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DOI 10.1016/j.exger.2017.05.016
ISSN 0531-5565
ESSN 1873-6815

Publisher: Elsevier

Experimental Gerontology 109 (2018) 67–74

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Review

Physical activity and cardiovascular aging: Physiological and molecular insights

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ARTICLE INFO

Article history:
Received 4 February 2017
Accepted 21 May 2017
Available online 22 May 2017

Keywords:
Aging
Cardiovascular
Heart
Arteries
Physical activity
Exercise

ABSTRACT

Aging is associated with significant changes in both cardiac and vascular structure and function that lower the threshold for clinical signs and symptoms, making older people more susceptible to cardiovascular diseases, morbidity and mortality. Understanding of age-related cardiovascular changes is necessary for effective and efficient prevention and treatment of cardiovascular disease in older people. Cardiac aging is associated with left ventricular remodelling marked by increased mass-to-volume ratio and accompanied by systolic and diastolic myocardial dysfunction, and reduced sensitivity to sympathetic stimuli that compromises myocardial contractility and pumping ability in older people. The vascular age-related remodelling is associated with increased arterial wall thickness, arterial stiffness, and an impaired endothelial vasoreactivity. Over the previous three decades of intensive research in cardiovascular aging, it became apparently clear that lifestyle factors such as physical activity and exercise play an important role in attenuating cardiovascular function decline with aging. This review highlights the effect of age on cardiac and vascular changes and their adaptations to exercise, providing physiological, molecular and cellular mechanisms that underlie diminished cardiovascular response in older age. It further describes cardiovascular differences between the individuals who maintain a physically active lifestyle, and who undergo exercise interventions in later life.

Contents

1. Introduction

Chronological age is identified as the major risk factor for cardiovascular morbidity and mortality, with older people significantly more likely to have cardiovascular disease (Lakatta and Levy, 2003a; Shih et al., 2011). In the absence of hypertension or clinically apparent cardiovascular disease, the cardiovascular system undergoes structural and functional changes with age that compromise cardiac reserve. These age-associated cardiovascular changes lower the threshold for the three major cardiac pathophysiological conditions such as left ventricular hypertrophy, chronic heart failure and atrial fibrillation, all seen with increasing age (Lakatta, 2002). In order to understand the effects of aging on the cardiovascular system, it is important to consider the complex interaction between the heart as a pump and the afterload on the heart imposed by the arterial system (Arbab-Zadeh et al., 2004).

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http://dx.doi.org/10.1016/j.exger.2017.05.016

Cardiac aging is associated with progressive loss of myocytes and compensating mild hypertrophy, but also with reduced sensitivity to sympathetic stimuli that compromises myocardial contractility and pumping ability in older people (Lakatta and Levy, 2003a; Lakatta, 2002; Olivetti et al., 1995). Using the most recent developments in cardiac magnetic resonance imaging with tissue tagging and spectroscopy, several studies have demonstrated age-related changes in intramyocardial strains, longitudinal shortening, systolic torsion and cardiac energetics (Lumens et al., 2006; Oxenham et al., 2003; Neubauer, 2007; Hollingsworth et al., 2012; Kostler et al., 2006; Jakovljevic et al., 2015). With advanced aging, the large arteries dilate, their walls become thicker and stiffer due to collagen and calcium deposition and fragmentation of the elastic fibres (Lakatta, 2002; Lakatta and Levy, 2003b).

Physical activity, exercise and associated high level of cardiorespiratory fitness reduce all cause and cardiovascular mortality, the risk of heart failure and myocardial infarction, and age-related arterial and cardiac stiffening (Lakatta and Levy, 2003a; Lakatta, 2002; Blair et al., 1995; Berry et al., 2013; Lakka et al., 2001; Hill and Olson, 2008; Fleg et al., 2005; Schulman et al., 1996; Shiroma and Lee, 2010; Lee, 2010). Epidemiologic studies investigating the association of physical activity with cardiovascular disease risk have been conducted for more than six decades now. The earliest studies from the 1950s in London by Morris and colleagues, showed that men who were physically active on the job experienced coronary heart disease mortality rates that were approximately half those of men who were sedentary at work (Morris et al., 1953a; Morris et al., 1953b). Following these observations, Paffenbarger and colleagues in the United States published similar findings from the Harvard Alumni Health Study in the 1960s showing that men who died from coronary heart disease were approximately 40% to 50% less likely to be recreationally active, compared with men who remained alive (Paffenbarger et al., 1966). Numerous epidemiological studies were published since these early investigations reporting strong association between physical activity in cardiovascular health with 30% to 40% reduction in all-cause and cardiovascular mortality in active men and women of different age (Blair et al., 1995; Shiroma and Lee, 2010; Talbot et al., 2007; Pate et al., 1995; Nelson et al., 2007; Haskell et al., 2007; Fletcher et al., 1992). Conversely, low active and sedentary behaviour are associated with 63% greater risk to develop cardiovascular disease (Chomistek et al., 2013). From the evidence available it is now clear that physical activity and exercise can attenuate the age-related cardiovascular changes by improving functional capacity of the cardiovascular system, cardiac function and metabolism (Wilson and Tanaka, 2000; Tanaka et al., 1997; Perseghin et al., 2009; Woo et al., 2006; Gates et al., 2003; Turkbey et al., 2010). This book chapter will provide an overview of the evidence demonstrating the physiological and molecular responses and adaptations in cardiovascular function induced by physical activity and exercise in relation to aging.

2. Cardiac response to acute exercise in relation to aging

One of the most important physiological changes that occur in response to advanced aging is a decline in maximal aerobic capacity (i.e. cardiorespiratory fitness) represented by peak exercise oxygen consumption. Low levels of aerobic capacity are strong predictors of quality of the life, functional independence, all-cause and cardiovascular mortality (Fleg et al., 2005; Sui et al., 2007). The age-associated decline in maximal aerobic capacity is nonlinear and increases progressively with each decade of life e.g. 3–6% in the third and fourth decades and >20% per decade after age 70 (Fleg et al., 2005; Wilson and Tanaka, 2000). This reduction in aerobic capacity can be attributed to changes that alter the delivery of oxygen to exercising muscles (i.e. cardiac function) or the ability of muscles to utilise oxygen. Peak exercise cardiac output and arteriovenous oxygen difference decline by ~25–30% with aging (Fleg et al., 2005; Fleg et al., 1995a; Goldspink et al., 2009), and this is consistent with marked reduction in capillary density, mitochondrial function, and mitochondrial enzyme activities (Dai et al., 2012). It should be noted that in that in the later life a decrease in aerobic capacity is more rapid in older men than in older women (Weiss et al., 2006). As a result, the gender differences dissipate in the later decades of life, suggesting a significant difference in age-associated changes in cardiac morphology and function between men and women and their response to acute exercise stress test (Lakatta and Levy, 2003a; Olivetti et al., 1995; Fleg et al., 1995a; Goldspink et al., 2009; Cheng et al., 2009; Ridout et al., 2010).

Age is associated with a phenotype of left ventricular remodelling marked by increased mass-to-volume ratio and accompanied by systolic and diastolic myocardial dysfunction that is not reflected by preserved ejection fraction (Jakovljevic et al., 2015; Cheng et al., 2009). This pattern of ventricular remodelling confers significant cardiovascular risk, particularly when presented earlier in life. Left ventricular diastolic function and early diastolic filling rate progressively slows after the age of 20 years so that by 80 years the rate is reduced, on average, up to 50% (Benjamin et al., 1992; Schulman et al., 1992). Despite the slowing the left ventricular filling early in diastole, more filling occurs in late diastole, due in part, more vigorous atrial contraction that is accompanied with atrial hypetrophy and enlargement and on auscultation manifested as a fourth heart sound (atrial gallop) (Lakatta and Levy, 2003a).

Data from the Baltimore Longitudinal Study of Aging demonstrate cardiac changes with aging in apparently healthy adults aged between 20 and 85 years (Fleg et al., 1995a). Despite significant changes in the diastolic filling pattern in older, healthy persons, their left ventricular end-diastolic volume index in the supine position is not compromised and does not substantially differ from their younger counterparts (Rodeheffer et al., 1986). However, with aging there is an alter response of cardiac volumes to postural changes e.g. assumption of the sitting position from the supine position reduces end diastolic volume index in younger persons to a greater extent than in older one (Fleg et al., 1995a). During short-term submaximal seated cycle exercise, end diastolic volume index increases equivalently to all ages, but during exhaustive exercise, it drops to the seated rest level in younger but remains elevated in older men (Fleg et al., 1995a). Therefore, acute end diastolic volume reserve during the postural change and during graded upright exercise is moderately greater at 85 years if age versus 20 years of age (Lakatta and Levy, 2003a; Lakatta, 2002). During acute vigorous exercise left ventricular end diastolic volume is greater in older than in younger men despite a reduction in early diastolic filling rate (Schulman et al., 1992); in women however end diastolic volume response to vigorous exercise is similar at older and younger ages (Jakovljevic et al., 2015; Fleg et al., 1995a).

While left ventricular systolic performance i.e. left ventricular ejection fraction appears to be unchanged with aging under resting condition, but significantly reduced during exhaustive upright exercise (Jakovljevic et al., 2015; Fleg et al., 1995a; Goldspink et al., 2009). This is due to a reduced end systolic volume with aging, with previous research demonstrating that the acute end systolic reserve at age 85 is only about one-fifth of that at age of 20, and there is a similar age-related loss of ejection fraction reserve (Lakatta and Levy, 2003a). Stroke volume index during and at peak exercise is preserved in older people due to age associated changes in end diastolic and end systolic volume and greater use of Frank-Starling mechanism. Although older people use the Frank-Starling mechanism during vigorous exercise, this mechanism is deficient because of an inability of the left ventricular emptying and to reduce the end systolic volume (Fleg et al., 1995a). In women, although end diastolic volume during exhaustive exercise is similar at older and younger ages (Jakovljevic et al., 2015), the change in end diastolic volume from rest to exercise increases significantly with age (Fleg et al., 1995a).

Heart rate in the supine position at rest does not change with age whereas change in body position from supine to seated results in slight increase in heart rate, but significantly less in older than in younger men

(Fleg et al., 1995a; Rodeheffer et al., 1986). The maximum heart rate is significantly reduced in older people and the magnitude of this age-associated reduction in peak exercise heart rate is about 30% between 20 and 85 years of age (Fleg et al., 1995a; Goldspink et al., 2009). This reduction in heart rate response to exercise is the reason why the maximum acute cardiac output reserve in healthy people decreases by about 30% between the ages 20 to 85 years (Fleg et al., 1995a).

The maximal cardiac pumping capability of the heart represented by peak exercise cardiac power output (the product of cardiac output and mean arterial blood pressure) is differently affected by age in men and women. A study of presbycardia evaluated the effect of aging on cardiac power output and its reserve in apparently healthy people (93 men and 125 women) (Goldspink et al., 2009). Results revealed important gender related differences demonstrating that maximal cardiac pumping capability and reserve decreased by 20–25% with age in male hearts but were preserved in older women (Goldspink et al., 2009).

2.1. Molecular and cellular mechanisms of cardiac aging and its response to acute exercise

A number of studies performed in rodents reported different molecular and cellular mechanisms can explain age-related changes in cardiac structure and function. An increase in left ventricular mass with aging is due to enlargement of myocyte size and focal proliferation of the matrix surrounding myocytes which can be linked to an altered cardiac fibroblasts number and function (Fraticelli et al., 1989). The number of cardiac myocytes becomes reduced because of necrosis and apoptosis, with the former predominating (Anversa et al., 1990; Goldspink et al., 2003). Putative stimuli for cardiac cell enlargement with aging include an age-associated increase in vascular load due to arterial stiffening and stretching of cells caused by drop out of neighboring myocyte. Stretch of cardiac myocytes and fibroblasts initiates growth factor signalling (e.g., angiotensin II/TGF-β), which, in addition to modulating cell growth and matrix production, also leads to apoptosis (Cigola et al., 1997). The expression of atrial natriuretic and opioid peptides, molecules that are usually produced in response to chronic stress, is increased in older age (Younes et al., 1995).

Altered calcium (Ca) homeostasis is one of the most important hallmarks of the aged heart, as it is involved in cardiac excitation-contraction coupling. During aging, the magnitude of the L-type Ca channel current becomes significantly increased in parallel with the enlargement of cardiac myocytes, resulting in an unaltered L-type Ca channel current density (Wei et al., 1984). Since the inactivation of L-type Ca channels is slowed, the action potential duration is prolonged, the Ca net influx during each action potential is increased in cells of senescent myocardium relative to cells of adult control (Wei et al., 1984). While neither mRNA nor protein levels of the sarcoplasmic Ca release channel (ryanodine receptor) significantly change with advancing age, the mRNA abundance and the density of sarcoplasmic reticulum Ca pump decrease with aging and are associated with diminished sarcoplasmic Ca sequestration rate in the aged heart (Walker et al., 1993). The multiple changes in in Ca cycling that occur during aging result in an augmented Ca influx, slowed sarcoplasmic reticulum sequestration, and prolonged duration of the Ca transient and contraction (Walker et al., 1993). These alterations which prolong electromechanical systole may be construed as an adaptation in that they prolong the force bearing capacity of the senescent cells following excitation (Janczewski et al., 2002). This helps maintaining the cardiac function in the aged heart. However, they also increase the risk of Ca overload and Ca dependant arrhythmias during stress and the senescent heart (Lakatta, 2003). Although reduced β-adrenergic receptor response to aging contributes to diminished contraction reserve, these may be viewed in part, as adaptive, in that they protect against Ca overload during stress (Lakatta, 2003).

With aging there is a reduced cardiac response to stress and exercise. Acute excess myocardial Ca loading leads to dysregulation of Ca homeostasis, impaired diastolic and systolic function, arrhythmias, and cell death (Lakatta, 1992). The cell Ca load is determined by membrane structure and permeability characteristics the intensity of stimuli that modulate Ca influx or efflux via their impact on regulatory function of proteins within membranes, and reactive oxygen species, which affect both membrane structure and function. Excessive cytosolic Ca loading occurs during physiological and pharmacological scenarios that increase Ca influx (e.g. neurotransmitters, postischemic reperfusion, or oxidative stress) (Hano et al., 1995). In hearts or myocytes from the older heart, enhanced Ca influx, impaired relaxation, and increased diastolic tone occur during pacing at an increased frequency (Brenner et al., 2001; Tate et al., 1990; Lim et al., 2000). This is a "downside" of the aforementioned age-associated adaptation that occurs within the cells of senescent heart (and also of young animals chronically exposed to arterial pressure overload). Causes of reduced Ca tolerance of the older heart include changes in the amounts of proteins that regulate Ca handling, caused in part by altered gene expression, and to an age-associated alteration in the composition of membranes in which Ca regulatory proteins reside, which includes an increase in membrane polyunsaturated fatty acids which are protective of cardiac calcium regulation (Pepe et al., 1999). An additional potential cause of the reduced threshold of senescent myocytes for Ca overload is an enhanced likelihood for intracellular generation of reactive oxygen species in cells from the senescent versus the younger adult heart during exercise stress testing (Lucas and Szweda, 1998).

Efficient communication between the nervous and cardiovascular systems is necessitated for efficient response to physiological stress during which the sympathetic component of the autonomic system is dominant (Lakatta, 2002). A diminished responsiveness to β-adrenergic augmentation with aging is associated with slower heart rate, blunted systolic emptying, larger end diastolic volume, and reduced ejection fraction and maximal heart rate (Lakatta and Levy, 2003a). The activity of the sympathetic nervous system increases with aging as demonstrated with increased sympathetic nerve activity (Iwase et al., 1991), increased norepinephrine production (Hogikyan and Supiano, 1994) or an increased spillover of the neurotransmitters (norepinephrine and epinephrine) form tissues into the circulation of older vs. younger individuals in response to exercise (Fleg et al., 1985). The elevated circulating levels of norepinephrine in the older persons results from an enhanced outflow from nerve endings, diminished reuptake into nerve endings and to a reduced plasma clearance (Lakatta, 2003). Elevated sympathetic neurotransmitter levels lead to a greater occupancy of cardiac cell surface receptors by the catecholamine, leading to a desensitization of the β-adrenergic receptor and its coupling to intracellular signalling pathways (Lakatta, 1993). Such desensitization accounts for the postsynaptic reduction in responsiveness to β-adrenergic stimuli with aging as demonstrated with reduced maximal heart rate and cardiac dilation during stress.

3. Vascular physiological adaptations to aging

The central arteries undergo significant structural and functional changes with aging. Both cross-sectional and longitudinal studies in healthy humans indicate that central elastic arteries dilate with age, leading to an increase in lumen size, their walls, particularly the intima, become thickened, and the media exhibits an increased collagen content and frayed elastin (Lakatta and Levy, 2003b; Lam et al., 2010). The thickness of the arterial wall, that occurs mainly in the intimal layer (Virmani et al., 1991), increases two-to three-fold between 20 and 90 years of age and therefore increasing the risk of atherosclerosis (Lakatta and Levy, 2003b; Nagai et al., 1998). Although factors other than atherosclerosis can influence an increase in intimal medial thickness, it remains a useful marker of subclinical vascular disease e.g. a 0.1 mm increase in carotid artery intimal medial thickens is associated with an 18% increase for stroke and 15% for myocardial infarction (Lorenz et al., 2007). Age-related increase in intimal medial thickening

is accompanied by both luminal dilatation and a reduction in compliance or distensibility, with an increase in arterial stiffness (Lakatta and Levy, 2003b). Pulse wave velocity, which is a non-invasive index of vascular stiffening, increases with age at the same rate at entire age range (20 to 100 years of age) in both in men and women (Scuteri et al., 2014). Pulse wave velocity is determined in part by the intrinsic stress/strain relationship (stiffness) of the vascular wall and by the mean arterial pressure (Lakatta and Levy, 2003b). Age-associated increases in pulse wave velocity have been demonstrated in populations with little or no atherosclerosis suggesting that vascular stiffening can occur independently of atherosclerosis (Avolio, 1995). As the walls of large arteries become stiffer, central systolic arterial pressure increases, diastolic arterial pressure decreases, and the pulse pressure increases for a given pattern of left ventricular ejection (Lakatta and Levy, 2003b). Elevated levels of pulse pressure in older age are associated with progression of intimal media thickening, which in turn is associated with widening of pulse pressure (Gimbrone, 1999).

The relationship between the steady and pulsatile components of flow and resulting pressure wave in the aorta defines the aortic input impedance (Mitchell, 2008). The aortic impedance is therefore usually presented as the ratio of oscillatory pressure and flow and is directly related to the stiffness of the arterial wall. The age-associated increase in aortic diameter dilation restrains impedance prior to 60 years of age, despite an increase in pulse wave velocity (Mitchell et al., 2008). Attenuation of the rate of increase in aortic diameter with age, along with a further increase in pulse wave velocity increases aortic impedance after 60 years of age (Mitchell et al., 2008). The research into vascular impedance response to exercise stress test has been conducted in animal models. Although it has been suggested that aortic impedance does not change with advanced aging at rest, it increases over a wide range of exercise stress intensities in older but not in younger subjects (Yin et al., 1981).

Arterial elastance is a composite measure that integrates many of the arterial parameters including arterial compliance, characteristics impedance, and systolic and diastolic time intervals, and thus reflects the net arterial load imposed on the left ventricular (Sunagawa et al., 1983). Most of the components of the arterial elastance (i.e. resistance, compliance, stiffness) change with age, thus leading to a gradual increase in arterial elastance with age (Redfield et al., 2005). Described physiological properties of the arterial system enables a direct comparison with changes in left ventricular function with age and this is defined as arterial-ventricular coupling (Chen et al., 1998). With increased age left ventricular elastance (chamber stiffness) also increases, suggesting that the heart undergoes adaptations to compensate for an increase in arterial elastance (Chen et al., 1998). Interestingly, the ratio between ventricular and arterial elastance is fairly well maintained with advanced age in healthy persons in an attempt that cardiovascular system maintains its efficiency (Redfield et al., 2005). During stress exercise, arterial-ventricular coupling declines to prioritize cardiac efficacy over energetic efficiency. Thus elastance of left ventricular must increase to a greater extent than the increase in arterial elastance (Najjar et al., 2004). With increasing age, however, elastance of left ventricular fails to increase in proportion to the increase in arterial eslastance (Najjar et al., 2004). Therefore arterial-ventricular coupling during exercise in older persons decreases to a lesser extent than it does in younger people (Najjar et al., 2004).

3.1. Vascular molecular and cellular adaptations to aging

Age-related arterial structural and functional remodelling is due to biochemical, cellular, and morphologic changes in the arterial wall, and which are modulated by the same factors that have been implicated in the genesis of various cardiovascular diseases (Najjar et al., 2004). Vascular smooth muscle cells are not terminally differentiated, and are subject to phenotypic modulation during which they revert to a proliferative, secretory and migratory mode, and undergo modifications of their contractile properties and control of Ca cycling by cell surface receptors (Lakatta, 2003). Such vascular smooth muscle phenotype repairs vascular damage and participates in vascular pathologies such as hypertension and atherosclerosis (Lakatta and Levy, 2003b). The diffusely thickened aging intima contains matric proteins, collagen and glycosaminoglycans, and also vascular smooth muscle cells that are thought to have migrated from the media, increased expression of aortic intimal adhesion molecules and increased adherence of monocytes to the endothelial surface (Li et al., 1999; Orlandi et al., 2000). There is also an increased level of the inflammatory chemokine monocyte chemoattractant protein-1 and its receptors (Spinetti et al., 2004). The expression and activity of transforming growth factor that regulates cell replication, synthesis of extracellular matrix components, and the response to injury are also increased in the aged intima (Sporn and Roberts, 1992; Wang et al., 2007). Age-associated changes also occur in the medial layer of the central arteries as demonstrated with the deposition of extracellular matrix proteins such as fibronectin and type 2 matrix metalloprotease which promote not only matrix protein degradation, facilitate vascular smooth muscle cells migration, but also activate transforming growth factor (Li et al., 1999; Wang et al., 2007).

Arterial endothelial function declines with aging as the endothelial cells, that are responsible for arterial tone, permeability, angiogenesis, and the response to inflammation, undergo considerable remodelling (Celermajer et al., 1994). Endothelial cells from older donors are flattened and enlarged, and the number of endothelial cells with polyploid nuclei increases with advanced age (Asai et al., 2000). There is an increased endothelial permeability, alterations in an arrangement and integrity of the cytoskeleton, the appearance of senescence-associated β-galactosidase staining, and the expression of several inhibitors of the cell cycle (Shi et al., 2004). Aged endothelial cells secrete more plasminogen activator inhibitor-1, favouring thrombosis formation (Comi et al., 1995). Aging is further associated with endothelial cell production of vasoconstricting growth factors such as angiotensin II and endhothelin increases, whereas vasodilatatory factors such as nitric oxide, prostacyclin are reduced (Wang et al., 2007; Csiszar et al., 2002). Endothelial cell capacity for replication and repair decreases with age and this is associated with increased apoptosis, telomere shortening, proinflammatory state, reduced nitric oxide bioavailability, and decreased number and the function of endothelial progenitor cell (Wang et al., 2007; Chang and Harley, 1995; Iwama et al., 1998; Csiszar et al., 2008). The loss of endothelial cell function with age is likely mediated partly by an imbalance between factors promoting growth, migration, survival; and factors enhancing oxidative stress and promoting senescence (Lakatta, 2003).

4. Cardiac adaptations to physical activity and exercise in relation to aging

Increased levels of physical activity and exercise are not only associated with a significant reduction in cardiovascular mortality and morbidity in later life (Shiroma and Lee, 2010; Lee, 2010; Byberg et al., 2009), but also have substantial impact on the “rate of aging” in the absence of disease (Lakatta, 2002). Furthermore, aging is associated with a significant decrease in physical activity and an increase in sedentary behaviour (sitting time) that together further increase the risk of cardiovascular mortality and morbidity (Chomistek et al., 2013; Sparling et al., 2015; ACSM Position Stand et al., 2009; van der Ploeg et al., 2012).

A large number of cross-sectional and longitudinal studies investigated the effect of physical activity and short- and long-term exercise interventions on age-related changes in cardiac structure, function, metabolism and performance. Physical activity has been defined as any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure performed in leisure or occupational hours, while exercise is a subcategory of leisure time physical activity that refers to planned, structured, repetitive bodily movement to improve or maintain one or more components of physical fitness (ACSM Position Stand et al., 2009).

In a community-based population free of clinically apparent cardiovascular disease, higher physical activity levels were associated proportionally greater left ventricular mass and end-diastolic volume and lower resting heart rate (Turkbey et al., 2010). A recent cross-sectional study evaluated the impact of daily physical activity on age-related cardiac changes in women (Jakovljevic et al., 2015). Results revealed that although higher levels of physical activity (i.e. >12,500 steps per day) preserved cardiac metabolism and exercise capacity with aging, they had limited effect on age-related changes in concentric remodelling, diastolic function, and cardiac performance in women. In contrast with daily physical activity levels which tend to be of lower intensity in older people (Talbot et al., 2000), structured exercise is usually of moderate to high exercise intensity and therefore hold greater physiological benefits (Samitz et al., 2011). The heart in older people undergoes important changes with exercise. Master athletes, in comparison with age-matched control subjects, demonstrate increased wall thickness, end diastolic volume, stroke volume, and cardiac energetics, but reduced end systolic volume, leading to improved overall cardiac function at rest and during exercise (Arbab-Zadeh et al., 2004; Schulman et al., 1996; Perseghin et al., 2009; Carrick-Ranson et al., 2014; Fleg et al., 1995b). However, it has been previously reported that Doppler measures of diastolic function of master athletes were similar to those of sedentary elderly subjects, suggesting that life-long exercise training does not prevent the age-related decline in left ventricular relaxation (Prasad et al., 2007). Although the rate of maximal oxygen consumption declines with age, it is well documented that trained older individuals show significantly higher rate of cardiorespiratory fitness than inactive individuals (Fleg et al., 2005; Wilson and Tanaka, 2000; Tanaka et al., 1997).

The use of cardiac power to determine the impact of exercise on overall performance of the heart and cardiac reserve demonstrate that veteran athletes, engaged in the endurance training over many years had a maximal pumping performance and functional reserve that was on average 26% greater than that of age-matched sedentary men (Goldspink, 2005). While these veteran athletes probably possess considerably less cardiomyocytes than younger men (Olivetti et al., 1995), this appears to have been compensated for (presumably through greater hypertrophy of the remaining myocytes) as their cardiac reserve and peak oxygen consumption were 19% and 7% greater than those of sedentary men who were nearly 40 years younger (Goldspink, 2005).

Exercise training interventional studies in older adults lasting between 6 and 12 months demonstrated improvements in peak oxygen consumption ranging from 15 to 29% (Woo et al., 2006; Ehsani et al., 1991; Spina et al., 1993; Stratton et al., 1994). A significant improvement in peak aerobic capacity was also shown following exercise training of shorter duration (i.e. ~9–12 weeks) in older people (Murias et al., 2010; Gass et al., 2004). Changes in exercise efficiency and maximal aerobic capacity with age and exercise training may be explained on the cellular level by a disproportionally larger degree of mitochondrial dysfunction in older people associated with a progressive decline in mitochondrial respiratory rate and enzyme activity (Dai et al., 2012). However, capillary density and mitochondrial enzyme activity have been shown to increase with training in older persons, to levels similar to those in young individuals (Coggan et al., 1992).

A time course and mechanisms of adaptations in maximal aerobic capacity with exercise training are different in older compared with younger people and suggest improvements in both cardiac function and peripheral muscles oxygen extraction (Murias et al., 2010). Improvement in peak oxygen consumption in young people during the first 3 weeks of exercise training is predominantly by an increase in arterial venous oxygen difference, whereas in older people the increase in oxygen consumption is associated with consistent improvements in maximal cardiac output (Murias et al., 2010). Further evidence suggests that peak exercise cardiac function is improved after exercise training in older people as demonstrated with increase in peak cardiac output, stroke volume, ejection fraction and left ventricular contractility but reduced end systolic volume (Schulman et al., 1996; Fujimoto et al., 2010). Despite changes in peak exercise cardiac performance, it appears that resting measures of cardiac function remain unchanged following an exercise intervention in older people (Schulman et al., 1996; Ehsani et al., 1991). Cardiac physiological (eccentric left ventricular) remodelling is associated with exercise training (Fujimoto et al., 2010; Spina et al., 1997). One-year of progressive and vigorous endurance exercise training in older sedentary healthy individuals was associated with an increase in left ventricular mass by 10% with no change in left ventricular mass-volume ratio, confirming physiological left ventricular remodelling with exercise in older people (Fujimoto et al., 2010). Exercise training did not however alter grouped left ventricular pressure-volume curves or individual left ventricular stiffness constants perhaps due to increased accumulation of advanced glycation end products in left ventricular wall tissue (Fujimoto et al., 2010).

The effect of age on cardiovascular system differs in men versus women. Also the influence of chronic physical activity and exercise interventions on cardiovascular aging demonstrates sex specificity in humans, with several studies reporting a more beneficial effect of physical activity in older men than women. Chronic exercise training is associated with a lower blood pressure response during submaximal exercise in young and older men and young women, but this is often less apparent in older women (Martin et al., 1991). Left ventricular remodelling and changes in filling dynamics observed in older men following exercise training are absent in women (Spina et al., 1993; Spina, 1999). Others have reported no sex differences in physiological adaptations to exercise training in older adults or conversely, a beneficial effect of female gender on improvements with exercise training (Ishikawa et al., 1999; Kohrt et al., 1991). Similarly, one study demonstrated that older women, but not older men, exhibited improved myocardial fatty acid metabolism in response to beta-adrenergic stimulation following 11 months exercise training. It appears that more investigations are warranted to clarify differences in physiological adaptations to exercise training between older men and women.

5. Vascular adaptations to physical activity and exercise in relation to aging

Aging is associated with a significant changes in the function and structure of arteries that increase the risk of cardiovascular disease (Lakatta and Levy, 2003b). In healthy sedentary people age is associated with increased stiffness (reduced compliance) of large elastic arteries, impaired vascular endothelial function, and increased intima-media wall thickness (Lakatta, 2002; Lakatta and Levy, 2003b). Regularly performed exercise training and demonstrated high level of physical fitness is associated with enhanced vascular function and reduced risk of cardiovascular disease (Blair et al., 1995; Sui et al., 2007; Green et al., 2004; Seals et al., 2008).

Older male endurance athletes demonstrate lower pulse wave velocity and augmentation index (measures of arterial stiffness) and systolic blood pressure than their sedentary peers (Vaitkevicius et al., 1993). Arterial stiffness and blood pressure were greater in postmenopausal compared with premenopausal sedentary women, but not in endurance exercise-trained women (Seals et al., 1999). Age-associated reduction in arterial compliance (i.e. ability of an artery to expand and recoil with cardiac pulsation and relaxation) was ~50% greater in men and women who undertake regular exercise compared with sedentary adults (Tanaka et al., 2000). An aerobic exercise intervention (daily brisk walking) for 3 months was associated with significantly improved arterial compliance in previously sedentary middle-aged/older men and postmenopausal women to levels observed in age-matched endurance exercise-trained adults (Tanaka et al., 2000; Moreau et al., 2003), suggesting that even moderate aerobic exercise may have a substantial effect on atrial compliance (Seals et al., 2008). It should be noted that improvements in arterial compliance with regular exercise training are independent of baseline compliance and changes in conventional

cardiovascular risk factors, body composition and aerobic capacity. In contrast with findings in healthy subjects, regular exercise training may not improve arterial stiffness in adults with clinically elevated arterial blood pressure (Ferrier et al., 2001). The mechanisms behind reduced arterial stiffness with exercise in older age is not dependant on structural changes in elastin and collagen, but rather expression of genes associated with local vasodilatory signalling are modified (Maeda et al., 2005). Also, it has been shown that ascorbic acid (vitamin C) improves carotid artery compliance in sedentary, but not endurance trained postmenopausal women (Moreau et al., 2005), suggesting reduced oxidative stress in the habitually exercising state (Seals et al., 2008).

In contrast with positive changes in arterial function associated with exercise in older age, it appears that habitual physical activity and exercise have limited effect on age-related changes in arterial structural remodelling. Intima-media wall thickness increase with aging in healthy men and women and both are independent predictors of cardiovascular events (O'Leary et al., 1999). Cross-sectional studies reported no different and even greater carotid intima-media wall thickness in physically active compared with sedentary adults (Avolio et al., 1985; Folsom et al., 1994). In rigorously screened healthy men and women, the age-associated increase in carotid intima-media wall thickness does not differ among sedentary, moderately active, and endurance trained adults (Moreau et al., 2002; Tanaka et al., 2002). It also appears that age-related arterial structural remodelling cannot be augmented with an exercise intervention (Moreau et al., 2002; Tanaka et al., 2002).

In contrast on its limited effect on arterial structural remodelling, exercise have major implications on endothelial function and endothelium-dependant dilation. Recent systematic review and meta-analysis revealed that exercise significantly improves endothelial function i.e. flow-mediated dilation (Ashor et al., 2015). Other studiers demonstrated that endothelium-dependant dilation is greater in middle-aged and older men who regularly perform exercise compared with their sedentary peers and it is similar to or modestly lower than that of young healthy sedentary and exercising men (DeSouza et al., 2000; Eskurza et al., 2004; Taddei et al., 2000). Three months of exercise intervention improves endothelium-dependant dilation in previously sedentary middle-aged and older healthy men (DeSouza et al., 2000). The greater endothelium-dependant dilation in middle-aged and older men who regularly perform aerobic exercise is mediated in part by enhanced nitric oxide bioavailability (Taddei et al., 2000). Exercise induced improvements in endothelium-dependant dilation and nitric oxide bioavailability are associated with an increase in endothelial nitric oxide synthesis gene and protein expression in animal models (Spier et al., 2004).

It should further be noted that changes to the arterial system may be related to the intensity of exercise performed and duration of the exercise stimulus (Ashor et al., 2015). Moderate exercise training improved endothelial function in a group of young healthy men, whereas no changes were observed for mild or high-intensity exercise training for 12 weeks (Goto et al., 2003). In healthy older population a simple brisk walk improved endothelial function (Spina et al., 2004). It is possible that high exercise intensity could diminish the effect of exercise due to increased oxidative stress, especially if basal oxidative stress levels are already high. Exercise interventions of shorter duration e.g. 10 days do not alter endothelial function or arterial stiffness despite improvements in aerobic capacity (Baynard et al., 2009). Based on previous studies it is reasonable to suggest that at least 10 weeks of exercise training is necessary to stimulate improvements in endothelial function (DeSouza et al., 2000; Clarkson et al., 1999).

6. Summary

Chronological age is identified as the major risk factor for cardiovascular morbidity and mortality in developed countries with older people significantly more likely to have cardiovascular complications. With aging both cardiac and vascular systems undergo significant functional and structural changes that lower the threshold for clinical signs and symptoms. Cardiac aging is associated with progressive loss of cardiomyocytes and compensating mild hypertrophy, but also with reduced sensitivity to sympathetic stimuli that compromises myocardial contractility and pumping ability in older people. With advanced aging, the large arteries dilate, their walls become thicker and stiffer due to collagen and calcium deposition and fragmentation of the elastic fibres. Today, it is apparently clear that lifestyle factors such as physical activity and exercise have a significant impact not only on preventing cardiovascular diseases later in life, but also attenuating age-related cardiovascular function decline in the absence of disease. Not only that long lasting exercise training of several years and/or decades is associated with improved cardiovascular function in later life, but also exercise interventions performed by previously sedentary individuals provide a significant health benefits, and can reverse, to some extent, age-related decline in cardiovascular function further leading to improved quality of life and functional independence. Future investigations are warranted to identify novel strategies and interventions that will attenuate age-related cardiovascular changes and improve overall cardiovascular function in later life.

Acknowledgements

Dr. Djordje Jakovljevic is supported by the Research Councils UK grant to Centre for Ageing and Vitality (L016354) at Faculty of Medical Sciences of Newcastle University.

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