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Ageing and activity: their effects on the functional reserve capacities of the heart and vascular smooth and skeletal muscles

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During perinatal life striated muscles grow through the acquisition of more contractile cells (myocytes or fibres) followed by their postnatal enlargement (i.e. hypertrophy). In the ageing adult these events are reversed, with a progressive loss of myocytes that cannot be fully compensated despite the presence of cell renewal systems or reactive myocyte hypertrophy. Hence the functional reserve capacities of the heart and skeletal muscles decline with age. This is probably a consequence of physiological ageing and diminished levels of physical activity. As a result daily tasks once taken for granted become progressively more difficult, and eventually impossible, to perform. For example, sufficient coordinated absolute muscle force is required for an individual to rise from a chair or climb stairs, and the reserve capacity of the heart is a major determinant of an individual's ability to remain active and cope with daily stresses and illnesses. Long-term participation in endurance-based activities helps to preserve cardiac reserve, and has both direct and indirect beneficial effects on vascular smooth muscle and health preservation within the cardiovascular system. In contrast, this type of activity does little to protect skeletal muscles against the age-related losses of fast-twitch fibres, small motor units, overall muscle mass and power output. While resistance exercise promotes fibre hypertrophy in skeletal muscles, and to a lesser extent in myocytes of the heart, the explosive power of muscles still declines with age. Hence, while physical activity is important in attenuating age-related changes in muscle function and its reserve capacity, it delays rather than prevents the deleterious effects of ageing *per se*. Despite this, in a culture where inactivity has become an accepted part of life we still need to explore in greater detail the benefits of habitual physical activity, and use this information as a community-based educational tool to help prevent or delay cardiovascular disease, obesity, arthritis and the frailty associated with old age.

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1. Introduction

In recent years the search for a single gene, or the functional deterioration of one major system in the body, that might be responsible for ageing has been replaced by the concept that ageing is the consequence of several complex and multi-factorial processes. Indeed, in the recent review by Weinert and Timiras (2003) no less than 15 different, but often interlinked, theories of ageing are presented. The most popular of these are the Disposal Soma Theory and the Accumulation of Errors and Mutations. The former argues that organisms only maintain their soma to achieve reproductive success, and thereafter the soma becomes disposable. The balance of resources devoted to reproductive fitness is considered to be antagonistic to somatic maintenance and longevity. The second concept embraces several theories, with an accumulation of deleterious errors arising from the impaired replication and repair of both genomic and mitochondrial DNA. Whether point mutations or deletions, these errors will be passed on in the DNA of daughter cells. This alone, or in combination with an impaired fidelity in transcribing and translating the codons on the DNA and mRNA transcripts, will result in the *de novo* synthesis of a greater proportion of abnormal proteins. The incidence of such intrinsic errors, together with possible structural damage to cellular lipids, proteins and DNA, could be further accentuated by increased levels of highly damaging reactive free radicals (and conversely lower levels of anti-oxidants) in old age. An accumulation of errors at a molecular level could lead to the malfunctioning of intracellular organelles (e.g. mitochondria) and ultimately cell death by either apoptosis or necrosis (see below).

The purpose of this review is to describe the known age-related changes in the functional integrity of cardiac, vascular smooth and skeletal muscle and to indicate how habitual physical activity can prevent, retard or reverse some of these changes.

2. Ageing in humans

Currently approximately 16–21% of the population in developed countries, and 8–10% in developing countries, are over 60 years of age, with women being the fastest growing segment. Substantial further increases in the numbers of older people are predicted based on better survival rates of infants and overall increases in longevity. The escalating costs to national budgets and health care services have helped to focus attention on the need to obtain a better understanding of this universal process, not only to prolong life further but also, and crucially, to enhance the quality of life. In humans ageing is known to be highly individual and dependent on socio-economic considerations and lifestyle, as well as genetic factors. Despite its obvious importance to all organisms and recent advances, our understanding of the basic biological mechanisms responsible for the gradual deterioration of body structures and functions remains rudimentary. The functional deterioration of skeletal, cardiac and vascular smooth muscle with increasing age will inevitably erode the reserve capacities of the cardiovascular and musculoskeletal systems. The ability to retain sufficient reserve in these systems is crucial if individuals are to remain mobile, active and independent.

Studying ageing *per se* in humans is not easy. First, it requires rigorous attempts to divorce normal physiological (primary or healthy) ageing from a variety of common diseases, the frequency and severity of which increase with advancing years and may be intrinsically linked to cellular ageing (Lakatta 2002). For example, age-related functional

changes in the heart and vascular smooth muscle need to be investigated in the absence of atherosclerosis, ischaemic heart disease, diabetes etc. Even then, biological, as opposed to chronological, ageing in healthy individuals will be influenced by lifestyle (e.g. choice of diet or levels of physical activity). As people become older they generally become less physically active, and it can be difficult to separate this trend towards a more sedentary lifestyle from the intrinsic changes associated with ageing. Age-related effects on the body clock also influence the sleep patterns, physical activity and performance of older people (Reilly *et al*. 1997). Hence it is necessary to study healthy human subjects in well-defined groups separated according to gender, age, levels of fitness and training etc.

In all mammals, the number of contractile cells (myocytes) make up only 75% and 30% of the total cell population in skeletal muscles and the heart, respectively. The responses of the remaining interstitial cells to ageing and any intervention can significantly complicate the interpretation of data derived from the analysis of whole muscles. Not surprisingly, given all these complications, some investigators prefer to study the process of ageing in well-defined cell lines *in vitro* where the culture media and environmental conditions can be rigorously controlled. Although very convenient, such studies *in vitro* fall well short of describing events *in vivo*, for example how fully differentiated innervated fibres in intact muscles interact (through autocrine and paracrine signalling) with other cell types, such as fibroblasts and the collagen that they secrete, in response to ageing etc.

2.1. *Age-related changes in muscle protein turnover*

All proteins in the body are subject to a continuous cycle of *de novo* synthesis followed by degradation back to their constituent amino acids (figure 1). Both pathways are under

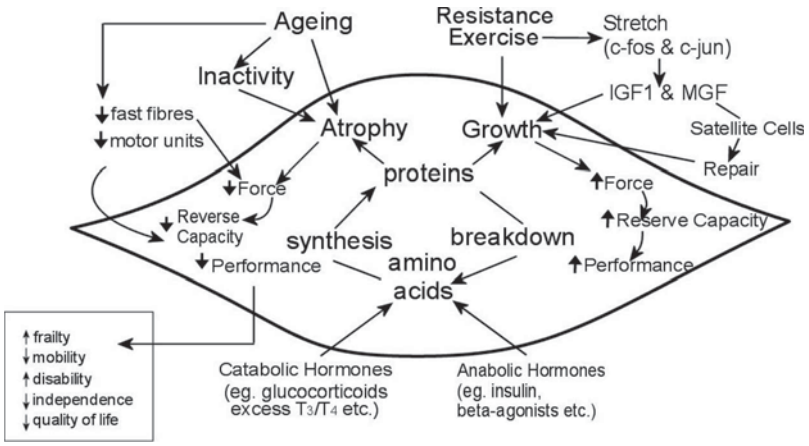

Figure 1. Cellular events leading to the preservation or loss of muscle functional reserve. The balance between the rates of protein synthesis and breakdown is crucial in determining whether muscles grow (i.e. accumulate protein) or undergo atrophy (i.e. a net loss of protein). Both chemical signals (e.g. hormones, growth factors and branched-chain amino acids) and mechanical signals (e.g. stretch or different patterns of activity) associated with exercise can influence protein turnover at all stages of life (Goldspink 1991), potentially improving the functional reserve of the heart or skeletal muscles. The timing of activity-based interventions may be critical, i.e. most effective before the irreversible loss of motor units, fast-twitch fibres or cardiomyocytes.

physiological control and can be changed independently or simultaneously in either a complementary or antagonistic manner (Goldspink 1991). Both pathways consume adenosine triphosphate (ATP), and at first sight this continuous turnover of proteins seems energetically wasteful. Nonetheless it provides great flexibility, with different types and amounts of proteins appearing as a result of rapid changes in gene expression as muscles adapt to new or different workloads etc. At all ages the average rates of protein synthesis outstrip those of protein breakdown during the development of skeletal, cardiac and smooth muscles, thereby facilitating a net gain in protein and hence muscle growth (Lewis *et al*. 1984). However, with increasing age these rates of protein synthesis and degradation decrease and converge such that steady-state conditions are reached in the muscles of the mature adult. At all ages, however, muscles remain plastic, changing their rates of protein turnover to effect work-induced hypertrophy (i.e. protein accretion) or inactivity-induced atrophy (i.e. net loss of protein) through associated mechanical and/or chemical stimuli. Some of the many factors capable of influencing the rate of protein synthesis or breakdown, or both, are indicated in figure 1.

2.2. *Age-related changes in skeletal muscle structure and function*

Collectively, skeletal muscles form the largest tissue in the body and serve three major functions. In addition to their commonly appreciated role in maintaining posture and locomotion, they are metabolically extremely important by virtue of containing the body's largest reserves of protein and amino acids, and as a key source of heat production. Overall muscle function represents the endpoint of a chain of events, many of which are affected in some way by the process of ageing.

Generally in humans beyond the age of 60 years muscle force and power decrease significantly, with the maximum voluntary force of contraction being reduced by 20–40% on average in the proximal and distal muscles of both men and women during their seventh and eighth decades (Frontera *et al*. 2000, Doherty 2003). For example, men aged 70–100 years have been shown to possess 42% weaker, and slower contracting, knee extensor and plantar flexor muscle groups than 26-year-old men (Harridge *et al*. 1997). Such changes may (Jubrias *et al*. 1997) or may not (Kent-Braun and Ng 1999) be greater than that explained by losses in muscle mass (sarcopenia) (Doherty 2003) and cross-sectional area. While being significantly stronger and more powerful on an age-for-age basis, even elite master weightlifters experience similar rates of decline in the explosive power of their muscles and isometric force as healthy non-trained individuals (Pearson *et al*. 2002).

Age-related losses in muscle mass have been explained by a combination of a greater atrophy, selective denervation (via degeneration of motor neurones) and loss of fast-twitch fibres (Einsiedel and Luff 1992, Doherty 2003). The latter will lead to an overall reduction of the velocity of shortening and a shift to the left (and resultant decrease) in the associated force–power relationship. There are also changes in muscle architecture, with the remaining fibres in the muscles of the elderly being approximately 10% shorter, their pennate angles of insertion decreased and tendons more compliant (i.e. absorbing more energy) particularly at higher loads (Tuite *et al*. 1997). Interfibre spaces, probably containing connective tissue that adversely affects both the passive and active properties (James *et al*. 1997), have also been observed in muscles of the elderly. Age-related changes also include decreases in excitation–contraction coupling, Ca^{2+} sensitivity, Ca^{2+} uptake by the sarcoplasmic reticulum (Hunter *et al*. 1999), the concentration of myosin and motility of myosin over actin filaments *in vitro* (Hook *et al*. 1999). Such changes at a

cellular and molecular level could possibly explain the losses in performance beyond those attributable to the decreases in muscle mass and cross-sectional area (Kent-Braun and Ng 1999). Fewer small motor units (Semmler *et al*. 2000) are apparent in senescent muscles, leading to decreases in the control of fine movements and muscle 'steadiness', particularly when attempting to perform dynamic activities. Such changes, coupled with increased activation of antagonist muscles, probably explain the poorer coordinated movements and greater instability found in the elderly. These, together with the slowing of muscle contractile characteristics (Doherty 2003), may be important factors contributing to a slower reflex ability to recover from a loss of footing or when falling forward (Wojcik *et al*. 1999).

Overall maximum oxygen consumption is lower in older individuals (Neder *et al*. 1999, Goldspink *et al*. 2003, Pimentel *et al*. 2003). This can be explained by lower activity levels, losses in muscle mass (Neder *et al*. 1999) and possible cardiovascular limitations (Hunt *et al*. 1998). At the cellular level there is a decrease in oxidative capacity (Conley *et al*. 2000) that is probably in excess of reported decreases in mitochondrial volume, their enzyme activities and DNA (Barazzoni *et al*. 2000, Conley *et al*. 2000). While some of the loss in aerobic power may be due to inactivity *per se*, it may also be due to reduced blood flow to the muscles (Dinenno *et al*. 1999), decreased capillarity or systemic cardiovascular function (Frontera *et al*. 2000). It is also known that anaerobic power declines with age and that this exceeds the decrease in muscle cross-sectional area (Marsh *et al*. 1999). However, it is not clear to what extent this represents a change in contractile efficiency or an age-related reduction in the concentrations of high-energy phosphates (Smith *et al*. 1998), rather than a decrease at the level of anaerobic glycolysis.

2.3. *Age-related changes in cardiac muscle structure and function*

Progressive age-related decreases in the aerobic capacity ($\dot{V}O_2max$) of men and women have been observed by several investigators (Goldspink *et al*. 2003, Pimentel *et al*. 2003). Although the absolute values of $\dot{V}O_2max$ are greater in men than in women, the rate of decline with age is very similar. Indeed, when allowance is made for the differences in body composition, i.e. normalized to lean tissue mass, the gender differences virtually disappear (Goldspink *et al*., unpublished results). This age-related decline in $\dot{V}O_2max$ can be explained, at least in part, by people generally adopting a less active lifestyle as they become older. Inactivity will lead to both peripheral adaptations (i.e. lower efficiency of oxygen extraction by muscles) and central adaptations (i.e. cardiac function). The latter will be discussed below.

The function of the heart involves providing sufficient hydraulic energy to overcome frictional and separational forces and maintain the circulation despite wide-ranging changes in the metabolic demands of the body's tissues at rest and during exercise. Several haemodynamic variables (e.g. left ventricular work or ejection fraction, cardiac output, cardiac index, pulmonary artery wedge pressure etc.) have been used to assess cardiac function. However, these variables measure only particular components of either blood flow or pressure, but both elements of pressure and flow are crucial to determine the overall pumping performance of the heart. A recent independent evaluation (Nicholl and Reilly 2001) concluded that the most meaningful measure of cardiac performance is the power output of the heart, measured both at rest (CPO_{rest}) and during maximal exercise (CPO_{max}). Both values can be measured non-invasively, and cardiac functional reserve (figure 2) determined as $CPO_{max} - CPO_{rest}$ (Cooke *et al*. 1998). So, what age-related changes in the senescent heart might affect its functional reserve capacity?

Between the ages of 17 and 90 years 30–35% of the cardiomyocytes in the male heart die and are presumed to be irreversibly lost (Olivetti *et al*. 1995). Although some of the remaining viable cardiomyocytes undergo adaptive hypertrophy, this does not fully compensate for the progressive decline in myocyte numbers. Interestingly, the rate of cardiomyocyte attrition in the female heart is considerably less (Olivetti *et al*. 1995). Currently, there is no good explanation for this interesting gender difference. It does not appear to be directly linked to female reproductive hormones, as there is no accelerated loss of these contractile cells beyond the menopause.

This study represents a good example of investigators attempting to study normal physiological or healthy ageing in the absence of disease. Only 6% of the hearts available at autopsy were studied after being scrutinized and deemed free from any signs of cardiovascular disease. Unfortunately, these investigators did not have any information

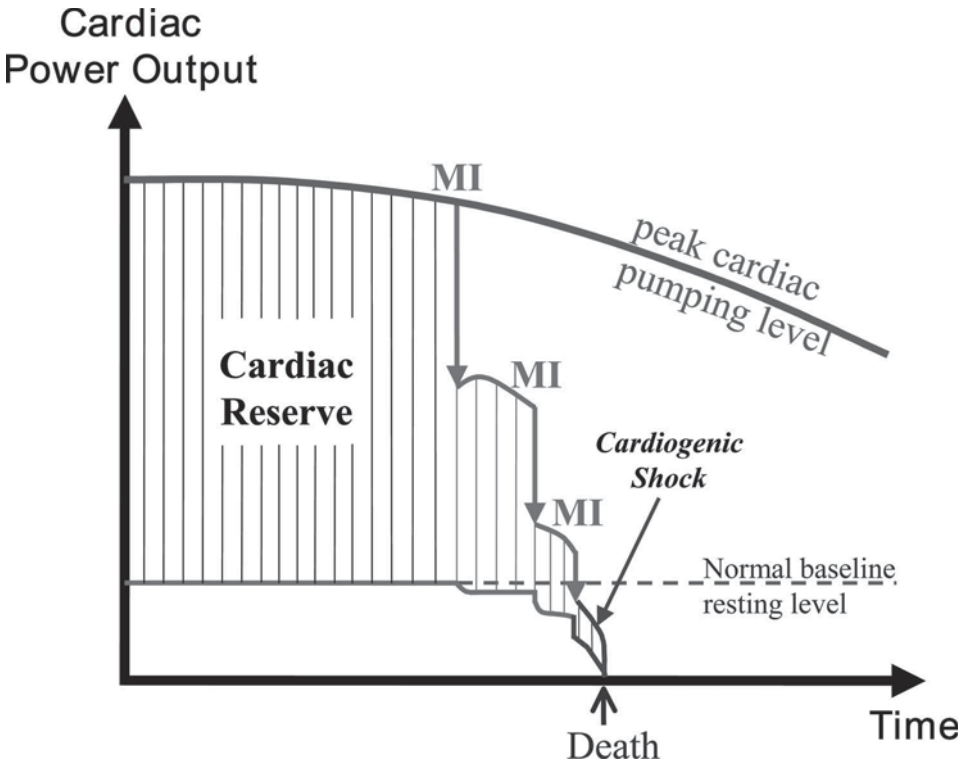

Figure 2. Schematic diagram indicating lifetime changes in cardiac functional reserve. The reserve capacity of the heart represents the difference between maximal power output measured at peak exercise (a variable value discriminating differences in age, fitness levels etc) and the baseline resting value (usually non-discriminatory at approx. 1 W). With increasing age and any additional ischaemic injury due to a myocardial infarction (MI), the number of contractile cells declines through a combination of apoptosis and necrosis (figure 3), leading to a fall in the peak pumping capacity and cardiac reserve. Less physical activity will further erode this functional reserve, while increased participation in endurance-based activity can preserve or improve it. (Reproduced by courtesy of L.-B. Tan and *Journal of Experimental Physiology*.)

relating to the lifestyle (e.g. sedentary or highly active) of these individuals prior to their death.

Like the rest of the myocardium, the sino-atrial node loses up to 90% of its specialized myocytes between the ages of 20 and 75 years. This, along with calcification and increasing deposits of fat, amyloid and collagen in the atrioventricular node, conducting system and ventricular walls predisposes to defects in the propagation and conduction of the cardiac action potential and rhythm disturbances (Pugh and Wei 2001).

In addition to these changes in cardiomyocyte number, various other age-related structural and functional adaptations become apparent in the myocardium. Ageing brings with it a prolongation of myocardial contraction and relaxation (Pugh and Wei 2001). These adaptations are thought to be explained by a prolongation of the cardiac action potential and calcium transients resulting from both a slower release and uptake of Ca^{2+} by the sarcoplasmic reticulum (Lompre 1998) and an increase in the expression of slow:fast myosin heavy chains (Lakatta 1999). The prolongation of myocardial relaxation and an increased stiffness in the senescent heart give rise to an elevated end-diastolic pressure, and a reduced early-passive phase (E) and increased late-active phase (A) of diastolic filling, i.e. a decrease in E:A. A decrease in the maximal achievable heart rate (Stratton *et al*. 1994, Pugh and Wei 2001), that is independent of fitness or training status, may be linked to a downregulation of β-adrenergic receptors in response to age-related increases in the circulating levels of catecholamines.

Despite all the above changes in the senescent heart, under basal conditions it operates well within its functional reserve. When measured at rest, cardiac power output is approx. 1 W, regardless of the age, gender or fitness levels of the subjects (figure 2). Indeed, the same is true of patients with moderate heart failure (Cotter *et al*. 2003, Goldspink *et al*. 2003). This further demonstrates that measurements made under resting conditions are unlikely to be of much discriminatory value. They also tell us nothing about the reserve capacity of the heart (figure 2) and hence its ability to respond to situations of stress. The power output of the heart (CPO), and hence the cardiac functional reserve, has seldom been measured in relation to normal healthy ageing. In agreement with the concepts shown in figure 2, we recently observed a statistically significant ($P < 0.05$) 12% fall in CPO_{max} and cardiac reserve (i.e. from 4.6 to 4.0 W) in sedentary men between the ages of 21 and 58 years (Goldspink *et al*. 2003, Chantler *et al*. 2004). Thereafter, CPO_{max} and cardiac reserve continued to decrease still further. These age-related effects based on measuring cardiac power output are not as pronounced as when cardiac output ($\dot{Q}$) alone is used as the index of cardiac function. While Q is commonly used to assess cardiac function, it clearly overestimates the changes in the overall function of the normal heart. This is because pressure generation increases with healthy ageing (see below) and is not allowed for when measuring only the flow-generating capacity of the heart. The reverse is true in patients with heart failure. Here, measurements of $\dot{Q}$ alone underestimate overall cardiac function because both the flow- and pressure-generating capacities of the heart decline in these patients. These examples clearly illustrate the need to measure both the flow- and pressure-generating capacities (i.e. CPO) of the heart to determine overall cardiac function meaningfully.

2.4. *Vascular smooth muscle*

The distensibility or compliance of the large elastic arteries, and the proximal aorta in particular, progressively decreases as the vessel walls become stiffer with increasing age (Seals 2003). Although not directly quantifiable, when pulse wave velocity was used to

estimate the changes in the compliance of the carotid artery it was found to decrease by 40 – 50% between the ages of 25 and 75 years (Tanaka *et al*. 2000). This increased stiffness of the vessel wall can be attributed to structural, compositional and chemoresponsive changes. First, the medial layer of smooth muscle is thicker as a result of myocyte hypertrohy. Muscle tone is also increased in response to greater sympathetic/α-adrenergic stimulation (Dinenno *et al*. 2001), increased local vasoconstrictor substances (e.g. endothelin 1 and angiotensin II) and decreased vasodilatory substances (e.g. oestrogens post-menopause, and nitric oxide) (Seals 2003). Secondly, more collagen is present in the extracellular matrix, but with increased cross-linking and glycosylation. In contrast, the density of elastin decreases and its fibres become more fragmented (Seals 2003). The existence of asymptomatic atherosclerosis may further impact on the vessel wall's composition (e.g. with deposits of lipids and minerals) and chemical responsiveness. Women generally exhibit better aortic compliance than men up to the menopause. Thereafter distensibility falls steeply, but can be improved by hormone replacement therapy (Pugh and Wei 2001).

The reduced abilities of the arterial wall to distend during systole and recoil during diastole causes systolic and pulse pressures to rise with age (Lakatta 1989). Stiffening of the ascending aorta and carotid sinus also reduces the sensitivity of the baroreceptors, which by transmitting efferent signals to the central nervous system normally controls intravascular pressure homeostasis (Hunt *et al*. 2001). Chronic increases in blood pressure can damage the endothelial cell lining and lead to atherosclerosis, thrombosis and obstruction of the coronary or cerebral vascular and increase the risk of a stroke, myocardial infarction etc.

Changes also occur further down the vascular tree, for example in the resistance and conduit vessels. In older people there is a decrease in maximal blood flow to both the muscles (Dinenno *et al*. 1999) and skin (Martin *et al*. 1995) of the limbs, suggesting that the potential for peak vasodilatory capacity has been diminished. The integrity of endothelial cells and the contractile state of vascular smooth muscle are major determinants of blood flow to active skeletal muscles and the peripheral microcirculation. Certain circulating hormones (e.g. oestrogen) can induce peripheral vasodilatation. The loss of the female reproductive hormones at the menopause may represent one factor contributing to the age-related decrease in blood flow to the extremities in women. The vascular endothelium produces vasoactive mediators such as nitric oxide and prostacyclin which, in addition to having atheroprotective and antithrombic properties, play an important role in the regulation of basal vascular tone (Duffy *et al*. 1998). It is thought that, while the responsiveness of the smooth muscle to these dilator pathways is largely unchanged, the basal endothelial function (i.e. nitric oxide and prostanoid pathways) decreases or is impaired, such that the normal endothelial-dependent dilatation diminishes with increasing age (Singh *et al*. 2002). The endothelium's sensitivity to apoptotic stimuli (Hoffmann *et al*. 2000) and free radical oxidant stress increases with age and may result in damage to the endothelial cells or interfere with some of the processes associated with the production of the endothelial relaxing factors.

2.5. *The importance of the functional reserve capacity*

The process of ageing clearly erodes the reserve capacities of both skeletal muscle (figure 1) and the heart (figure 2). At critical thresholds routine daily tasks gradually become difficult and then impossible to perform. For example, rising from a chair unaided or climbing stairs requires certain absolute forces to be generated by relevant groups of

agonist and antagonist skeletal muscles. Even completely healthy individuals will probably experience a decline of 1.5% per year in their muscle strength during the sixth and seventh decades of life (Harridge *et al*. 1997). Women are more likely to be disadvantaged than men because their muscle reserve capacities are age-for-age lower. Also, the functional reserve of the heart is a major determinant of the individual's capacity to exercise or remain active and provides the ability to cope with daily stresses, especially during illnesses when greater demands are placed on the circulatory system. The age-related decline in cardiac reserve will be further eroded following one or more myocardial infarctions, the incidence of which become more prevalent from the sixth decade onwards (figure 2). In the extreme, patients with severe heart failure will have little or no cardiac reserve (figure 2) (Cotter *et al*. 2003) to call upon, and their experience of exercise may be restricted to walking across a room.

Such age-related changes in muscle mass and performance will not be experienced in isolation. There will be inevitable 'knock-on' effects on other tissues, such as the skeleton. Bone is known to be sensitive to mechanical stimuli and the erosion of muscle force in the elderly will lead to reductions in bone density, increasing the propensity for osteoporosis, falls resulting in fractures, slower healing and recovery, disability etc. As part of a reinforcing feedback loop, the longer rehabilitation takes the less active individuals will become, with consequent negative effects on cardiac and skeletal muscle reserves (figure 1).

3. The effects of lifestyle on longevity and muscle function

Calorie intake (Lewis *et al*. 1985) and habitual physical activity (Erikssen 2001) have been identified as important factors influencing longevity in animals and humans alike. Not surprisingly, the mechanisms involved have been investigated in greater depth in the various animal models that have been studied. The same factors are crucially involved in preventative and therapeutic interventions designed to tackle the major clinical problems of our time, i.e. cardiovascular disease, obesity and the frailty associated with the elderly.

While the benefits and limitations of exercise continue to be discovered, it is already clear that in general most individuals who have participated in regular exercise, and have done so over many years, possess larger cardiac and skeletal muscle reserves (Harridge *et al*. 1999, Pearson *et al*. 2002, Chantler *et al*. 2004), retain more efficient control over their circadian rhythms (Reilly *et al*. 1997) and experience fewer pathologies (Farrell 1998, Erikssen 2001). Less information is available concerning the acute benefits gained by increasing the levels of physical activity to increase fitness levels later in life. Also, the minimum level or volume of activity that guarantees physiologically measurable benefits has yet to be clearly defined. This is a crucial shortcoming in our knowledge as it is likely to be of greatest relevance and interest to the majority of people in today's society with its dichotomous culture of inactivity versus the inability to find sufficient time to exercise.

For convenience, exercise is often divided into two extreme forms predominantly consisting of either short-duration high-resistance activities (e.g. weight lifting or sprinting) or longer-duration low-intensity activities (e.g. endurance running or swimming). Their known effects on muscle function in humans will be briefly considered.

3.1. *The cardiovascular system*

Endurance-based training is known to have a positive impact on several aspects of ageing in the cardiovascular system. Although maximum oxygen consumption declines with age

in both sedentary men and endurance-trained veteran athletes, age for age the aerobic capacity remains higher in the trained individuals (Goldspink *et al*. 2003, Pimentel *et al*. 2003). This remains true whether $\dot{V}O_2$max is expressed in absolute terms or is normalized to allow for differences in body weight or fat-free mass (Pimentel *et al*. 2003, Chantler *et al*. 2005). Precisely how much of this phenomenon can be attributed to changes in habitual activity, as opposed to ageing *per se*, is difficult to assess. Regardless of age and initial fitness levels, overall aerobic capacity and cardiac functional reserve can be increased by participation in endurance exercise.

Various indices of left ventricular performance, such as diastolic filling and relaxation (Pugh and Wei 2001), peak exercise ejection fraction or cardiac output (Ehsani *et al*. 1991, Schulman *et al*. 1996) and cardiac index (Stratton *et al*. 1994, Schulman *et al*. 1996) have all been shown to improve after several months of aerobic conditioning of older, but healthy, individuals. However, the use of cardiac power output (Cooke *et al*. 1998) to determine the impact of exercise on the overall performance of the heart and cardiac reserve has only been employed in a few studies. Using this non-invasive approach we found that veteran athletes (58 years old) who had engaged in endurance training over many years (a minimum of 10 years) had a maximal pumping performance and functional reserve (5.1 W) that was on average 26% greater than that of age-matched sedentary men. Interestingly, 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 $\dot{V}O_2$max values were 19% and 7%, respectively, greater than those of sedentary men who were nearly 40 years younger (Goldspink *et al*. 2003, Chantler *et al*. 2004). Much shorter periods of training (i.e. 8 weeks) have also proved effective. After performing 20 min of cycling at 75–80% of their $\dot{V}O_2$max for 5 days a week, 58-year-old men significantly improved their $\dot{V}O_2$max, CPO_{max} and cardiac reserves by 9%, 16% and 21%, respectively (Marshall *et al*. 2001).

Despite these beneficial changes, not all aspects of ageing appear to be attenuated by training (e.g. the age-related decrease in maximal heart rate). This could conceivably be because exercise increases the circulating levels of catecholamines and these are known to desensitize and/or downregulate β-adrenergic receptors (Eysmann *et al*. 1996). As already mentioned, the levels of catecholamines tend to increase with age *per se*, and so exercise may, if anything, accentuate rather than attenuate these particular changes associated with ageing.

Exercise-induced changes also occur in the vasculature. For example, while arterial stiffness still occurs in regularly active men and women as they age, the loss of compliance is significantly less than that found in their age-matched sedentary counterparts (Seals 2003). As well as attenuating these age-related changes in the large elastic vessels, vigorous endurance exercise has been shown to reverse some of the changes already established (Seals 2003). After 3 months of moderately intensive exercise based on walking, the compliance of the carotid artery had improved by 20–25% in previously sedentary middle-aged and older men and women, with concomitant beneficial effects on blood pressure. Moderately intensive exercise is also known to stimulate nitric oxide release from the endothelial cells of resistance vessels (d'Alessio 2004). This is presumably one of several possible exercise-induced changes that, while protecting the endothelium from stress-linked pro-inflammatory disease, also decreases peripheral resistance (Schulman *et al*. 1996), thereby enhancing blood flow to the peripheries.

3.2. *Skeletal muscles*

In young subjects resistance exercise increases muscle mass and the ability to generate more explosive power, but has little or no effect on aerobic power or resistance to fatigue. In contrast, endurance exercise is beneficial in increasing the aerobic capacity of the cardiovascular system, but does little to improve skeletal muscle force or power. Although less intensively studied, similar adaptations appear to hold true for older subjects. For example, former elite weightlifters retain higher (30 – 35%) muscle forces and power compared with non-trained age-matched subjects, despite experiencing similar rates of decline in their explosive power with increasing age (Pearson *et al*. 2002). Nonetheless, this does mean that at 85 years of age these resistance-trained men have an advantage of approximately 20 years over their age-matched non-trained counterparts with respect to their muscle reserve capacities (Pearson *et al*. 2002).

More acute adaptive responses have also been demonstrated. After 12 weeks of strength training of their knee extensor muscles, women aged 85 to 97 years experienced a 10% increase in the cross-sectional area of their quadriceps muscles, as well as significantly increasing their maximum isometric force and ability to lift heavier weights (Harridge *et al*. 1999). Large energetic adaptations, as assessed using magnetic resonance spectroscopy, have also been demonstrated in 70-year-old men and women 6 months after commencing either resistance or endurance training (Jubrias *et al*. 2001). This study indicates that the aerobic pathway in senescent muscles is particularly sensitive and adaptable (increases of 30 – 60%) to both forms of exercise training, even when structural adaptations (at 10%) were considerably less.

Men aged 70 – 100 years who have maintained a very high level of endurance-based activity since adolescence were found to demonstrate similar age-related losses in their muscle mass and force generation as age-matched untrained men, despite having 100% higher maximal oxygen consumption levels (Harridge *et al*. 1997). Hence, in contrast with the benefits to the cardiovascular system, endurance-based physical activity may be of little use in maintaining either the speed of contraction or force development in old age (Harridge *et al*. 1997). A better understanding of the compositional changes induced by endurance-based activities comes from animal studies.

3.3. *Adaptations to exercise as viewed from extreme examples of disuse or continuous activity*

The effects of disuse and different patterns of contractile activity on muscle size, gene expression and force generation have been well documented in animal models. In some instances these can be readily extrapolated to similar situations in humans. In others it must be appreciated that they represent extreme situations or experimental procedures that are applied acutely whilst designed to mimic processes that usually take several months or years to develop in humans, e.g. aortic banding to induce cardiac hypertrophy in response to hypertension. Nonetheless, they provide useful insight into the remarkable plasticity of striated muscles.

3.3.1. Disuse in skeletal muscles. Animal models of inactivity have been developed to demonstrate muscle atrophy (i.e. a net loss of muscle protein) in response to the simulated weightless conditions of space travel or immobilization of specific joints and selected muscle groups. While all muscle types undergo atrophy in response to disuse, the slow-oxidative and usually more active postural muscles undergo the greatest degree of

atrophy. These atrophic changes are explained by both a decrease in the average rates of protein synthesis and a complementary increase in protein breakdown (Goldspink 1991). All these adaptations can be readily reversed, with evidence of 'catch-up' growth, once normal levels of contractile activity are returned to the disused muscles (Goldspink 1991). These models are directly relevant and useful for comparison with situations of restricted muscle usage in humans (table 1).

3.3.2. Increased activity and changes in gene expression. Buller *et al*. (1960) were the first to demonstrate that the distinctive contractile characteristics of fast and slow skeletal muscles could be altered by cross-reinnervating their respective nerve supplies. This approach was followed by the equally innovative application of low-frequency (10 Hz) electrical stimulation to the normal intact nerve supply. In this way several research groups (Pette and Simoneau 1990, Salmons and Jarvis 1990) illustrated that different activity patterns influence the expression of specific genes within existing muscle fibres, for example preferentially activating the genes responsible for the slow isoforms of myosin over the former predominantly expressed fast isoforms (Sreter *et al*. 1973). Many well-documented earlier changes, including increases in capillary density, the number of mitochondria and the activities of their oxidative enzymes, and decreased volumes of the sarcoplasmic reticulum and its rate of sequestering Ca^{2+}, have been demonstrated in association with the conversion of a fast-twitch into a slow-twitch muscle. While helpful in understanding the effects of endurance activity on muscle composition and performance, these effects are nonetheless extreme. This regimen produces a muscle that possesses almost 100% slow-oxidative fibres and is highly fatigue resistant. However, this transformation is achieved only after several weeks of continuous stimulation for 24 h a day, and therefore is unlike any activity patterns adopted by humans. Also, the resultant muscle mass and maximal power output are reduced dramatically by 40% and 90%, respectively (Salmons and Jarvis 1990). While an overall loss of muscle mass would be predicted with the conversion of larger fast fibres in to smaller slow ones, the magnitude of the atrophy and loss of power cannot be regarded as a purely normal physiological adaptation. In the rabbit model, where the tibialis anterior muscle is stimulated at 10 Hz, the hind foot appears to be driven into operating at a less loaded and shorter length than is normal. It is known that under such conditions the myofibrils lose sarcomeres, both in series and in parallel (Goldspink 1991). Hence the transformed muscle fibres would become shorter and undergo a greater degree of atrophy than purely accounted for by a conversion of fast fibres into slow ones.

It is possible to increase the fatigue resistance of a muscle without losing muscle mass and as much of its original force and power output. We have previously shown that static stretch is a powerful stimulus inducing changes in protein turnover (Goldspink *et al*. 1995) that lead to both longitudinal growth and fibre hypertrophy (Goldspink 1991,

Table 1. Sporting and clinical situations giving rise to inactivity-induced muscle wasting.

Localized muscle wasting	Whole-body muscle wasting
Fractures	Prolonged bed rest
Tendon disruption/ligament damage	Space travel
Joint disease/injury	Severe heart failure, cancer, HIV/AIDS
Stroke	Spinal injury
	Surgery

1999, James *et al*. 1997, Cox *et al*. 2000). The stretched (10%) latissimus dorsi (LD) muscle added on more sarcomeres in series, with this adaptation being complete within 5–7 days, thereby allowing the muscle to be stretched further on a weekly basis. After 3 weeks of incrementally stretching the LD it was 25% longer and 35% heavier than its non-stretched contralateral control (Cox *et al*. 2000). This further demonstrates the remarkable plasticity of skeletal muscles (Goldspink 1991, Cox *et al*. 2000).

When stretch was combined with 10 Hz electrical stimulation there was no longer a loss in muscle mass and more of the original maximal power (i.e. 25% instead of 15%) was preserved than after 10 Hz stimulation alone (James *et al*. 1997). The now combined mechanical and electrical stimuli induced a rapid (60 min) increase in the mRNA levels of c-*fos* and c-*jun* (Osbaldeston *et al*. 1995). The protein products of these proto-oncogenes can dimerize to form the AP-1 transcriptional factor, which may be responsible for the ensuing rapid increase in expression levels of growth factors, such as IGF-1 and the more recently discovered smaller-spliced variant mechano-growth factor (MGF) (Goldspink 1999, Hill and Goldspink 2003). Both growth factors are increased in statically stretched and dynamically exercised human and animal muscles (Goldspink *et al*. 1995, Goldspink 1999, Harridge 2003).

Dynamic training, which incorporates rhythmic stretching and stimulation of a muscle, is even more effective in increasing (34%) the mass of the LD and preserving more of its power output after just 2 h a day for 2 weeks (Ashley 1997, Askew *et al*. 2002). Positively stained fibres for the mitochondrial enzyme succinic dehydrogenase increased from 60% to 95% and the number of capillaries per millimetre increased by 43%. As a consequence, the fatigue resistance of the dynamically trained LD more than doubled and acquired slower contractile properties (Ashley 1997, Askew *et al*. 2002).

Such animal models provide more precise control over the experimental conditions and variables, both in terms of manipulating the training protocols and of evaluating changes in muscle performance. The latter is well illustrated in the use of the oscillatory work loop technique on individual muscles *in situ* with their nerve and blood supplies intact (James *et al*. 1996). When subjected to 'length change cycles' ($\pm 5\%$ of the resting length) and phased electrical stimulation the muscle generates a series of loops, the internal area of which reflects the net work done. Unlike the more traditional purely isometric or isotonic recordings, the generation of work loops more closely reflects normal muscle function which incorporates both non-shortening and shortening phases of contraction (James *et al*. 1996). In addition, the performance of an individual muscle can be isolated from its agonist and antagonist muscles. Changes in whole-muscle function can also be explained by reference to histochemical adaptations evident at a cellular level, such as changes in passive force (or compliance) in relation to modulations in collagen content and alterations in contractile characteristics and power as a consequence of changes in fibre-type profiles and cross-sectional areas. This integrative approach represents a powerful research tool.

3.4. *The timing of activity-based interventions*

Clearly, increased physical activity and exercise training can improve the reserve capacity of both cardiac and skeletal muscles. An appropriate mix of endurance- and resistance-based activities is most likely to have the broadest beneficial effect in countering the effects of ageing. However, while the imposition of relevant activity-based interventions is likely to delay or reverse muscle fibre atrophy, shortening and fibrosis, other adaptations, such as the degeneration of motor neurones, loss of contractile cells and modulations in

motor unit size, muscle coordination and stability, may be irreversible. Hence the full benefits of such activity-based interventions will only be experienced if undertaken before any such irreversible events become established. The onset and time course of these age-related manifestations need to be studied in greater detail. Similarly, the threshold of preventative or therapeutic increases in physical activity need to be established, especially if these are to be undertaken by the general population in a recreational setting.

4. The regenerative capacity of myocytes

One area that is crucial to both forms of striated muscle and the erosion of their functional reserve capacities is the age-related death and loss of their contractile cells. Fewer myocytes in the muscles of older individuals must inevitably diminish their full potential for hypertrophic growth in response to increased workloads, even assuming that the myocytes of senescent muscles retain the same capacity as 'younger' muscles to undergo such adaptive growth; a fact that has yet to be definitively established. So, is myocyte death irreversible or do muscles contain some intrinsic regenerative capacity?

Low levels of myocyte death have been observed in the hearts of healthy rats with increasing age (Kajstura *et al*. 1996) as well as in relation to heart disease (Goldspink *et al*. 2003). This cell death represents only a very brief event (a few hours) in the animal's overall lifespan. While myocyte death by apoptosis and necrosis does indeed occur with healthy ageing (Goldspink *et al*. 2003), the question is whether these cells can be replaced. On the face of it studies like that of Olivetti *et al*. (1995) would suggest not.

We have used sensitive immunohistochemical techniques to specifically detect and quantify myocytes that are undergoing both apoptosis and necrosis in the heart and soleus muscle (figure 3) of the rat (Ng *et al*. 2002, Tan *et al*. 2003, Goldspink *et al*. 2003). To illustrate this, myocyte damage was induced by a single injection of the synthetic catecholamine isoprenaline (figure 3). These experiments were designed to test the hypothesis that the high levels of catecholamines, as found in heart failure patients (Anker *et al*. 1997), are directly linked to the death of cardiac and skeletal myocytes, with consequent muscle wasting, weakness and malfunction. Five days after isoprenaline administration, the soleus muscle had lost 17% of its total number of fibres (Ellison *et al*. 2003). However, within these areas of damage small regenerating myotubes and fibres were clearly evident after 5 and 7 days as a result of the activation, proliferation and fusion of satellite cells (i.e. dormant myoblasts) (Grounds *et al*. 2002). After 28 days the total number of fibres had been completely restored and innervated (Ellison *et al*. 2003), demonstrating the remarkable regenerative capacity in skeletal muscles. It has been suggested that the effectiveness of this regenerative system diminishes with increasing age (Renault *et al*. 2002). It is also possible that, owing to the age-related degeneration of motor neurones, newly regenerated fibres in senescent muscles may not become properly innervated, leaving them functionally denervated.

As far as the heart is concerned, the traditionally held belief has been that little or no regenerative capacity exists and therefore, unlike skeletal muscle, is not available to replenish the cells of the myocardium after they have been injured. This dogma is now being actively challenged and this represents one of the most important, exciting and yet controversial areas of biomedical research. The recent detection of cardiac stem cells that are capable of proliferating and giving rise to primitive myocytes, together with small cardiomyocytes still capable of dividing, in the midst of large and fully differentiated myocytes strongly suggests the potential for regenerating cardiomyocytes (Nadal-Ginard *et al*. 2003, Sussman and Anversa 2004). Whether this newly discovered

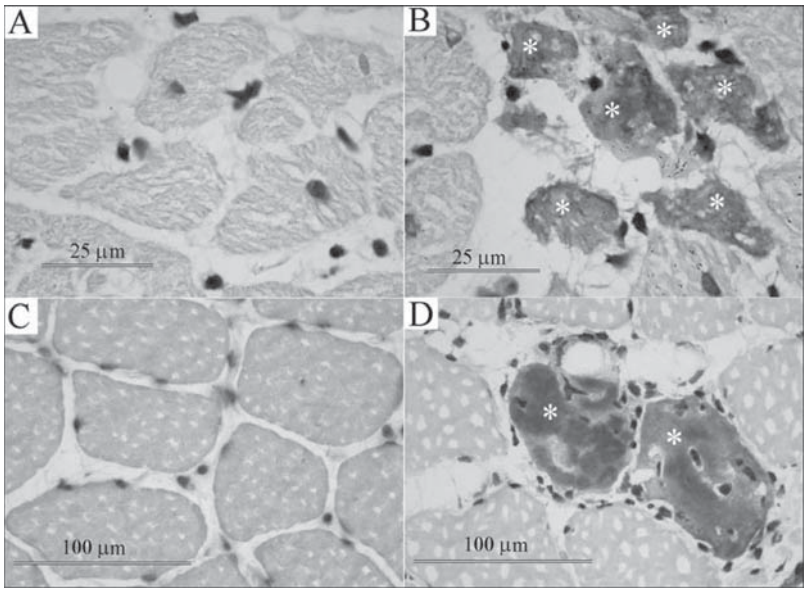

Figure 3. Myocte death by apoptosis and necrosis in the heart and skeletal muscle. Contractile cells (i.e. myocytes) in both the heart (A,B) and skeletal muscle (C,D) die by either necrosis (B) or apoptosis (D) during normal ageing or as a consequence of accidental injury or disease. If not accompanied by matched levels of myocyte regeneration, the net loss of myocytes will probably result in a decline in muscle functional reserve (see figures 1 and 2). In this illustration myocyte death in a Wistar rat was induced by a single injection of 5 mg/kg of the synthetic catecholamine isoprenaline. (Courtesy of J. G. Burniston.)

regenerative capacity in the mammalian heart declines with age is an important supplementary question (Sussman and Anversa 2004). Nonetheless, current progress suggests significant hope for future therapeutic interventions to replace dying cardiomyocytes during either normal healthy ageing or after suffering ischaemic injury or heart failure. It is likely that such interventions will need to minimize cell death while encouraging the replacement of dead and senescent myocytes through stem cell activation and myocyte regeneration.

In all these situations, maintaining cardiac functional reserve into old age is vital for both survival and quality of life. Since endurance exercise can preserve cardiac reserve (Chantler *et al*. 2004), we are currently seeking to answer important related questions. For example, does exercise training attenuate the net loss of cardiomyocytes during ageing by inhibiting apoptotic and necrotic cell death pathways? It has recently been shown that exercise can protect the myocardium from ischaemic damage through the induction of heat shock proteins (e.g. HSP 72) and antioxidant enzymes such as catalase (Lennon *et al*. 2004). On the other hand, exercise may stimulate cardiac regeneration by encouraging stem cells to proliferate and differentiate into mature cardiomyocytes thereby replacing at least some of those vital contractile cells. This would also provide a complementary mechanistic explanation to cardiomyocyte hypertrophy, i.e. an increase in cell number as well as size. The answers to such questions could have important implications for the general health of our ageing population and exercise-based rehabilitative interventions.

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