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Pharmacy and Exercise as Complimentary Partners for Successful Cardiovascular Ageing

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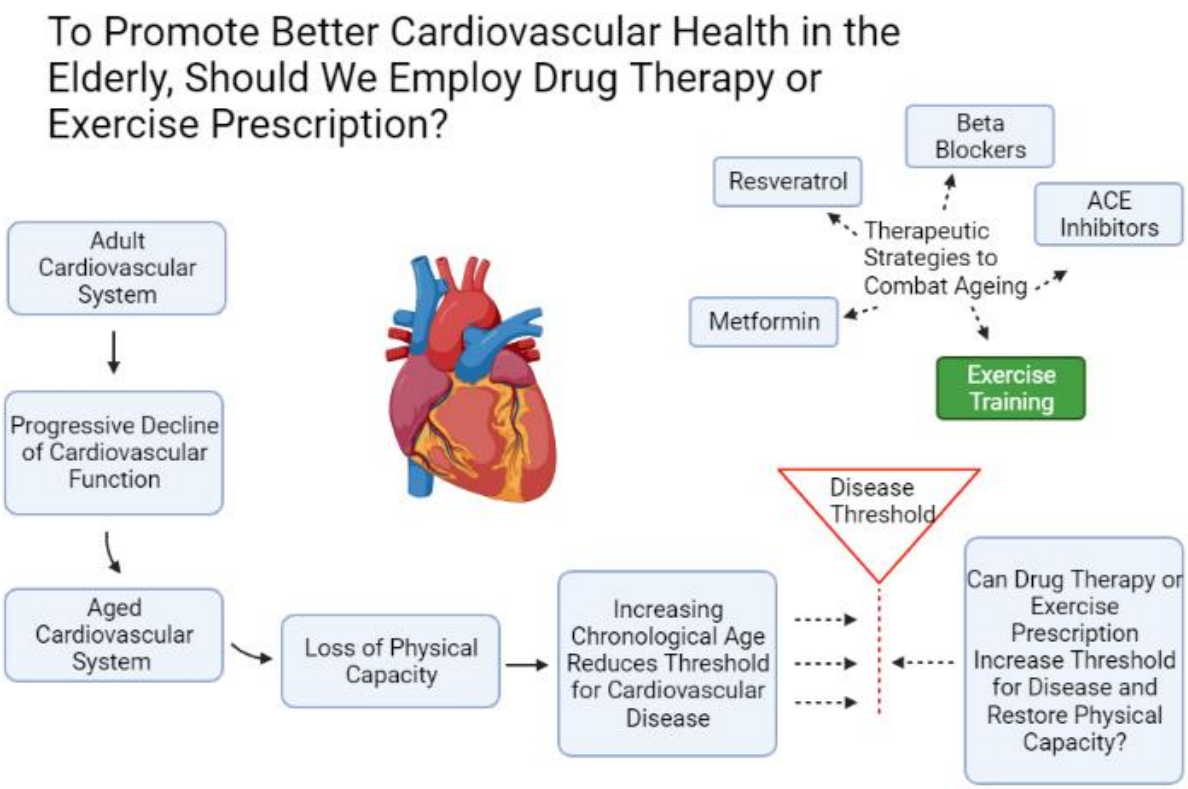
Graphical Abstract



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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.

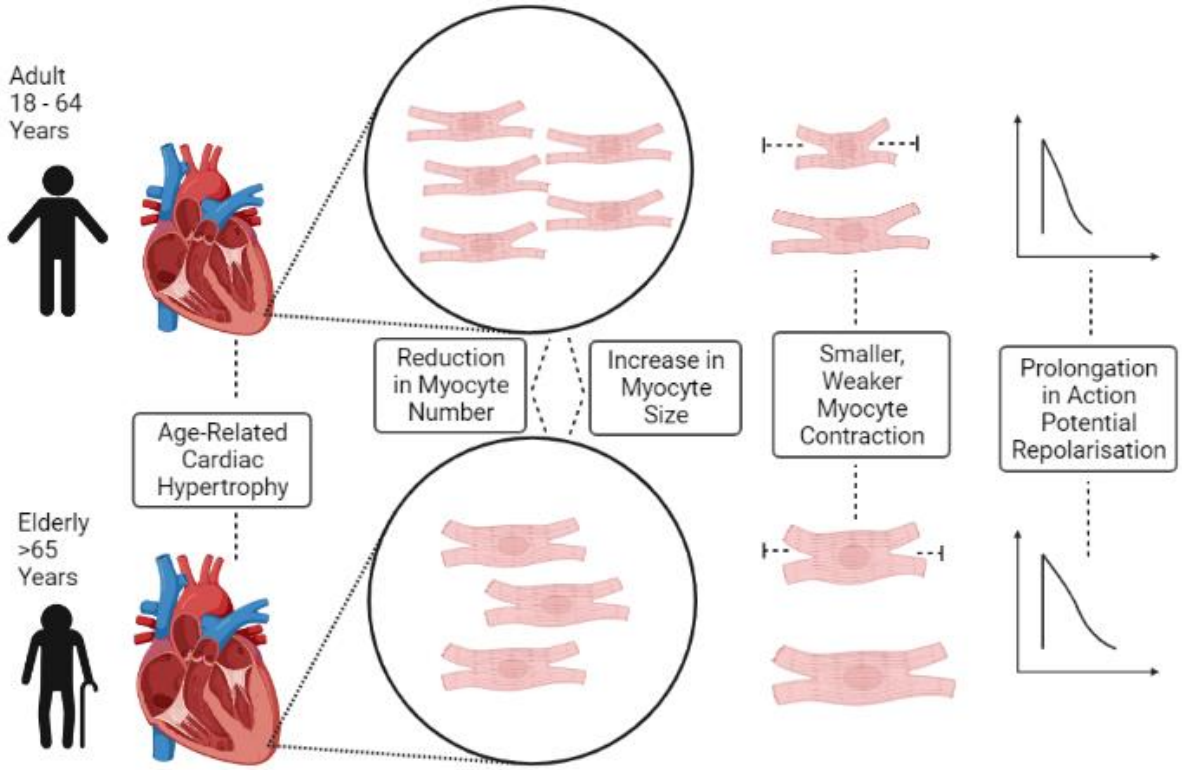

Figure 1. Depiction of some adaptations observed in age-related cardiac remodelling. Image created with BioRender.

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].

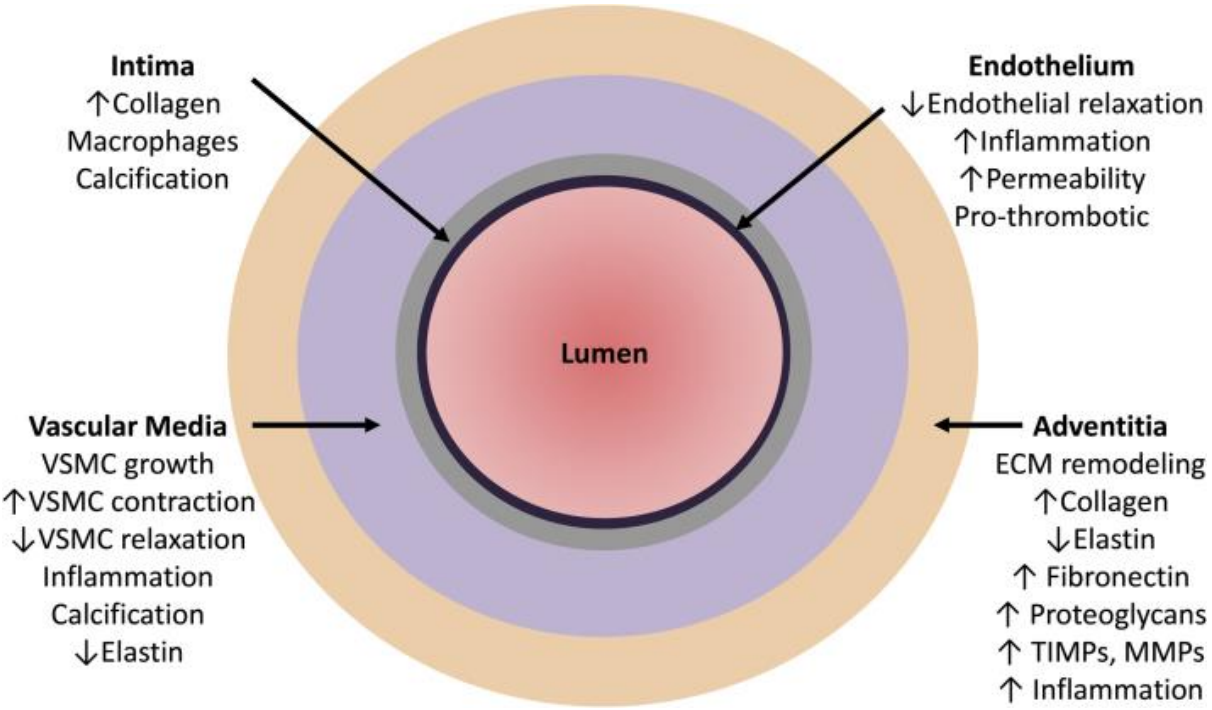

Figure 2. *The vascular phenotype in aging and hypertension. With aging and during the development of hypertension, the endothelium, vascular wall, and adventitia undergo functional and structural changes. Endothelial function is impaired, and the vascular media is thickened. The adventitial extracellular 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]. Copyright © (2016) by Harvey, Montezano, Lopes, Rios and Touyz. Reprinted in accordance with the CC-BY license and Elsevier's open access policy.

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.

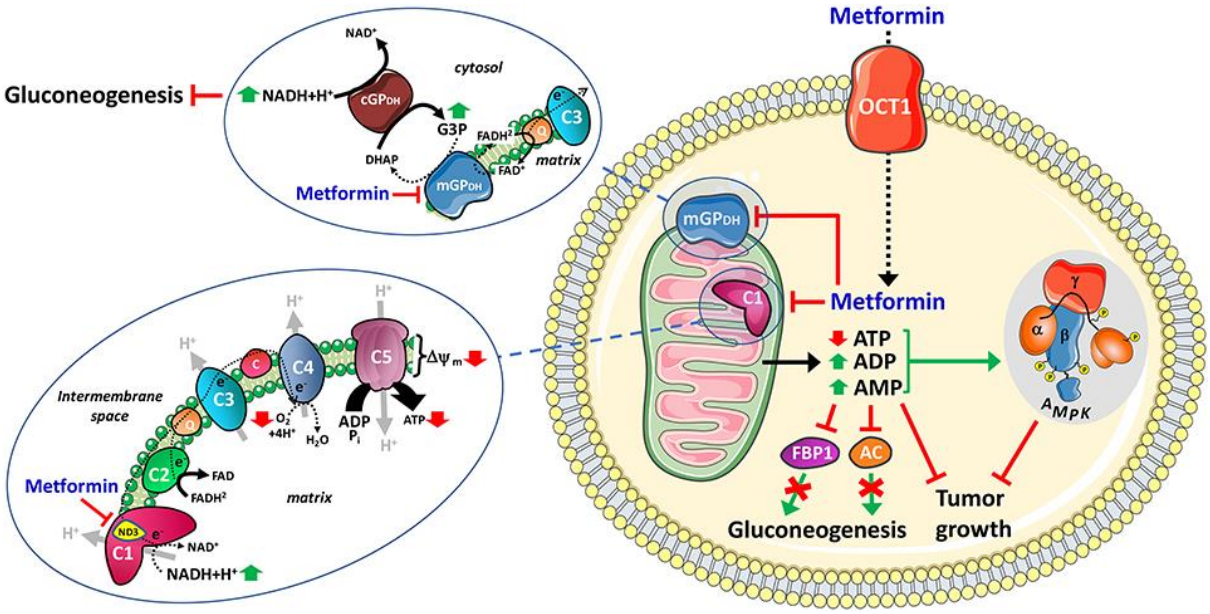

Figure 3. *Mitochondrial mechanisms of action of metformin. After cellular uptake, mainly through organic cation transporter 1 (OCT1) in hepatocytes, the mitochondria is the primary target of metformin which exerts specific inhibition on the respiratory-chain complex 1, presumably through direct interaction 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).

Figure reprinted from “Role of Mitochondria in the Mechanism(s) of Action of Metformin” by G. Vial, D. Detaille and B. Guigas. (2019). *Frontiers in Endocrinology,* 10, p. 294 [2]. Copyright © (2019) by Vial, Detaille and Guigas. Reprinted in accordance with the CC-BY license and Frontiers in Endocrinology’s open access policy.

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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