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The ageing cardiovascular system

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Summary

The increase in the ageing population has generated much interest and research into what constitutes normal ageing. By identifying normal ageing processes it is hoped it will be possible to distinguish risk factors for the development of abnormal or premature ageing.

This review discusses biological, structural and mechanical changes in the cardiovascular system with ageing that are thought to increase the risk of cardiovascular disease with ageing. Contributory factors are thought to be genetic and lifestyle related. Measurements of biological as opposed to chronological ageing such as vascular stiffness are explored as a possible useful predictor of cardiovascular morbidity and mortality, indicating its possible utilization as a non-invasive screening tool in older people.

The identification of those at risk of cardiovascular disease and modification of risk factors may minimize interactions of the ageing process and therefore reduce the incidence of cardiovascular disease within the UK population.

Key words: cardiovascular, ageing, risk factors, structural changes, functional changes, molecular changes, lifestyle effects.

Introduction

The UK population is ageing; national census data have estimated a 4-fold increase in the population aged over 65 since 1951.[1] Cardiovascular disease remains the leading cause of death in the UK,[2] and continues to be a significant cause of mortality and morbidity in the ageing population.

Ageing has traditionally been considered a non-modifiable risk factor for cardiovascular disease. Epidemiological data from The Framingham Study suggest that risk factors accumulate with ageing, therefore increasing the risk of developing disease over time.[3] Thus ageing remains the biggest non-modifiable risk factor for cardiovascular disease.

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A biological definition of ageing is described as the decline in various physiological body processes culminating in the death of that organism. The relationship between biological and chronological age is not necessarily linear, as environmental impact upon genetics influences the rate and course of ageing. Estimates of arterial function have been found to be more consistent with chronological age. As Thomas Sydenham[4] remarked: 'A man is as old as his arteries.'[4] Vascular ageing is characterized by mechanical and structural changes within the cardiovascular system (summarized in Table 1) resulting in altered properties of the arterial wall. These changes with ageing are thought to be a contributing factor in the increased incidence of cardiovascular disease amongst the ageing population. These structural and mechanical changes are also affected by modifiable and non-modifiable risk factors that accumulate with ageing, including hypertension, obesity, smoking, lack of exercise, ethnicity and gender.

Literature search

A literature search was conducted using several databases including Embase, Ovid, Wiley, Cambridge Journals, Proquest, Pubmed and Cochrane. Medical Subject Headings (MeSH) terms ageing, aging, cardiovascular, arterial, myocardium, vasculature, elderly, changes, evolution, structure, function, heart, physiology, cellular and senescence were used.

Structural changes in the vascular system with ageing

The arterial system is made up of larger elastic arteries rich in elastin and collagen and smaller muscular peripheral arteries. The arterial wall is made up of three layers: tunica adventitia, tunica media and tunica intima. Between the blood and vessel wall lies a single monolayer of endothelial cells. Larger arteries such as the aorta buffer the flow and pressure variation generated by intermittent cardiac contraction, maintaining

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Table 1. *Changes in the myocardium and vasculature with ageing.*
Summary of cardiovascular changes with ageing, the mechanisms driving the changes and their effects on function and clinical picture

Changes with ageing	Mechanism of change	Effect on function	Clinical effect of changes
Heart rate variability	Blunting of the baroreceptors	Reduced variability with positioning, and respiration	Less able to compensate effectively at times of stress
Early diastolic filling reduction	Fibrous changes within myofilament	Adaptive to maintain contractile function	Increased risk of developing preserved ejection fraction heart failure
	Residual myofilament Ca^{2+} activation		
Increased filling in late diastole	Vigorous left atrial contraction	As above	Atrial enlargement and hypertrophy
			Clinically manifests as 4th heart sound
Stroke volume (males)	Increase in end-diastolic volume	Cardiac output remains stable	Allow men to engage in greater physical activity
Stroke volume (females)	No change in volume	Cardiac output decreases	None
Increased arterial compliance	Increased large vessel thickness through collagen-mediated changes Structural endothelial changes	Earlier return of the reflected pulse wave causing rises in systolic and pulse pressure	Increased risk of cardiovascular disease and related mortality
Blood pressure	Baroreceptor blunting	Increase systolic blood pressure Decrease diastolic blood pressure	Increased risk of cardiovascular disease and related mortality
		Widening of pulse pressure	

oxygen supply to tissues and reducing cardiac preload. Loss of elastic recoil impairs coronary flow and may contribute to cardiovascular disease. In the young, blood pressure is determined largely by peripheral vascular resistance but in older people is determined by large vessel stiffness.

In larger arteries such as the aorta the walls thicken with age, elongate and dilate.[5] With ageing aortic wall thickness has been associated with an increase in intima thickness in those with a low incidence of atherosclerosis.[6] A study looking at carotid intima thickness post-mortem supports these findings[6] with increased intima thickness caused by increased collagen content, covalent cross-linkage of collagen, and elastin fracture, reduction and calcification with ageing. Lifestyle changes and medications such as statins and ACE inhibitors are thought to slow the progression of intima media thickness.

The endothelium plays an essential role in regulating the vascular tone, permeability and response to inflammation by producing vasoactive substances including nitric oxide (a potent vasodilator) and endothelin (a vasoconstrictor and pro-coagulant). Ageing animal studies have demonstrated that endothelial cells become flatter, enlarge and the polypoid nucleus increases.[7,8] Structural integrity of the cytoskeleton becomes altered, affecting mobility, migration, proliferation, and proteomic secretions of the endothelial cell.[7–10] Complex links between endothelial cells in rats decrease with age, causing breaches in the endothelial cell layer.[11] This may reveal the mechanism in humans which leads to the acceleration of arterial stiffening or atherosclerosis.

Functional changes in the vascular system with ageing

Compliance of any material is defined as the unit change in volume induced by a unit change in pressure. Arterial compliance is a functional property of the artery and it starts to decrease from the age of ten secondary to changes described above, and can be independent of atherosclerosis.[12] Reduced arterial compliance causes earlier return of the reflected pulse wave,[13,14] causing the wave

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Table 2. *Blood pressure changes with ageing.*
Summary of the changes in blood pressure with ageing (adapted from data in Franklin et al.[15])

Age (years)	Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Vascular resistance	Arterial stiffness
<50	↑	↑		↑	↑
50–60	↑	←→	↑	↑	↑
>60	↑	↓	↑		↑

to return to the heart in systole rather than diastole, instigating a rise in systolic pressure and an increase in pulse pressure.[15] This combined with the altered wall properties of reduced arterial compliance reduces coronary blood flow in diastole and increases cardiac work load.[16] Arterial stiffness has been identified as an independent predictor of mortality secondary to a cardiovascular event.[17,18]

Arterial pressure when abnormal results in hypertension; current National Institute of Clinical Excellence (NICE) guidelines are to maintain BP <140/90mmHg.[19] The Framingham heart study in the US found that with ageing, systolic blood pressure continues to increase; however, diastolic pressure rises until middle age, balances out, and then begins to decrease after the age of 60 years as demonstrated in Table 2.[15] In addition to stroke volume, blood pressure relies on the interplay of peripheral vascular resistance and central arterial stiffness. Peripheral vascular resistance has been identified as a key component in raising systolic and diastolic blood pressure, particularly in young people. Central blood pressure changes affect the blood pressure differently, increasing systolic blood pressure and contributing to a reduction in diastolic pressure, resulting in a widening of pulse pressure. Physiologists have suggested that arterial stiffening may contribute to a resetting of the baroreceptor response within the carotid arteries, resulting in an increase in systolic blood pressure. A blunted neuronal response from the baroreceptors due to an increased resistance to circulating catecholamine as described above may also contribute to a rise in systolic blood pressure in the ageing population.[20]

The interplay between the myocardium and vasculature

Changes in the vasculature and myocardium are interlinked and both play a role in the pathogenesis of cardiovascular disease. Bouthier *et al*.[21] found that subjects with altered myocardial structure and function also had altered arterial dispensability.[21] Clinically, in those with moderate to large coronary artery disease, arterial stiffness was a key determinant of the ischaemic threshold of the myocardium.[22]

Structural changes of the myocardium with ageing

Macroscopic

Normotensive patients within the Baltimore longitudinal study on ageing demonstrated that left ventricular (LV) cavity size somewhat increased with ageing, but remained within the normal range.[23] The left ventricle can also become hypertrophic in those with long-standing hypertension in response to increased strain, and studies have suggested that even in those without hypertension LV wall thickness can increase with age.[24] Atrophy can occur, although this is usually confined to disease states. In healthy ageing adults, left atrial enlargement can occur.[25]

Microscopic

Left ventricular myocytes enlarge and decrease in number with ageing.[26] Decreasing myocyte numbers are attributed to drop-out by apoptosis or necrosis, the subsequent outline and valves of the myocardium being replaced by fibrous and calcified tissue.[27] Amyloid deposits in the myocardium are a common finding in those aged over 70 years with deposits located mainly in the atria or ventricles. Senile amyloidosis is not associated with cardiomegaly but with atrophied myocardial fibres.[25] Apoptosis of atrial pacemaker cells occurs, with 50–70% of cells lost by the age of 50;[28] atrial ventricular node cell numbers are preserved but fibrosis and cellular loss within the bundle of His is thought to contribute to the increasing risk of developing arrhythmia.

Functional changes within the myocardium

Heart rate

With ageing the heart rate in the supine position remains unchanged,[23] although in the sitting

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position the heart rate decreases with ageing in both sexes.[29] Heart rate variability and adjustments to respiration when measured over a 24-hour period decrease with ageing. This alteration of heart rate is controlled by the sympathetic and parasympathetic nervous system. The activity of the sympathetic nervous system increases with age, resulting in desensitization of the catecholamine receptors driving the sympathetic response, due to the decreasing heart rate with ageing.[30]

Left ventricular systolic and diastolic function

At rest, left ventricular function measured as the ejection fraction is expected to be on average 65%, and is preserved with ageing.[15] On exercise the ejection fraction decreases with age[15] and this will be discussed later.

The early diastolic filling rate slowly declines from the age of twenty, and at 80 years the diastolic filling rate has reduced by half.[31,32] This has been attributed to structural fibrous changes within the myocardium and residual myofilament calcium (Ca^{2+}) activation from previous myocardial contraction in systole. The length of Ca^{2+} activation is determined by diastolic stretch and myofilament contraction in systole. Myofilament binding to Ca^{2+} is thought to combine with structural fibrous alterations of the heart to increase myocardial stiffening; this prolongs early diastolic filling. This is supported by studies undertaken in rats where Ca^{2+} release from the myoplasm by the sarcoplasmic reticulum resulted in an extended transient rise in Ca^{2+}.[33] These changes are thought to be adaptive to maintain the contractile function of the ageing myocardium.[30] Despite alterations within the diastolic component of the cardiac cycle, the end-diastolic volume in the supine position remains unchanged in ageing women[23,29] but increases in men.[32] Vigorous left atrial contraction has been the suggested mechanism leading to increased late diastolic filling.[32,34] The atria are prone to enlargement and hypertrophy, which clinically manifests as a fourth heart sound and giant 'a' wave.

In ageing adults free of cardiovascular disease the ejection fraction is not reduced[23] despite common misconceptions. Stroke volume in men increases with age due marginally to the increase in end-diastolic volume, but in women it remains unaltered.[23] Changes in cardiac output are defined by gender and sedentary lifestyle. Cardiac output in men remains stable with ageing in women; however, cardiac output decreases with ageing. This is thought to be due to the lack of compensation of stroke volume for a lower heart rate. The gender difference is thought to be due to a difference in activity levels between men and women.

Heart failure with preserved ejection fraction in adults

Heart failure is when the heart can no longer pump efficiently enough to meet the body's demands. Of those diagnosed, 40% will die within a year of diagnosis with £635 million of NHS money spent on managing those with heart failure each year.[35] It is a clinical syndrome that impairs ventricular filling or ejection.[36] Preserved ejection fraction describes patients with heart failure but normal or near-normal ejection fraction. This contributes to an estimated 50% of the patients with heart failure. Preserved ejection fraction heart failure is thought to be caused by poor left ventricular diastolic filling that in turn requires higher filling pressures in order to maintain left ventricular volume. Elevated pressures increase right-sided pressures and result in increased pulmonary pressures and decreased lung compliance. In advanced disease, low stroke volume may lead to a reduced ejection fraction.

The effects of ageing on the cardiovascular system at a molecular level

Cellular signalling changes

Signalling pathways within the arterial tree include renin, angiotensin I, angiotensin II, angiotensin converting enzyme (ACE), chymase and angiotensin I and II receptors, all of which have been found to be increased in several species.[36–40] Studies have shown that all components of the RAS system are up-regulated in the aged arterial wall. Molecules linked to the signalling cascade are also up-regulated; these include calpain-1, matrix metalloproteinase types 2 and 9 (MMP-2 and MMP-9), monocyte chemotactic protein-1 (MCP-1) and transforming growth factor beta-1 (TGF-β1).[36–40] Studies on rats to mimic these signalling changes have been shown to cause the structural, functional and biochemical alterations seen in ageing arteries.[37]

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Decreasing endothelial cell capacity for replication and repair has been linked to a decrease in nitric oxide production with ageing.[41] It is thought with ageing signalling pathway imbalances disrupt the harmony of oxidase and dismutase. This results in increased levels of superoxide and hydrogen peroxide and a decrease in nitric oxide bioavailability in the coronary and aortic walls of ageing rats, favouring a pro-coagulant state and stimulating new vascular smooth muscle growth. In diseases such as hypertension and diabetes this process is exaggerated and is thought to increase risk of cardiovascular events.[42]

Telomere biology and cardiovascular ageing

Telomeres make up the ends of eukaryotic chromosomes. They are made up of sequences of DNA laid out in tandem repeats. They are an essential part of the cell cycle, maintaining chromosomal stability.[43] As cells divide in mitosis some telomere DNA is lost with each division; the amount that can be lost is variable and can be influenced by oxidative stress.[44] The process of losing DNA in each cell division provides a potential mechanism for senescence. Transition to senescence may be when the telomere reaches a critical value[45] or from cell signalling driving the shortened telomeres.[43] Both theories support telomere length as a possible biological marker of ageing, with shorter telomeres indicating increased biological age.[46] One study showed that subjects over 60 years of age with shorter than average telomere length in circulating leucocytes were more than three times more likely to die of cardiac disease.[47] Shorter telomere length has also been associated with increased likelihood of developing carotid atherosclerosis in individuals with hypertension,[48] decreased left ventricular function[49] type 1 diabetes,[50] type 2 diabetes[51] and insulin resistance.[52] It has been inversely correlated with pulse pressure and pulse wave velocity.[53]

Genetics and cardiovascular ageing

Male and females

Androgen receptors are expressed in all vascular tissues, including the endothelium, smooth muscle and myocardium.[54] The effect of androgens upon the cardiovascular system has long been debated, with oestrogens being considered protective against cardiovascular disease until the recent Women's Health Initiative Study[55] demonstrated the relationship between hormone replacement therapy (HRT) and an increased incidence of non-fatal heart attacks, stroke and thromboembolic disease.[55] In men circulating testosterone declines progressively with ageing, but the high levels of testosterone associated with exogenous administration of anabolic steroids are associated with increased cardiovascular morbidity.[56] In postmenopausal women on hormone replacement therapy arterial stiffness increases[57] when HRT is withdrawn, demonstrating that hormonal changes affect vascular compliance.[58] Increased arterial stiffness, reduced systemic arterial compliance and endothelium-dependent dilation have been associated with low androgen levels in men and women.[57,59] Growing evidence concludes that extremes of androgen excess or deficiency cause an increase in cardiovascular morbidity, but physiological androgen levels may be protective.[60]

Race

Afro-Caribbean populations are at a higher risk of developing cardiovascular disease;[61] they are also more likely to have end organ damage from hypertension than anticipated at given levels of blood pressure. Studies have shown that in comparison with European and Asian populations, Afro-Caribbeans have accelerated arterial ageing,[62] increased aortic stiffness, increased left ventricular wall thickness[63] and greater carotid intima thickness.[64]

Lifestyle

Research suggests that a combination of the following leads to significant premature ageing: smoking, consumption of fruits and vegetables less than 3 times daily, less than 2 hours of physical activity per week, and weekly consumption above the recommended limits for alcohol ingestion in the UK. All-cause mortality data suggested that participants aged 12 years earlier.[65] Suggested mechanisms for the effects that lifestyle interactions have, which may accelerate ageing, are summarized in Table 3.

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Table 3. *Lifestyle effects upon the vascular system.*
The interplay of lifestyle and its effects summarized may result in the pathophysiological changes seen in cardiovascular disease more common with ageing

	Lifestyle	Effect on the vascular system
Diet	Low sodium diet	Increases vascular compliance
	Fish oil	Increases arterial distension
		Improves endothelial function
		Increases arterial compliance
	Isoflavones	Reduce arterial stiffness
	Obesity	Increased arterial stiffness
Smoking		Decreased carotid artery compliance
		Decreased brachial artery distensibility
	Acute inhalation	Increased augmentation index
		Increased pulse wave velocity
	Passive smoking	Reduced arterial compliance
Alcohol	Alcohol low–moderate ingestion	Decreases arterial stiffness
		Lowers cardiovascular risk
	Post-alcohol ingestion	Decrease in blood pressure
		Decrease in pulse wave velocity
		Decrease in augmentation index
		Blood pressure rise 10 hours post-ingestion
	Increased alcohol ingestion	Increased augmentation index
		Hypertension

Diet

Evidence and public health messages have associated systolic hypertension and high-salt diets. Low-sodium diets improve vascular compliance in older adults.[66] Fish oil improves arterial distension, endothelial function and arterial compliance.[67] Soy food is associated with a reduced risk of cardiovascular disease,[68] and isoflavones found in soy, tofu and some beans reduce arterial stiffness.[69–70]

Elderly adults with higher levels of visceral fat have increased aortic stiffness.[71]

Smoking and alcohol

Smoking has harmful effects on the arterial wall. Studies have shown that smokers have a decrease in compliance of the carotid artery and distensibility of the brachial artery.[72] They also have increased augmentation index and pulse wave velocity in comparison with non-smokers and can be affected acutely post-cigarette.[73] Passive smoking is also associated with modified vascular compliance.[74]

Alcohol in low to moderate amounts decreases arterial stiffness and is associated with a lower cardiovascular risk.[75] In the acute phase post-alcohol ingestion there is a decrease in blood pressure, pulse wave velocity and augmentation index. This gives rise to an increase in blood pressure 10 hours after ingestion.[76] In those who ingest high amounts of alcohol (>21 units a week), increases are seen in augmentation index and blood pressure.[77]

Exercise and ageing

The effect of ageing upon individuals is variable, and this is demonstrated in variability in peak exercise capacity and peak oxygen consumption decline in ageing individuals. This shows that physical fitness as opposed to ageing *per se* interacts with cardiorespiratory function. The evidence-based effects of exercise upon ageing are summarized in Table 4. Peak heart rate reduces with ageing, and heart volume in end-diastole enlarges. The early diastolic filling rate remains unchanged with age, but the end-diastolic volume in the left ventricle increases as the heart utilizes the Frank-Starling mechanism to maintain stroke volume.[23] With vigorous exercise the maximal oxygen consumed (VO_2,max) declines little when measurements are adjusted to the decrease in lean muscle mass with ageing.[78] Pulse wave velocity, carotid augmentation index and pulse pressure measurements decrease following a period of exercise in previously sedentary subjects.[79,80]

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Table 4. *Cardiovascular effects of exercise on a senescent adult.*
A summary of the effects of ageing on the cardiovascular system during exercise in comparison with a young adult[23,78–83]

Cardiovascular property	Change during in exercise	
Peak heart rate	Reduces	↓
Heart volume in end-diastole	Enlarges	↑
Early diastolic filling rate	Unchanged	←→
Diastolic volume	Increases	↑
Maximal oxygen consumed (VO_2,max)	Declines	↓
Pulse wave velocity	Reduces	↓
Carotid augmentation index	Reduces	↓
Pulse pressure	Reduces	↓
Baroreflexes	Improves	↑
Endothelial function	Improves	↑

Baroreflexes are also improved,[81] as is endothelial function,[82] illustrating that exercise also can illicit intrinsic changes in the arterial wall. With ageing a positive association has been found between increased systemic arterial compliance and exercise tolerance, indicating that either exercise allows acquisition of lower compliance, or that more strenuous exercise is permitted with a more compliant arterial system.[83]

Conclusions

The biological, structural and mechanical changes in the cardiovascular system in senescence are thought to contribute to the increasing incidence of cardiovascular disease with ageing. Intrinsic genetic factors such as sex and race have been found to influence the ageing myocardial process, demonstrating possible mechanisms of causation for the higher incidence of clinical disease in males *versus* females, and the implications of race upon the ageing cardiovascular system. Lifestyle factors such as diet, smoking, alcohol ingestion and exercise have also been demonstrated to interact with the ageing cardiovascular system synergistic to the development of cardiovascular disease.

Vascular stiffness has been demonstrated as a useful predictor of biological *versus* chronological ageing, and independently has been identified as a predictor of mortality secondary to a cardiovascular event.[17,18] The value of using vascular stiffness measurements has yet to been transferred into clinical practice. However, with increasing evidence that vascular stiffness is a marker of cardiovascular disease and predictive of mortality, a role for measuring arterial stiffness clinically may assist in the early diagnosis and screening of patients at risk of cardiovascular disease.

Elderly medicine presents great challenges as normal changes meet with pathophysiology to manifest as symptoms often vague and non-specific. Cardiovascular disease in older people is still the leading cause of death in the UK and contributes to significant morbidity and mortality within the elderly population. The identification of those at risk of cardiovascular disease and modification of risk factors may minimize interactions of the ageing process and therefore reduce the incidence of cardiovascular disease within the UK population.

Conflicts of interest

The authors declared no conflicts of interest.

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