ, Damman K. Renin–angiotensin system inhibition, worsening renal function, and outcome in heart failure patients with reduced and preserved ejection fraction: a meta-analysis of published study data. Circulation: Heart Failure, 2017; 10: e003588.

[168] Fukuta H, Goto T, Wakami K, Kamiya T, Ohte N. Effect of renin-angiotensin system inhibition on cardiac structure and function and exercise capacity in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. Heart Failure Reviews, 2020: 1-8.

[169] Cruickshank J. Are we misunderstanding beta-blockers. International journal of cardiology, 2007; 120: 10-27.

[170] Raposeiras-Roubín S, Abu-Assi E, Redondo-Diéguez A, González-Ferreiro R, López-López A, Bouzas-Cruz N, Castiñeira-Busto M, Gil CP, García-Acuña JM, González-Juanatey JR. Prognostic benefit of beta-blockers after acute coronary syndrome with preserved systolic function. Still relevant today? Revista Española de Cardiología (English Edition), 2015; 68: 585-591.

[171] Choo EH, Chang K, Ahn Y, Jeon DS, Lee JM, Kim DB, Her S-H, Park CS, Kim HY, Yoo K-D. Benefit of β-blocker treatment for patients with acute myocardial infarction and preserved systolic function after percutaneous coronary intervention. Heart, 2014; 100: 492-499.

[172] Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. New England Journal of Medicine, 1998; 339: 489-497.

[173] Ladage D, Schwinger RH, Brixius K. Cardio-selective beta-blocker: pharmacological evidence and their influence on exercise capacity. Cardiovascular therapeutics, 2013; 31: 76-83.

[174] Ziff OJ, Samra M, Howard JP, Bromage DI, Ruschitzka F, Francis DP, Kotecha D. Beta-blocker efficacy across different cardiovascular indications: an umbrella review and meta-analytic assessment. BMC medicine, 2020; 18: 1-11.

[175] Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H, Danchin N, Deanfield JE, Hemingway H, Fox KA. β-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. Journal of the American College of Cardiology, 2017; 69: 2710-2720.

[176] Liao Y, Asakura M, Takashima S, Ogai A, Asano Y, Shintani Y, Minamino T, Asanuma H, Sanada S, Kim J. Celiprolol, a vasodilatory β-blocker, inhibits pressure overload–induced cardiac hypertrophy and prevents the transition to heart failure via nitric oxide–dependent mechanisms in mice. Circulation, 2004; 110: 692-699.

[177] Bristow MR. β-Adrenergic receptor blockade in chronic heart failure. Circulation, 2000; 101: 558-569.

[178] Spindler SR, Mote PL, Li R, Dhahbi JM, Yamakawa A, Flegal JM, Jeske DR, Lublin AL. β1-Adrenergic receptor blockade extends the life span of Drosophila and long-lived mice. Age, 2013; 35: 2099-2109.

[179] Suojanen L, Haring A, Tikkakoski A, Koskela JK, Tahvanainen AM, Huhtala H, Kähönen M, Sipilä K, Eräranta A, Mustonen JT. Haemodynamic influences of bisoprolol in hypertensive middle-aged men: a double-blind, randomized, placebo-controlled cross-over study. Basic & clinical pharmacology & toxicology, 2017; 121: 130-137.

[180] Leosco D, Rengo G, Iaccarino G, Filippelli A, Lymperopoulos A, Zincarelli C, Fortunato F, Golino L, Marchese M, Esposito G. Exercise training and β-blocker treatment ameliorate age-dependent impairment of β-adrenergic receptor signaling and enhance cardiac responsiveness to adrenergic stimulation. American Journal of Physiology-Heart and Circulatory Physiology, 2007; 293: H1596-H1603.

[181] Eijsvogels TM, Molossi S, Lee D-c, Emery MS, Thompson PD. Exercise at the extremes: the amount of exercise to reduce cardiovascular events. Journal of the American College of Cardiology, 2016; 67: 316-329.

[182] Thijssen DH, Maiorana AJ, O'Driscoll G, Cable NT, Hopman MT, Green DJ. Impact of inactivity and exercise on the vasculature in humans. European journal of applied physiology, 2010; 108: 845-875.

[183] Roh JD, Houstis N, Yu A, Chang B, Yeri A, Li H, Hobson R, Lerchenmüller C, Vujic A, Chaudhari V. Exercise training reverses cardiac aging phenotypes associated with heart failure with preserved ejection fraction in male mice. Aging Cell, 2020: e13159.

[184] Beaumont A, Campbell A, Grace F, Sculthorpe N. Cardiac Response to Exercise in Normal Ageing: What Can We Learn from Masters Athletes? Current Cardiology Reviews, 2018; 14: 245-253.

[185] Leosco D, Parisi V, Femminella DG, Formisano R, Petraglia L, Allocca E, Bonaduce D. Effects of exercise training on cardiovascular adrenergic system. Frontiers in physiology, 2013; 4: 348.

[186] Jakovljevic DG. Physical activity and cardiovascular aging: Physiological and molecular insights. Experimental gerontology, 2018; 109: 67-74.

[187] Pinckard K, Baskin KK, Stanford KI. Effects of exercise to improve cardiovascular health. Frontiers in cardiovascular medicine, 2019; 6: 69.

[188] Stratton JR, Levy WC, Cerqueira MD, Schwartz RS, Abrass IB. Cardiovascular responses to exercise. Effects of aging and exercise training in healthy men. Circulation, 1994; 89: 1648-1655.

[189] Scarpace PJ, Shu Y, Tumer N. Influence of exercise training on myocardial beta-adrenergic signal transduction: differential regulation with age. Journal of applied physiology, 1994; 77: 737-741.

[190] Høydal MA, Stølen TO, Kettlewell S, Maier LS, Brown JH, Sowa T, Catalucci D, Condorelli G, Kemi OJ, Smith GL. Exercise training reverses myocardial dysfunction induced by CaMKIIδC overexpression by restoring Ca2+ homeostasis. Journal of Applied Physiology, 2016; 121: 212-220.

[191] Bohm M, Dorner H, Htun P, Lensche H, Platt D, Erdmann E. Effects of exercise on myocardial adenylate cyclase and Gi alpha expression in senescence. American Journal of Physiology-Heart and Circulatory Physiology, 1993; 264: H805-H814.

[192] Leosco D, Rengo G, Iaccarino G, Filippelli A, Lymperopoulos A, Zincarelli C, Fortunato F, Golino L, Marchese M, Esposito G. Exercise training and-blocker treatment ameliorate age-dependent impairment of-adrenergic receptor signaling and enhance cardiac responsiveness to adrenergic stimulation. Cardiovasc Res, 2008; 78: 385-394.

[193] Tate CA, Helgason T, Hyek MF, McBride RP, Chen M, Richardson MA, Taffet GE. SERCA2a and mitochondrial cytochrome oxidase expression are increased in hearts of exercise-trained old rats. American Journal of Physiology-Heart and Circulatory Physiology, 1996; 271: H68-H72.

[194] Thomas MM, Vigna C, Betik AC, Tupling AR, Hepple RT. Cardiac calcium pump inactivation and nitrosylation in senescent rat myocardium are not attenuated by long-term treadmill training. Experimental gerontology, 2011; 46: 803-810.

[195] Iemitsu M, Miyauchi T, Maeda S, Tanabe T, Takanashi M, Matsuda M, Yamaguchi I. Exercise training improves cardiac function-related gene levels through thyroid hormone receptor signaling in aged rats. American Journal of Physiology-Heart and Circulatory Physiology, 2004; 286: H1696-H1705.

[196] Walton RD, Jones SA, Rostron KA, Kayani AC, Close GL, McArdle A, Lancaster MK. Interactions of short-term and chronic treadmill training with aging of the left ventricle of the heart. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 2015; 71: 1005-1013.

[197] Spina RJ, Turner MJ, Ehsani AA. β-Adrenergic-mediated improvement in left ventricular function by exercise training in older men. American Journal of Physiology-Heart and Circulatory Physiology, 1998; 274: H397-H404.

[198] Stewart KJ, Bacher AC, Turner KL, Fleg JL, Hees PS, Shapiro EP, Tayback M, Ouyang P. Effect of exercise on blood pressure in older persons: a randomized controlled trial. Archives of internal medicine, 2005; 165: 756-762.

[199] Tanaka H. Antiaging effects of aerobic exercise on systemic arteries. Hypertension, 2019; 74: 237-243.

[200] Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. Circulation, 2000; 102: 1270-1275.

[201] Sugawara J, Komine H, Hayashi K, Yoshizawa M, Otsuki T, Shimojo N, Miyauchi T, Yokoi T, Maeda S, Tanaka H. Systemic α-adrenergic and nitric oxide inhibition on basal limb blood flow: effects of endurance training in middle-

aged and older adults. American Journal of Physiology-Heart and Circulatory Physiology, 2007; 293: H1466-H1472.

[202] Thijssen DH, Rongen GA, Van Dijk A, Smits P, Hopman MT. Enhanced endothelin-1-mediated leg vascular tone in healthy older subjects. Journal of applied physiology, 2007; 103: 852-857.

[203] Van Guilder GP, Westby CM, Greiner JJ, Stauffer BL, DeSouza CA. Endothelin-1 vasoconstrictor tone increases with age in healthy men but can be reduced by regular aerobic exercise. Hypertension, 2007; 50: 403-409.

[204] Brandon L, Sharon B, Boyette L. Effects of a four-month strength training program on blood pressure in older adults. The journal of nutrition, health & aging, 1997; 1: 98-102.

[205] Ben-Sira D, Oliveira J. Hypertension in aging: physical activity as primary prevention. European Review of Aging and Physical Activity, 2007; 4: 85-89.

[206] Tanaka H, Dinenno FA, Seals DR. Reductions in central arterial compliance with age are related to sympathetic vasoconstrictor nerve activity in healthy men. Hypertension Research, 2017; 40: 493-495.

[207] Campbell A, Grace F, Ritchie L, Beaumont A, Sculthorpe N. Long-term aerobic exercise improves vascular function into old age: a systematic review, meta-analysis and meta regression of observational and interventional studies. Frontiers in physiology, 2019; 10: 31.

[208] DeSouza CA, Shapiro LF, Clevenger CM, Dinenno FA, Monahan KD, Tanaka H, Seals DR. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. Circulation, 2000; 102: 1351-1357.

[209] Taddei S, Galetta F, Virdis A, Ghiadoni L, Salvetti G, Franzoni F, Giusti C, Salvetti A. Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. Circulation, 2000; 101: 2896-2901.

[210] Spier SA, Delp MD, Meininger CJ, Donato AJ, Ramsey MW, Muller-Delp JM. Effects of ageing and exercise training on endothelium-dependent vasodilatation and structure of rat skeletal muscle arterioles. The Journal of physiology, 2004; 556: 947-958.

[211] Moreau KL, Gavin KM, Plum AE, Seals DR. Ascorbic acid selectively improves large elastic artery compliance in postmenopausal women. Hypertension, 2005; 45: 1107-1112.

[212] Seals DR, DeSouza CA, Donato AJ, Tanaka H. Habitual exercise and arterial aging. Journal of applied physiology, 2008; 105: 1323-1332.

[213] Moreau KL, Donato AJ, Seals DR, Dinenno FA, Blackett SD, Hoetzer GL, Desouza CA, Tanaka H. Arterial intima-media thickness: site-specific associations with HRT and habitual exercise. American Journal of Physiology-Heart and Circulatory Physiology, 2002; 283: H1409-H1417.

[214] Tanaka H, Seals DR, Monahan KD, Clevenger CM, DeSouza CA, Dinenno FA. Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men. Journal of Applied Physiology, 2002; 92: 1458-1464.

[215] Donato AJ, Lesniewski LA, Delp MD. Ageing and exercise training alter adrenergic vasomotor responses of rat skeletal muscle arterioles. The Journal of physiology, 2007; 579: 115-125.

[216] Spina RJ, Bourey RE, Ogawa T, Ehsani AA. Effects of exercise training on α-adrenergic mediated pressor responses and baroreflex function in older subjects. Journal of gerontology, 1994; 49: B277-B281.

[217] Silva AS, Zanesco A. Physical exercise, ß-adrenergic receptors, and vascular.

[218] Leosco D, Iaccarino G, Cipolletta E, De Santis D, Pisani E, Trimarco V, Ferrara N, Abete P, Sorriento D, Rengo F. Exercise restores β-adrenergic vasorelaxation in aged rat carotid arteries. American Journal of Physiology-Heart and Circulatory Physiology, 2003; 285: H369-H374.

[219] Cadeddu C, Nocco S, Cugusi L, Deidda M, Fabio O, Bandino S, Cossu E, Incani M, Baroni MG, Mercuro G. Effects of metformin and exercise training, alone or in combination, on cardiac function in individuals with insulin resistance. Cardiology and therapy, 2016; 5: 63-73.

[220] Cadeddu C, Nocco S, Cugusi L, Deidda M, Bina A, Fabio O, Bandinu S, Cossu E, Baroni MG, Mercuro G. Effects of metformin and exercise training, alone or in association, on cardio-pulmonary performance and quality of life in insulin resistance patients. Cardiovascular diabetology, 2014; 13: 1-9.

[221] Viskochil R, Malin SK, Blankenship JM, Braun B. Exercise training and metformin, but not exercise training alone, decreases insulin production and increases insulin clearance in adults with prediabetes. Journal of Applied Physiology, 2017; 123: 243-248.

[222] Linden MA, Fletcher JA, Morris EM, Meers GM, Kearney ML, Crissey JM, Laughlin MH, Booth FW, Sowers JR, Ibdah JA. Combining metformin and aerobic exercise training in the treatment of type 2 diabetes and NAFLD in OLETF rats. American Journal of Physiology-Endocrinology and Metabolism, 2014; 306: E300-E310.

[223] Malin SK, Nightingale J, Choi SE, Chipkin SR, Braun B. Metformin modifies the exercise training effects on risk factors for cardiovascular disease in impaired glucose tolerant adults. Obesity, 2013; 21: 93-100.

[224] Konopka AR, Laurin JL, Schoenberg HM, Reid JJ, Castor WM, Wolff CA, Musci RV, Safairad OD, Linden MA, Biela LM. Metformin inhibits mitochondrial adaptations to aerobic exercise training in older adults. Aging Cell, 2019; 18: e12880.

[225] Malin SK, Braun B. Impact of metformin on exercise-induced metabolic adaptations to lower type 2 diabetes risk. Exercise and sport sciences reviews, 2016; 44: 4-11.

[226] Gliemann L, Schmidt JF, Olesen J, Biensø RS, Peronard SL, Grandjean SU, Mortensen SP, Nyberg M, Bangsbo J, Pilegaard H. Resveratrol blunts the positive effects of exercise training on cardiovascular health in aged men. The Journal of physiology, 2013; 591: 5047-5059.

[227] Gliemann L, Nyberg M, Hellsten Y. Effects of exercise training and resveratrol on vascular health in aging. Free Radical Biology and Medicine, 2016; 98: 165-176.

[228] Gliemann L, Olesen J, Biensø RS, Schmidt JF, Akerstrom T, Nyberg M, Lindqvist A, Bangsbo J, Hellsten Y. Resveratrol modulates the angiogenic response to exercise training in skeletal muscles of aged men. American Journal of Physiology-Heart and Circulatory Physiology, 2014; 307: H1111-H1119.

[229] Buford TW, Anton SD. Resveratrol as a supplement to exercise training: friend or foe? The Journal of physiology, 2014; 592: 551.

[230] Smoliga JM, Blanchard OL. Recent data do not provide evidence that resveratrol causes ‘mainly negative’or ‘adverse’effects on exercise training in humans. The Journal of physiology, 2013; 591: 5251.

[231] Dolinsky VW, Jones KE, Sidhu RS, Haykowsky M, Czubryt MP, Gordon T, Dyck JR. Improvements in skeletal muscle strength and cardiac function induced by

resveratrol during exercise training contribute to enhanced exercise performance in rats. The Journal of physiology, 2012; 590: 2783-2799.

[232] Kan N-W, Ho C-S, Chiu Y-S, Huang W-C, Chen P-Y, Tung Y-T, Huang C-C. Effects of resveratrol supplementation and exercise training on exercise performance in middle-aged mice. Molecules, 2016; 21: 661.

[233] Alway SE, McCrory JL, Kearcher K, Vickers A, Frear B, Gilleland DL, Bonner DE, Thomas JM, Donley DA, Lively MW. Resveratrol enhances exercise-induced cellular and functional adaptations of skeletal muscle in older men and women. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 2017; 72: 1595-1606.

[234] Lin C-H, Lin C-C, Ting W-J, Pai P-Y, Kuo C-H, Ho T-J, Kuo W-W, Chang C-H, Huang C-Y, Lin W-T. Resveratrol enhanced FOXO3 phosphorylation via synergetic activation of SIRT1 and PI3K/Akt signaling to improve the effects of exercise in elderly rat hearts. Age, 2014; 36: 1-10.

[235] Muhammad MH, Allam MM. Resveratrol and/or exercise training counteract aging-associated decline of physical endurance in aged mice; targeting mitochondrial biogenesis and function. The Journal of Physiological Sciences, 2018; 68: 681-688.

[236] Ziada AM. Additional salutary effects of the combination of exercise training and an angiotensin-converting enzyme inhibitor on the left ventricular function of spontaneously hypertensive rats. Journal of hypertension, 2009; 27: 1309-1316.

[237] Kinoshita M, Nakaya Y, Harada N, Takahashi A, Nomura M, Bando S. Combination therapy of exercise and angiotensin-converting enzyme inhibitor markedly improves insulin sensitivities in hypertensive patients with insulin resistance. Circulation journal, 2002; 66: 655-658.

[238] Ziada AM, Hassan MO, Tahlilkar KI, Inuwa IM. Long-term exercise training and angiotensin-converting enzyme inhibition differentially enhance myocardial capillarization in the spontaneously hypertensive rat. Journal of hypertension, 2005; 23: 1233-1240.

[239] Steen MS, Foianini KR, Youngblood EB, Kinnick TR, Jacob S, Henriksen EJ. Interactions of exercise training and ACE inhibition on insulin action in obese Zucker rats. Journal of Applied Physiology, 1999; 86: 2044-2051.

[240] Xu X, Wan W, Ji L, Lao S, Powers AS, Zhao W, Erikson JM, Zhang JQ. Exercise training combined with angiotensin II receptor blockade limits post-infarct ventricular remodelling in rats. Cardiovascular research, 2008; 78: 523-532.

[241] Sumukadas D, Band M, Miller S, Cvoro V, Witham M, Struthers A, McConnachie A, Lloyd SM, McMurdo M. Do ACE inhibitors improve the response to exercise training in functionally impaired older adults? A randomized controlled trial. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 2014; 69: 736-743.

[242] Guo Q, Minami N, Mori N, Nagasaka M, Ito O, Kurosawa H, Kanazawa M, Kohzuki M. Effects of estradiol, angiotensin-converting enzyme inhibitor and exercise training on exercise capacity and skeletal muscle in old female rats. Clinical and experimental hypertension, 2010; 32: 76-83.

[243] Nishi I, Noguchi T, Iwanaga Y, Furuichi S, Aihara N, Takaki H, Goto Y. Effects of exercise training in patients with chronic heart failure and advanced left ventricular systolic dysfunction receiving β-blockers. Circulation Journal, 2011: 1105171230-1105171230.

[244] Medeiros WM, de Luca FA, de Figueredo Júnior AR, Mendes FA, Gun C. Heart rate recovery improvement in patients following acute myocardial infarction: exercise training, β-blocker therapy or both. Clinical physiology and functional imaging, 2018; 38: 351-359.

[245] Dunkley JC, Irion CI, Yousefi K, Shehadeh SA, Lambert G, John-Williams K, Webster KA, Goldberger JJ, Shehadeh LA. Carvedilol and exercise combination therapy improves systolic but not diastolic function and reduces plasma osteopontin in Col4a3−/− Alport mice. American Journal of Physiology-Heart and Circulatory Physiology, 2021; 320: H1862-H1872.

[246] Vanzelli AS, Medeiros A, Rolim N, Bartholomeu JB, Cunha TF, Bechara LG, Gomes ER, Mattos KC, Sirvente R, Salemi V. Integrative effect of carvedilol and aerobic exercise training therapies on improving cardiac contractility and remodeling in heart failure mice. Plos one, 2013; 8: e62452.

[247] Minami N, Yoshikawa T, Kataoka H, Mori N, Nagasaka M, Kurosawa H, Kanazawa M, Kohzuki M. Effects of exercise and β-blocker on blood pressure and baroreflexes in spontaneously hypertensive rats. American journal of hypertension, 2003; 16: 966-972.