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THE IMPACT OF AGING ON THE CARDIOVASCULAR SYSTEM

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ABSTRACT

The cardiovascular system, particularly the major arteries, is affected significantly by age. Despite the fact that many cardiovascular studies have looked at both young and old people, there are still many unsolved concerns about how the genetic pathways that regulate aging in model organisms. The review looks at the effects of ageing on the heart and blood vessels, arterial stiffness, as well as molecular characteristics of CVD. The world's aging population underscores the need to better understand how ageing increases CVD so that new measures can be developed to combat the problem.

Keywords: Age, Cardiovascular diseases, Arteries, Vascular, Molecular characteristics, Functional

INTRODUCTION

Aging is an integral part of life and is unfortunately the most important risk factor for cardiovascular disease (CVD). Aging is linked to a gradual decline in many physiological processes, leading to an increased risk of complications and diseases. Aging has a remarkable effect on the heart and arterial system, leading to an increase in CVD including atherosclerosis

(ASVD), hypertension (HTN), myocardial infarction (MI), and stroke (CVA) **[1]**.

The health of the arterial and cardiac systems is not mutually exclusive, as each system has a large impact on the other. Since age is the predominant risk factor for the development of cardiovascular disease, their prevalence increases considerably with age. The prevalence of heart failure among adults in developed countries is between 1% and 2%, increasing to more than 10% among people aged 70 and older **[1, 2]**.

Because there is a strong link between population ageing and an increase in the prevalence of cardiovascular disease, cardiovascular ageing is anticipated to alter pathophysiological pathways that are also involved in the development of cardiovascular disease **[3]**.

Aging is now considered a consequence of prolonged exposure to risk factorse. g., an unfavourable lipid profile, smoking and diabetes, during which accumulation of damage increases the risk to develop vascular dysfunction and associated disease. Increasing age leads to progressive and functional damage to tissues and organs and increases their vulnerability to stress. Damage to proteins, enhances their vulnerability to stress **[4-6]**.

Aging is an important factor in the study of cardiac re-modelling. The majority of patients suffering from most debilitating cardiovascular diseases, including heart failure (HF), are age-specific **[7]**. Heart failure is an age-related condition that increases in incidence with age. At the cellular, extracellular, and whole-heart levels, age-related alterations in cardiac physiology occur. Apoptotic or necrotic mechanisms may be involved in the steady loss of myocytes with ageing. The age-related decline in autophagic activity has been documented **[8-13]**.

In youth, the human vascular system is exquisitely built to receive spurts of blood from the left ventricle and distribute it as a continuous flow through peripheral capillaries. Stiffening causes enlargement of the left ventricle (LV), lower capacity for myocardial perfusion, and greater pressures on tiny artery arteries, especially those in the brain and kidney. Aortic stiffness is the major cause of cardiovascular illness in persons who do not develop atherosclerotic problems, although it is not a therapeutic target. The major target is smooth muscle in the distributing arteries, which relaxes with little effect on peripheral resistance but induces a large reduction in wave reflection magnitude **[14]**.

A better understanding of the effect of age on CV diseases will be crucial to counteract the ongoing epidemiological shift. Several age-related factors have been recognized as

predictors of CV disease to date. Among these, isolated systolic hypertension represents a key burden **[15]**.

The structural vessel wall alterations characterized by increased collagen and decreased elastin content mediate aortic stiffening and lead to increased systolic and decreased diastolic blood pressure. Such conditions, increase myocardial oxygen demand (augmenting left ventricular after-load and, in chronic, left ventricular thickness) and decreases oxygen supply by reducing coronary perfusion **[16]**.

Despite the fact these conditions have a significant negative impact on the quality of life of older patients and result in higher expenses for healthcare systems around the world wide **[17]**.

In this review, we emphasise the relationships between ageing, Cardiovascular, and Cardiovacular disorders.

1. Assessing the Heart and Vasculature's Effects on Aging

Aging is linked to a gradual reduction in a variety of physiological processes, increasing the likelihood of health issues and disease. The oxygenated blood is essential for the health of all tissues and the longevity of the organism as a whole because it delivers oxygenated blood to all tissues in the body.

Pathological changes in aging cardiovascular tissues include hypertrophy, altered left ventricular (LV) diastolic function, and decreased LV systolic reverse capacity, as well as increased arterial stiffness and impaired endothelial function. When arterial stiffness rises, the myocardial responds with LV hypertrophy and fibroblast growth, resulting in decreased cardiac output and an increase in fibrotic tissue **[1, 18]**.

Age has an impact on heart rate modulation, with a decrease in both rate variability and maximal heart rate **[19]**. The LV diastolic filling rate begins to fall at an early age, which is compensated for by increasing arterial contraction to maintain stroke volume and workload while maintaining adequate ejection fraction.

A decrease in cardiac output due to age-related decline in function induces the myocardium to compensate by increasing muscle mass through cardiac hypertrophy; while this may improve cardiac output temporarily, hypertrophy has the long-term impact of reducing cardiac function **[20]**.

Vascular dysfunction associated with ageing causes a number of age-related diseases, such as ischemia (lack of proper tissue perfusion), hypertension (insufficient vascular development or regression), and excessive growth and remodelling (resulting in age-

related macular degeneration). The vasculature experiences well-documented structural and functional changes with age, such as luminal enlargement with wall thickening and a reduction in endothelial cell activity, which inhibits endothelium-dependent dilatation and promotes arterial stiffness **[21]**.

Systolic pressure and LV after-load rise in the stiffened aorta, causing LV hypertrophy and increased myocardial oxygen demand, whereas aortic diastolic pressure falls, causing perfusion-metabolism mismatch and myocardial ischemia. Myocardial ischemia can also be caused by a malfunction of the coronary endothelium **[22]**.

Cardiomyocytes become more vulnerable to stress as they age, particularly oxidative stress. As a result of the increased oxidative stress due to increased reactive oxygen species (ROS) production with age, the rate of cardiomyocyte mortality increases **[23]**.

Age-related angiogenesis impairment leads to the increased end-organ damage seen in the elderly and is directly linked to systemic tissue homeostasis **[24]**.

2. Age and arterial stiffness

Since the ratio of collagen to elastin determines vascular compliance, ageing is linked to a decline in this ratio as a result of increased elastin degradation and buildup of stiffer collagen. Aortic stiffness progression and mortality are additionally linked to this elastin degradation **[25]**.

'In extreme old age, the arteries themselves, the grand instrument of the circulation, become hard and as if they were bony, until, having lost the power to contract themselves, they can no longer propel the blood, even through the largest channels, in which case death occurs naturally.'**[26]**

2.1 Increased pulse pressure and systolic hypertension

Because of increased collagen and decreased elastin, the aorta stiffens with age **[27]**. These changes in the extracellular matrix of the aorta play a significant role in its loss of distensibility. Increased stiffness causes reflected waves to rise and systolic pressure to rise. However, diastolic pressure decreases with ageing. Pulse pressure rises as aortic pulse wave velocity rises **[28]**.

Heart failure with preserved ejection fraction (HFpEF) affects the elderly, mainly women, and is linked to the development of aortic stiffness and re-modelling of the myocardium, extracellular matrix, and microvasculature. With increasing age, the risk of developing HFpEF increases dramatically **[29, 30]**.

2.2 Calcification of the valve and cardiac skeleton

Calcium in the axial skeleton declines with age, but calcium accumulates in CV structures. The understanding the disorders like calcific aortic stenosis are the result of a systemic process has grown **[31]**.

2.3 Amyloidosis and the deteriorating cardiovascular system

Certain types of amyloidosis are more common in the elderly population.

The incidence of amyloid light-chain amyloidosis increases with age, which is linked to the rise in multiple myeloma **[32]**.

Cardiac amyloidosis caused by wild-type transthyretin (wtTTR) is more common in older people, especially men **[33]**.

3. Molecular characteristics of CVD caused by age

3.1 Cellular senescence and telomeres

The accumulation of senescent cells in the arterial wall and heart can contribute to the structural and functional degeneration of the CV system as people get older, and evidence suggests that telomere shortening is involved in cellular senescence **[34]**.

Telomeres are repetitive nucleotide sequences (TTAGGG) at the ends of mammalian chromosomes that prevent chromosome deterioration or fusion with neighbouring chromosomes. Reduced calcium re-uptake by the myocardial sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2a) is another key feature of cardiomyocyte ageing, resulting in impaired early dias **[35]**.

The amplitude of calcium transients declines with age, becoming 3.2-fold smaller in myocytes from patients 75 years old than in those younger than 55 years old **[36]**.

3.2 Oxidative stress in mitochondria

Mitochondrial overproduction of reactive oxygen species (ROS) is thought to contribute to cellular senescence **[16]**. This process eventually results in the formation of highly reactive products such as O2 or H_2O_2, whose accumulation and diffusion promotes senescence, DNA mutations, inflammation, and multiple cell death pathways **[37]**.

3.3 Instability in the genome

The accumulation of genetic damage over time is anticipated to play a significant role in ageing. There are three types of genome changes: 3) epigenetic changes, which impact gene activity without changing DNA sequence. Organisms have evolved very capable DNA repair systems to deal with genetic lesions, which can, in most situations, restore the right base pair sequence **[38]**.

Defects in DNA repair may occur, however, and can contribute to cellular senescence and organ malfunction **[39]**. The CV system is particularly vulnerable to genomic instability **[40]**. The Hutchinson–

Gilford progeria syndrome, which is characterized by severe nuclear DNA damage, is linked to early atherosclerosis and CVD, which leads to catastrophic MI or stroke by the age of 13 **[41]**.

3.4 Changes in chromatin

Growing data demonstrates that epigenetic changes can disrupt transcriptional processes involved in oxidative stress, inflammation, angiogenesis, and cellular metabolism, promoting vascular ageing and maladaptive pathways **[42]**.

Epigenetic changes made during life appear to be long-lasting and stable, creating a molecular framework through which the environment interacts with the genome to change gene expression **[43]**.

3.5 Angiogenesis impairment

Stroke, peripheral artery disease, and MI are all more common in the elderly, and they also have worse outcomes than younger people. Patients above the age of 65 with acute limb ischemia have a greater mortality rate and a higher rate of limb amputation **[44]**.

In CACs of elderly males, Kushner *et al*. discovered a 60 percent decrease in telomerase activity (56 to 67 years of age). In mice with ischemic hind limbs, over-expression of human telomerase reverse transcriptase in CACs retained telomerase activity, delayed cell senescence, and corrected age-related CAC dysfunction **[45]**.

Senescent cell alterations are caused by an increase in ROS generation and a decrease in antioxidant enzyme expression **[46]**.

Glutathione peroxidase-1 activity is reduced in early endothelial progenitor cells (EPCs) from elderly people, which is associated with increased cell death.

Increased angiotensin II levels may potentially promote the generation of reactive oxygen species (ROS) and cellular senescence in early EPCs **[47]**.

3.7 Cardiovascular Aging Mechanisms

The risk of cardiovascular disease is heavily influenced by age **[48]**. Excessive oxidative stress and chronic low-grade inflammation are the main culprits, which are compounded by the poor heart regeneration potential stress from oxidation **[49]**. Mitochondria, the largest intracellular generator of reactive oxygen species, are thought to be fundamental ageing controllers **[50]**.

4. The Aging Heart

Cheng *et al*. employed cardiac magnetic resonance imaging (CMR) to study the shape and function of the left ventricle in 5,004 healthy people. With age, the mass-to-volume ratio grew significantly (+5 mg/ml/year). Despite a marginally improved LVEF (+0.1

percent/year), age was linked with a significant decrease in stroke volume (0.4 ml/year), as well as strain patterns showing systolic and diastolic myocardial dysfunction **[51]**.

In healthy people (n = 2,355, mean age 44 years, 66 percent women), Nayor *et al*. calculated age-specific reference limits for echocardiographic parameters of diastolic dysfunction. Diastolic dysfunction was uncommon until the age of 50, after which it became more common and severe. By the age of 70 to 80, more than half of the subjects had diastolic dysfunction, and more than two-thirds had it by the age of 80 **[52]**.

Another feature of cardiovascular ageing is a drop in maximal heart rate, which is caused by a decline in intrinsic heart rate and chronotropic reactivity to -adrenergic stimulation **[49]**.

Because of the lower maximal heart rate and lower LV stroke volume despite higher LV filling pressure due to decreased LV relaxation and compliance, ageing causes a drop in maximal cardiac output, resulting in a weakened cardiac reserve capacity **[53, 54]**.

Significant intrinsic electrical abnormalities in an ageing myocardial are controlled by the cardiac autonomic nervous system and predispose the elderly patient to arrhythmic risk **[55]**.

Age has an impact on LA volume and function. Increase in LA maximum and minimal volume, especially in people with cardiovascular risk factors **[56]**.

4.1 Fibrosis of myocardium

The development of cardiac fibrosis is linked to ageing. Fibrotic tissue is stiffer and less flexible, leading in cardiac dysfunction and an increased risk of heart failure **[57, 58]**.

Excess collagen builds up and inhibits the viscoelasticity of myocardium, affecting the shortening of cardiac muscle fibres and during diastole, limiting torsional recoil and ventricular suction **[59]**.

4.2 Amyloidosis of the heart

Autopsy studies revealed that over 25% of all persons over the age of 85 have developed wild-type variant (ATTRwt) cardiac deposits, with 5% to 10% displaying the clinical presentation of cardiac ATTRwt. Gonzalez-Lopez *et al*. found that 13 percent of patients admitted with HF, LVEF 50 percent, and LV hypertrophy (12 mm) exhibited ATTRwt cardiac amyloid in a prospective analysis of 60-year-old patients.

The extracellular matrix deposition of amyloid fibrils enhances ventricular wall thickness and myocardial stiffness **[58-63]**.

5. Aging and diseases

5.1 Hypertension

For middle-aged, normotensive adults, the lifetime risk of hypertension reaches 90%.[63] The standard theory is that pressure overload causes concentric LV hypertrophy, which causes cardiac re-modelling in hypertension **[62]**.

HF with near-normal/normal LVEF develops when pressure overload is prolonged. Eccentric hypertrophy with diminished LVEF is the final stage of hypertension heart illness. Although high blood pressure is the most common cause of LV structural changes, other factors (ethnicity, sex, salt intake, obesity, diabetes, neurohumoral activity, and genes) can also affect LV mass and geometry. As a result, concentric hypertrophy is not the sole geometric pattern found in hypertension patients; eccentric hypertrophy can also be detected **[65]**.

5.2 Ischemic cardiomyopathy

According to autopsy studies, around 60% of people over the age of 60 have obstructive coronary artery disease **[66]**.

In comparison to younger persons, older patients with coronary artery disease have more severe and diffuse coronary atherosclerosis. In coronary artery disease, LV re-modelling usually occurs after a myocardial infarction (MI).

Gaudron *et al*. used gated single-photon emission computed tomography to assess LV volumes in 70 patients following their first myocardial infarction. Within four weeks following their first myocardial infarction, nearly 26% of patients developed modest LV dilatation, while 20% showed growing structural LV dilation **[67]**.

5.3 Obesity

Between 2007 and 2010, around 35% of persons aged 65 and up in the United States were obese as measured by their BMI **[68]**.

Obesity (particularly visceral adiposity) has been linked to heart failure with low LVEF, heart failure with near normal/normal LVEF, and heart failure with high output. Excessive aldosterone secretion and salt retention define all three kinds. Obesity is also associated with increased signaling through the leptin receptor, which can boost sympathetic nervous system and renin-angiotensin system activation, as well as directly stimulate aldosterone release **[69]**.

5.4 Influences of lifestyle

With age, low-active and sedentary behaviour increase, whereas physical activity and exercise decrease cardiovascular function **[70]**. Dietary habits can influence arterial ageing. Furthermore, some micro-nutrients have significant effects on cardiovascular ageing. High sodium intake, for example, is linked to endothelial dysfunction and increased arterial stiffness **[71]**.

Through mechanisms involving nitric oxide and endothelin 1 production, as well as oxidative stress and inflammation, alcohol can impact arterial characteristics in a positive or negative way depending on the dose **[72]**. Smoking hastens the ageing process, both directly and indirectly, by promoting the establishment of numerous illnesses **[73]**.

5.5 Atrioventricular Fibrillation

In the elderly, AF promotes HF and vice versa. Participants in the Framingham Heart Study with new-onset AF or HF were studied by Santhanakrishnan *et al*. More over one-third (37%) of 1,737 people diagnosed with new AF (mean age 75 12 years; 48% women) developed HF. In contrast, more than half (57%) of the 1,166 people diagnosed with new HF (mean age 79 11 years; 53% women) had AF **[74]**.

6. Heart Failure and Aging

6.1 Determinants of phenotype

The patient's risk factors, comorbidities, and disease modifiers are superimposed on the cardiovascular ageing process, which works as a scaffold, to establish each HF phenotype.

Concentric remodeling/hypertrophy and near-normal/normal LVEF are more common in elderly women with HF than they are in men. This has been linked to sex-biased microRNAs that are regulated by E2 or are expressed from X-chromosome locus due to inadequate inactivation **[75, 76]**.

CONCLUSION

As people get older, their myocardium undergoes fibrotic re-modelling, resulting in diminished myocardial compliance and impaired functionality. The growing importance of collagen cross-linkers and matricellular proteins in post-synthetic collagen regulation, as well as MMPs as pro-fibrotic mediators, adds to the complexity of the ageing "fibrosis" process. The utilisation of older animal models in study, as well as imaging technologies like late gadolinium enhancement CMR imaging, will surely assist our knowledge of these processes.

Novel mediators of collagen re-modelling may become future therapeutic targets in the ageing and sick heart as a result of our research **[77]**. The majority of our understanding of molecular alterations in heart ageing comes from animal models. Threfore, experiments to decipher molecular pathways implicated in human cardiac ageing and illness should be done to improve the overall picture of common pathways in human cardiac ageing and disease **[78]**.

Cellular senescence is linked to both normal vascular ageing and atherosclerosis. Due to an accumulation of nuclear and mitochondrial DNA damage, increased ROS, and a pro-inflammatory state, cellular senescence hampers cell proliferation and

survival, resulting in irreversible growth halt. Both vascular ageing and cellular senescence are linked to increased expression of pro-inflammatory cytokines and adhesion molecules, which promote inflammation and influence extracellular matrix protein creation and maintenance. Both structural alterations and a number of senescence-associated indicators can be used to detect ageing **[79]**.

Age and hypertension have distinct consequences. Indeed, isolated systolic hypertension, the most prevalent clinical manifestation of arterial stiffness and a disease associated with significant increased cardiovascular risk, is closely linked to ageing **[80]**.

New findings suggest that non-adaptive systems that are interrelated, linked, and overlap are primarily responsible for cardiovascular ageing. Because the mechanisms underlying cardiovascular ageing can be altered, it may be possible to delay or mitigate the difficulties that result. An effective method in this condition is to target fundamental ageing processes like inflammation or autophagy in order to prevent cardiovascular problems that lead HF epidemic in the elderly **[81]**.

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