

The Effects of Ageing, Endurance Exercise and Heart Failure on Cardiac Power Output

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Abstract

Ageing is a complex multi-factorial process, which is characterised by a decreased ability of the human body to interact, respond and defend itself against numerous stimuli. As average life span continues to increase, it becomes increasingly important to understand what impact ageing or disease has on physiological functions and the efficacy of interventions such as exercise. Cardiac power output (CPO) is the best indicator of overall cardiac function (Cooke *et al.*, 1998) and can be measured non-invasively at rest (CPO_{rest}) and maximal exertion (CPO_{max}), enabling the heart's functional reserve (CR) to be calculated. The aims of these studies were to use CPO to measure changes that occurred as a result of healthy ageing, long-term endurance training, and chronic heart failure, and compare these effects in men and women.

After further developing the techniques and protocols to measure CPO, seventy healthy men and one-hundred and thirteen women aged nineteen to seventy six years were recruited and studied. Healthy ageing resulted in a 49%, 23% and 22% decrease in $\dot{V}O_{2max}$, CPO_{max} and CR respectively in men. In marked contrast, there were no significant age-related changes in CPO_{max} or CR in healthy women. Forty-two habitually active men and eighteen women were recruited across the same age range. The active men had significantly higher CR (~17%-36%) than age-matched sedentary men. In contrast, the active women showed no increase in CR over the sedentary women.

These sex-specific differences in response to ageing and exercise were independent of changes in body size.

The CPO_{max} and CR of twenty-one male heart failure patients were respectively ~57% and ~64% below that of the healthy sedentary men.

These results indicate for the first time that healthy ageing has a negative impact on CPO in men which can be attenuated by long-term endurance training, or made worse by heart failure. Importantly, no decrease occurred in CPO in women with ageing, and the cardiac adaptations in response to exercise were also less marked.

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Abbreviations

ATP	Adenosine triphosphate
$a - \bar{v} O_2 \text{diff}$	Arteriovenous oxygen difference
$a - \bar{v} O_2 \text{diff}_{\text{max}}$	Maximum arteriovenous oxygen difference
BMC	Bone mineral content
BMI	Body mass index
BSA	Body surface area
$C_a \text{CO}_2$	Arterial concentration of carbon dioxide
Ca^{2+}	Calcium ions
CHD	Coronary heart disease
CO_2	Carbon dioxide
CPO	Cardiac power output
CPO_{max}	Maximum cardiac power output
CPO_{rest}	Resting cardiac power output
CR	Cardiac functional reserve
$C \bar{v} \text{CO}_2$	Venous concentration of carbon dioxide
CVD	Cardiovascular disease
DEXA	Dual-energy X-ray absorptiometry
DNA	Deoxyribonucleic Acid
DBP_{max}	Diastolic blood pressure measured at $\dot{V}O_{2\text{max}}$
DBP_{rest}	Resting diastolic blood pressure
ECG	Electrocardiogram
FM	Body fat mass
HR_{max}	Maximum heart rate
HR_{rest}	Resting heart rate
HRT	Hormone replacement therapy

Abbreviations Continued...

IGF	Insulin-like growth factor
Km/h	Kilometres per hour
LBM	Lean body mass
MAP _{max}	Mean arterial blood pressure $\dot{V}O_{2max}$
MAP _{rest}	Resting mean arterial blood pressure
MGF	Mechano-growth factor
MI	Myocardial infarction
NYHA	New York Heart Association
N ₂	Nitrogen gas
P _{eq} CO ₂	Equilibrium of carbon dioxide pressure
P _{ET} CO ₂	End tidal pressure of carbon dioxide
P \bar{v} CO ₂	End venous pressure of carbon dioxide
\dot{Q}_{max}	Maximum cardiac output
\dot{Q}_{rest}	Resting cardiac output
RER	Respiratory exchange ratio
SBP _{max}	Systolic blood pressure measured at $\dot{V}O_{2max}$
SBP _{rest}	Resting systolic blood pressure
SV _{max}	Maximum stroke volume
SVI _{max}	Maximum stroke volume index
SV _{rest}	Resting stroke volume
SVR _{max}	Maximum systemic vascular resistance
SVR _{rest}	Resting systemic vascular resistance
TBM	Total body mass
$\dot{V}CO_2$	Carbon dioxide production

Abbreviations Continued...

\dot{V}_E	Minute ventilation
\dot{V}_{O_2}	Oxygen consumption
$\dot{V}_{O_{2max}}$	Maximum aerobic power
V_T	Tidal volume
V_{Tmax}	Maximum tidal volume

Chapter 1

Introduction

1.0 Healthy Ageing

In the twenty-first century the average life expectancy of humans is continuing to increase, and shows no sign of stopping. Between 1971 and 2001 the number of people in the UK over sixty-five years of age grew by 28%. Today the over sixty-fives account for 16.6% of the total European population, and represent the fastest growing age group. With this trend towards an older population it is increasingly important to understand what impact ageing has on physiological function, and the role that interventions such as exercise can play in promoting a better quality of life.

Studying the effects of ageing *per se* is increasingly difficult. This is due to the fact that normal ageing is increasingly associated with numerous disease processes such as atherosclerosis, diabetes mellitus, coronary heart disease (CHD) and obesity. These diseases are intrinsically linked to cellular mechanisms (Lakatta, 2002) which are superimposed on the changes which occur as a consequence of ageing. Investigating the effects of ageing on cardiovascular function is further complicated when you consider that cardiovascular disease (CVD) was the biggest single cause of death in the UK in 2003, accounting for just under two hundred and thirty three thousand deaths. Coronary heart disease (CHD) accounted for more than one-half of this total, and is the single biggest cause of premature death (under seventy-five years of age) in the UK (Peterson *et al.*, 2005).

Clearly, to study the effects of ageing *per se* the ageing process must be separated from the various common diseases. Previous studies have often failed to adequately do this and as a result have attributed significant changes

to ageing, which may in fact be the result of disease processes. In an attempt to describe ageing Masoro (2001) stated that ageing should be regarded as a synonym for senescence, and defined it as “the deteriorative changes, during the adult period of life, which underlie an increasing vulnerability to challenges, thereby decreasing the ability of the organism to survive”.

1.1 Theories of Ageing

Several theories of what causes ageing have evolved in recent years. Today, ageing is viewed as an extremely complex multi-factorial process. This notion has replaced the traditional concept that a single gene, or deterioration in one key body system, was the cause of senescence in human physiological function. In a review by Weinert and Timiras (2003), a total of fifteen different theories of what causes ageing were highlighted. These theories were separated into four distinct categories; evolutionary, molecular, cellular, and system-based. The evolutionary theories postulate that ageing results from a decline in the force of natural selection. The molecular theories believe that ageing is the result of mutations in deoxyribonucleic acid (DNA) and changes in gene expression. Cellular theories are based on belief that cells have a limited replicative capacity, and that once this capacity has been reached the cells terminally arrest and physiological function is altered. This cellular senescence can also occur in response to distinct molecular events such as stress-induced damage. Finally, the system-based theories of ageing are based on the decline of organ systems. This decline in turn limits the ability of the human body to control and maintain other systems, and its ability to communicate and adapt to the environment in which it lives. All of the systems in human body are considered indispensable, but the nervous, endocrine and immune

systems play key roles in co-ordinating all the other systems of the body, and the ability of the human body to interact, respond, and defend itself to both external and internal stimuli.

All of the theories of what causes ageing have a degree of overlap and they all agree that ageing is characterised by an inability to maintain homeostasis, and finally death. But, ultimately the precise causes of ageing remain unknown.

This thesis is going to initially focus on what changes occur in aerobic power and overall cardiac function as a result of:

1. Healthy ageing in both sedentary men and women.
2. Habitually engaging in long-term endurance exercise.
3. Heart failure.

1.2 Age-Related Changes in Aerobic Power

Maximal aerobic power ($\dot{V}O_{2\max}$) is traditionally defined as the maximal rate at which oxygen can be taken up and used by the body during exercise (Hill and Lupton, 1923). It is widely used in exercise and clinical science to measure performance (Shephard, 1984), the effects of training (Bassett and Howley, 2000) and as a prognostic tool (Osman *et al.*, 2000). Its usefulness is based on the fact that it is a functional measure that integrates the pulmonary diffusion capacity of the lung, cardiac output, the oxygen carrying capacity of blood and the ability of the skeletal muscle to extract and utilise oxygen. There has been debate surrounding which of these aspects is the limiting factor in determining $\dot{V}O_{2\max}$. Exponents such as Bassett and Howley (1997) argue oxygen

transport and delivery is the limiting factor, while Noakes (1998) proposes a “central governor” theory and believes that skeletal muscle recruitment is the limiting factor.

As with the theories on what causes ageing, there is a degree of overlap in the theories concerning what controls or limits $\dot{V}O_{2\max}$. The detrimental impact of ageing on $\dot{V}O_{2\max}$ has been known for many years (Åstrand *et al.*, 1973).

Hawkins and Wiswell (2003) conducted a review of the research relating to $\dot{V}O_{2\max}$ and the effect of ageing. Maximum aerobic power has been found to decline from as little as 4% per decade to 12% per decade with increasing age. But ageing can have both a direct (mechanistic) and an indirect (an age-related decrease in activity levels) influence on $\dot{V}O_{2\max}$. It has been proposed that ageing which is independent of disuse or disease results in a decrease in $\dot{V}O_{2\max}$ of approximately 5% per decade (Bortz and Bortz, 1996).

Previous research has also proved inconclusive in determining if the age-related impact on $\dot{V}O_{2\max}$ is gender specific. The decrease in $\dot{V}O_{2\max}$ was found to be comparable in men (Jackson *et al.*, 1995) and women (Jackson *et al.*, 1996) between twenty and seventy-years of age. Importantly, they also recognised that in both sexes 50% of the observed decrease in $\dot{V}O_{2\max}$ could be accounted for by the self-reported decline in activity levels, and concomitant decreases in muscle mass. In contrast, in a group of sixty-two subjects Stathokostas *et al.* (2004) found that $\dot{V}O_{2\max}$ decreased by 14% in men, but only 7% in women per decade.

1.3 The Effect of Endurance Exercise on Aerobic Power

Prescribed aerobic exercise provides a stimulus to increase $\dot{V}O_{2\max}$ (Strømme *et al.*, 1977). Some studies have concluded that the ability of the human body to increase $\dot{V}O_{2\max}$ in response to exercise is reduced with increasing age. Research by Tanaka and Seals (2003) and Pollock *et al.* (1987), has contested this conclusion. They found that individuals who were sixty years of age, or older, retained their ability to increase $\dot{V}O_{2\max}$. Malbut *et al.* (2002) supported this conclusion with specific reference to older women (over eighty years of age), but found that the same twenty-four week aerobic training stimulus was insufficient to significantly improved the $\dot{V}O_{2\max}$ in men of the same age. In contrast, the ability of older individuals to increase their $\dot{V}O_{2\max}$ was found by Kohrt *et al.* (1991) to apply to both men and women. These researchers attributed that lack of change observed in other studies (Adams and DeVries, 1973; Benestad, 1965; Niinimaa and Shephard, 1978; Suominen *et al.*, 1977) to be the result of insufficient training stimuli.

Rogers *et al.*, (1990) found that the $\dot{V}O_{2\max}$ of master athletes who had a mean age of sixty-two year was 50% greater than that of age-matched sedentary individuals. But it is important that a sufficient exercise stimulus is maintained if the adaptation in $\dot{V}O_{2\max}$ is to be preserved in spite of increasing age.

Research by Pimentel *et al.* (2003) into the effects of exercise and ageing in men, and similarly Tanaka *et al.* (1997) in women, found that between twenty and seventy-five years of age exercise significantly increased $\dot{V}O_{2\max}$ values when compared to sedentary individuals. However, there was still an age-related decline in the $\dot{V}O_{2\max}$ of endurance-trained individuals. Further, if the

training stimulus was withdrawn the rate of decline in $\dot{V}O_{2\max}$ was greater in the previously trained individuals than in their sedentary counterparts.

The measurement of $\dot{V}O_{2\max}$ is widely used because it determines the ability of the whole human body to consume and utilize oxygen, integrating many different physiological processes which are crucial to the maintenance of quality of life. Ageing appears to have a negative impact on $\dot{V}O_{2\max}$, but this can be offset to a degree by engaging in regular endurance exercise.

Nonetheless, the changes which occur in $\dot{V}O_{2\max}$ as a result of ageing must arise from localised changes in the ability of the human body to take up, transport and utilise oxygen. Two key components in this are skeletal and cardiac muscles.

1.4 Age-Related Changes in the Structure and Function of Skeletal Muscle

Healthy ageing in humans is well known to be associated with a decline in neuromuscular function and performance (Doherty *et al.*, 1993a). This decline is characterised by a decrease in skeletal muscle mass which is commonly termed sarcopenia, and consequently in skeletal muscle force generation. In his review article, Doherty (2003) highlighted the fact that the term sarcopenia encompasses the changes which occur in skeletal muscles as a result of altered central and peripheral nervous system innervation, hormonal status, inflammatory effects, and caloric and protein intake.

The average reported age-related decrease in skeletal muscle mass is between 20-40% (Doherty, 2003), but greater reductions (over 50%) have been reported in individuals who survive past the ninth decade of life (Murray *et al.*, 1980). The relative decrease in skeletal muscle force with increasing age is similar in both men and women, although the absolute loss is greater in men.

Work which has used electrical stimulation to invoke supra-maximal muscular contractions, compared to maximal voluntary contractions has sought to determine if age-related decreases in force are the result of reductions in central drive. Work looking at the biceps brachii and brachialis (Doherty *et al.*, 1993b), the adductor pollicis (Phillips *et al.* 1992) and the tibialis anterior (Belanger and McComas, 1981) muscles in humans has established that both older men and women were able to fully activate their motor neuron pool maximally. It therefore appears that cellular changes which occur within the muscle are the major factors which contribute to the reduction in muscle force with increasing age.

Various techniques have been used to determine skeletal muscle cross-sectional area in humans *in vivo*, the most widely used techniques are ultrasound, computed tomography and magnetic resonance imaging. Studies by Young *et al.* (1985 and 1984) reported decreases of 25-35% in the cross-sectional area of the quadriceps muscles in older men and women, when compared to young controls. But, as with muscle force the reduction in cross-sectional area appears to accelerate with increasing age (Lexell *et al.*, 1988).

Factors which have been postulated as the cause of the age-related decreases in muscle cross-sectional area are physiological fibre atrophy which is related to decreases in activity levels (Goldspink, 1991), and hormonal factors such as a reduced liver and muscle production of the growth factor IGF-1 and its spliced variant mechano-growth factor (MGF) (Goldspink and Yang, 2001).

However, the observed age-related reduction in skeletal muscle performance is often greater than the reduction in cross-sectional area. Cellular mechanisms which also contribute to the loss in performance of skeletal muscle with increased age include a decrease in excitation-contraction coupling resulting from a decrease in myosin concentration and its decreased motility (Hook *et al.*, 1999), and reduced calcium sensitivity and uptake by the sarcoplasmic reticulum (Hunter *et al.*, 1999).

Generally in humans from the seventh decade onwards there is a loss of muscle fibres, particularly fast fibres, due in part to the degeneration of the motor neurons (Doherty *et al.*, 1993b; Frontera *et al.*, 2000). In addition to these changes in fibre number and size, there is a shortening of the remaining muscle fibres, and a decrease in angles of pennation. Age-related increases in non-muscular tissue (fat and connective tissue) have been reported to be as high as 59% and 127% in the quadriceps and hamstrings of healthy men, respectively (Overend *et al.*, 1992). The same group has also reported age-related increases in the non-muscular tissue within the muscle of the upper body, 27% in the arm flexors and 45% in the arm extensor muscles (Rice *et al.*, 1989). These changes all contribute towards a reduction in skeletal muscle

performance. Furthermore, there is an age-associated increase in tendon compliance. With increasing age tendons become less rigid and thus absorb more force (Tuite *et al.*, 1997), this inhibits the ability of older people to transfer generated muscle force into limb movement.

1.5 Exercise-Induced Changes in Skeletal Muscle Function

Skeletal muscle atrophy is recognised by changes in protein turnover (Goldspink, 1991). In early postnatal life protein synthesis exceeds protein breakdown, the result is a net accumulation and skeletal muscle growth (Lewis *et al.*, 1984). In later adulthood the rates of protein synthesis and breakdown become equal, resulting in a cessation of the growth of skeletal muscles. If old humans become inactive, protein breakdown will exceed protein synthesis and skeletal muscles lose protein and atrophy progresses. However, if sufficient exercise is undertaken which delivers the appropriate amounts of mechanical stress it appears that even older skeletal muscles retain their ability to accumulate protein, undergo hypertrophy and improve their overall performance (Goldspink, 1991).

High-resistance, low-repetition training has been shown to increase isometric muscle force. In a study by Young *et al.* (1983) men of thirty years of age and women of twenty-three years of age showed that this form of training significantly increased quadriceps force generation. There was also a highly significant amount of hypertrophy in the trained limbs, but this was insufficient to fully explain the functional improvements. Furthermore, there were no significant improvements in the untrained contralateral limbs. Similarly, increases of 134% and 9.8% have been reported in maximal voluntary

contraction and lean muscle cross-sectional area, respectively, following twelve weeks of high-resistance strength training in older people aged between eighty-five and ninety-seven years (Harridge *et al.* 1999). Previously, neural adaptations and improved co-ordination had been postulated as a reason for improvements in muscle performance in older subjects. This was not the case in this study. The subjects failed to fully activate their quadriceps muscle group both before and after the training intervention, despite the adaptation in force-generation. Therefore, it appears that the skeletal muscles of older humans do not lose their ability to adapt given a sufficient stimulus or increased workload.

Engaging in high-resistance training on a long-term basis also has a beneficial impact on skeletal muscle force and power. Pearson *et al.* (2002) examined elite master weightlifters, compared to sedentary controls. At all ages the weightlifters were significantly stronger. But, importantly the relative declines that were observed in both force and power over the course of ageing were similar in both groups. Although no anatomical measures were made in this study, possible mechanisms that accounted for the increases in power exhibited by the trained groups included a greater lean-leg volume, a relative increase in the size of Type II muscle fibres, and finally a training adaptation towards faster contracting muscle fibres.

The ability of high-resistance exercise training to restore the cellular mechanisms associated with skeletal muscle function in the elderly was confirmed by Canepari *et al.* (2005). This study found that twelve-weeks of high resistance training was effective in increasing the velocity of sliding of

actin filaments on pure myosin isoforms during contraction in both young (between twenty-three and twenty-nine years of age) and elderly (between sixty-eight and eighty-two years of age) men. This was despite the training having no significant impact on the myosin heavy chain isoform composition in the elderly subjects.

In contrast to the high-resistance activities that have been shown to improve skeletal muscle performance, the trained groups who will be the focus of this thesis are long-term endurance trained athletes who regularly participate in aerobic based activities such as long-distance running. A study by Harridge *et al.* (1997) compared the skeletal muscle characteristics of fifteen endurance-trained individuals who had been maintaining this type of activity from adolescence and were at the time of the study between seventy and one-hundred years of age. When this group was compared to an age-matched group of sedentary individuals there were no significant differences in either muscle force or contraction time of the knee extensors. Furthermore, both elderly groups showed significant decreases in muscle power and prolonged contraction times when compared to a control group of young (twenty-six years of age) men.

Ageing has a significant impact on the structure and function of skeletal muscle. Presented with a sufficient mechanical stimulus, it appears that skeletal muscles of older humans retain their capacity to adapt accordingly (Newton *et al.*, 2002). High-resistance low-repetition exercise appears to be effective in providing this stimulus (Pearson *et al.*, 2002). While endurance exercise does not improve a muscles ability to generate more force, it does

increase its oxidative capacity through the acquisition of more mitochondria (Holloszy and Coyle, 1984), and an increase in the number of capillaries per muscle fibre (Holloszy, 2001). This ability to improve the oxidative capacity of skeletal muscle does not appear to diminish with age (Coggan *et al.*, 1992), thereby increasing the need for more oxygen and hence $\dot{V}O_{2\max}$.

1.6 Age-Related Changes in Cardiovascular Composition and Structure

The major function of the heart is to operate as a hydraulic pump. To ensure the circulation of blood each ventricular contraction results in blood flow (cardiac output; \dot{Q}) and blood pressure (the hydrostatic pressure exerted by the blood against the vessel walls). The blood transports oxygen and nutrients that are critical to maintaining the function of all the organs and tissues of the human body, and subsequently eliminates the waste products that are produced during the physiological processes.

There are very few studies which have examined the effects of ageing on the human heart at a cellular level due to the obvious ethical constraints of obtaining human hearts. In two studies by Olivetti *et al.* (1991 and 1995) autopsies were conducted on the preserved hearts of healthy humans within twenty-four hours of death. These studies confirmed that the hearts were free from overt cardiovascular disease by first examining the medical history of the deceased, and then by conducting both macro and micro anatomical analysis. In men between seventeen and ninety years of age healthy ageing resulted in a loss of 30-36% of the total number of myocytes (Olivetti *et al.*, 1995; Fig. 1). This loss was accompanied by a compensatory hypertrophy of the remaining

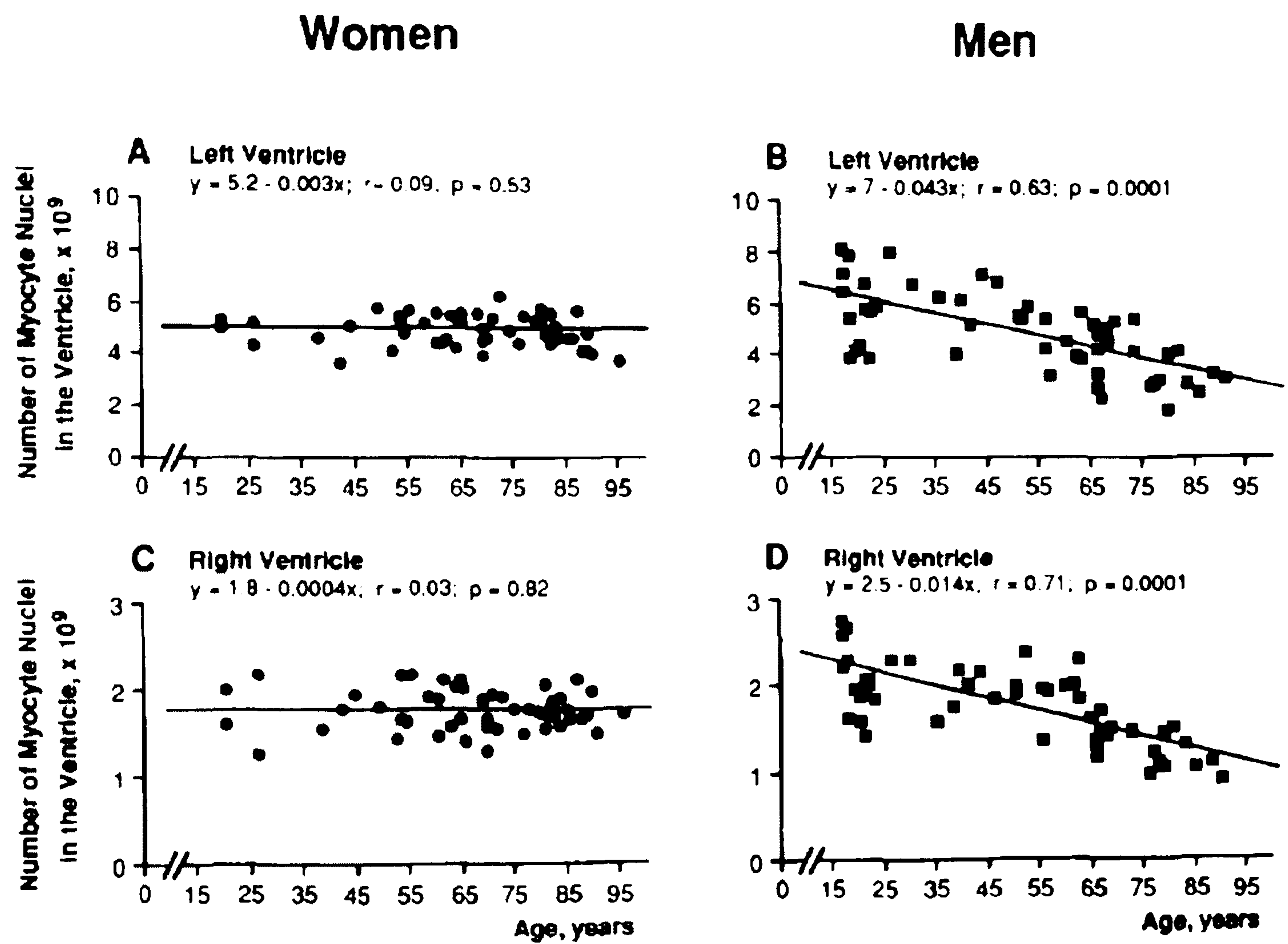


Figure 1 – Effects of ageing on the total number of ventricular myocyte nuclei in the human heart.

Figure adapted from Olivetti *et al.* (1995).

contractile cells. But despite this there was still a significant decrease in the weight or mass of both the left and right ventricles. In stark contrast there were no significant changes in either the number or volume of myocytes in the hearts obtained from previously healthy women over the same age range (Olivetti *et al.*, 1995). Furthermore, the reduction in sex hormones after the menopause had no significant impact on the number or size of myocytes in these women. Hence, there are striking sex-related differences in the rate of loss or retention of the number of myocytes with ageing. One thing the male and female hearts did have in common was a build up of collagen in both the right and left myocardium after forty-years of age. This accumulation of collagen, together with increases in fat, elastin and lipofusion is required to maintain the structural integrity of the heart.

These changes in myocardial composition have been confirmed in animal studies where the loss of myocytes from both the left and right ventricles has been observed (Anversa *et al.*, 1990a and 1990b; Nadal-Ginard *et al.*, 2002). As in humans there was a reactive hypertrophy of the remaining cells, the mean volume has been reported to be increased by 53% and 26% in the left and right ventricles, respectively in ageing rats (Anversa *et al.*, 1986). Similarly there was a 22% increase in the fraction of collagen contained within the myocardium (Anversa *et al.*, 1990b).

Also, within the conduction system there is an age-related loss of the specialized conducting tissue. This is accompanied by increased fibrosis, fat infiltration, and the loss of up to 90% of the pacemaker cells within the sinus node between twenty and seventy-five years of age (Lev, 1954).

The heart and myocardium have been regarded for many years as a postmitotic organ, and unlike skeletal muscle it has been regarded as having no regenerative capacity. Stem-cell research is now beginning to question this traditional principle. Researchers are attempting to harness what appears to be a limited self-renewal potential to restore cardiac function after acute and chronic cardiac events (Nadal-Ginard *et al.*, 2002; Sussman & Anversa, 2004). But it does appear that in men healthy ageing results in a net decrease in the total number of myocytes, while in healthy women the number remains unchanged. Presumably this sex-related difference represents differences in either the rate of myocyte death (by apoptosis and necrosis), and/or the rate of myocyte regeneration from endogenous stem-cells in the male and female heart.

Other age-related structural changes that occur within the human heart include a shortening of the base-to-apex dimension, this leads to a decrease in the size of the left ventricle and a dilation of the left atrium (Henry *et al.*, 1980). The thickness of the leaflets of the aortic and mitral valves increases as a result of collagen and lipid accumulation (Sahasakul *et al.*, 1988). The collagen which makes up the pericardium also becomes thicker and stiffer over the course of ageing (Kitzman and Edwards, 1990).

1.7 Regulation and Age-Related Changes in the Control of Cardiovascular

As well as the age-related changes that occur within the human heart, changes also occur in the structure of blood vessels and in the regulation of blood pressure. Several interconnected negative feedback systems control

vascular resistance, along with heart rate and stroke volume. The cardiovascular centre in the medulla oblongata controls these feedback systems along with neural and hormonal feedback. Within the cardiovascular centre are numerous neurons, some control vessel diameter (vasomotor centre) by stimulating vasoconstriction or vasodilatation, while others stimulate or inhibit heart rate and contractility.

The cardiovascular centre receives input from both higher regions of the brain and from sensory receptors. There are three types of sensory receptors that provide feedback to the cardiovascular centre. They are:

1. Proprioceptors which monitor the movements of joints and muscles.
2. Baroreceptors that are located in the aorta, internal carotid arteries and other large arteries which monitor changes in the pressure and stretch of the walls of blood vessels.
3. Chemoreceptors which monitor the concentration of oxygen, carbon dioxide and hydrogen in the blood. They are located close to the baroreceptors of the carotid sinus and aortic arch.

Sympathetic output from the cardiovascular system reaches the heart via cardiac accelerator nerves, while the opposing parasympathetic stimulation is transmitted along the vagus nerves. These opposing signals control heart rate and contractility.

The vasomotor region of the cardiovascular centre sends continual impulses to the smooth muscle in the blood vessel walls via vasomotor nerves, thus determining vasomotor tone.

1.7.1 Neural Regulation of Cardiovascular Function

Baroreceptor and chemoreceptor reflexes provide the negative feedback which determines the neural regulation of blood pressure. When blood pressure falls the baroreceptors are stretched less, in response they send nerve impulses at a slower rate to the cardiovascular centre, which then decreases parasympathetic and increases sympathetic stimulation. The consequence is an increase in heart rate and contractility, and an increase in the secretion of epinephrine and norepinephrine by the adrenal medulla. This results in increases in systemic vascular resistance and blood pressure.

When blood pressure increases, conversely the baroreceptors send impulses at a faster rate. Parasympathetic stimulation increases, while sympathetic stimulation is decreased. Heart rate, contractility and cardiac output all decline. The rate at which sympathetic impulses are sent along the vasomotor neurons is also slowed, which results in vasodilatation and a lowering of systemic vascular resistance.

Chemoreceptors are stimulated to send impulses to the cardiovascular centre by hypoxia, increased acidosis or hypercapnia of the blood. In response the cardiovascular centre increases sympathetic stimulation to arterioles and veins, causing vasoconstriction and an increase in blood pressure.

1.7.2 Hormonal Regulation of Cardiovascular Function

Several hormones also play active roles in the regulation of blood pressure and blood flow. Epinephrine and norepinephrine are released by the adrenal medulla. These hormones increase the rate and force of cardiac contraction.

They also play a very important role in increasing the blood flow to skeletal muscle during exercise by causing the vasoconstriction of arterioles and veins in the skin and abdominal region, and the vasodilatation of arterioles in cardiac and skeletal muscle.

When blood volume falls or blood flow to the kidneys is reduced renin is secreted into the blood stream. Renin and angiotensin converting enzyme act on their substrates to produce the active hormone angiotensin II, which raises blood pressure. Antidiuretic hormone can also be released from the posterior pituitary gland in response to dehydration or decreased blood volume, resulting in vasoconstriction which in turn also increases blood pressure.

Finally, in terms of the hormonal regulation of blood pressure atrial natriuretic peptide is released by the cells in the atria of the heart. Atrial natriuretic peptide lowers blood pressure by causing vasodilatation and by promoting the loss of salt and water in urine.

1.7.3 Autoregulation of Blood Pressure

Autoregulation is the ability a tissue has to adjust its blood flow to match its metabolic demand. In tissues such as skeletal muscle, where demand for oxygen and nutrients and the removal of waste products can increase by tenfold during physical activity autoregulation is critical to increasing blood flow through the tissue.

Two types of stimuli cause autoregulatory changes; the first of these stimuli is physical changes. Warming causes vasodilatation, whereas cooling causes

vasoconstriction. Smooth muscle in arteriole walls also exhibit a myogenic response, contracting more forcefully when stretched and relaxing when stretch is reduced. The secondly type of stimuli are chemicals that are produced by cells including white blood cells, platelets, smooth muscle cells and endothelial cells that alter the diameter of blood vessels. Vasodilators include nitric oxide, lactic acid, adenosine, hydrogen and potassium. Vasoconstrictors include superoxide radicals, serotonin and endothelins.

1.7.4 Age-Related Changes in the Regulation of Cardiovascular Function

In healthy individuals there are age-related increases in the afterload which resists the flow of blood leaving the left ventricle, and in resting blood pressure. These changes are partially caused by the age-related increase in vascular resistance. The walls of conduit arteries thicken, and the vessels become dilated and elongated. This thickening is the result of a diffuse process that has not been fully explained (Lakatta, 1993). Within the vessel walls total mucopolysaccharide content (ground substance of the interstitial matrix) remains unaltered, chondroitin sulphate and heparin sulphate levels increase, while hyaluronate and chondroitin content decreases (Kaplan and Meyer, 1960). Within the vascular media there is an age-associated change in the distribution of un-stretched collagen, a fragmentation of the internal elastin membrane and a relative loss of elastin and glycoprotein content (Lakatta, 2000). The intimal wall thickness of the carotid artery has been reported to increase by two- to three-fold between twenty and ninety years of age (Lakatta and Levy, 2003). These age-related changes result in the arterial structure

becoming less elastic and thus render it less compliant with the advancing years.

As well as the structural changes that occur with ageing that contribute towards increases in blood vessel stiffness and blood pressure, the changes may also be partly modulated by increases in arterial tonus, such as enhanced arterial smooth muscle cell calcium loading in response to a natriuretic hormone (Lakatta, 1989). Aged blood vessels also show an increased endothelial permeability and reduced nitric oxide-dependant vasodilator responsiveness (Taddei *et al.*, 1995). Also there is a reduced vasodilator response because of a reduced number and affinity of specific receptors, and a reduced vasoconstrictor response (Ferrari *et al.*, 2003).

There also appears to be an age-related increase in blood pressure during exercise. This appears to be partly due to the reduced vasodilatory capacity of the arterial tree (Fleg, 1986). There is also an age-related decline in the ability of arterial baroreceptors to modulate chronotropic activity. Ferrari *et al.*, 2003 supported this notion concluding that with ageing, baroreceptor control of blood pressure is quantitatively preserved but has a significantly slower time course.

1.8 Age-Related Changes Cardiac Function

Given all the compositional and structural changes which occur in the heart and vasculature as a consequence of ageing there inevitably have to be changes in function.

In terms of cardiac function, the older human heart has thicker myocardial walls, which therefore become less compliant (Labovitz and Pearson, 1987). As the leaflets of the aortic and mitral valves become less compliant there is an increase in the regurgitation of blood (Sahasakul *et al.*, 1988). The senescent heart also exhibits prolonged contraction and relaxation phases (Pugh and Wei, 2001). This is the result of a slower action potential thought to be caused by a prolongation of calcium transients which results from both a slower release and uptake of Ca^{2+} by the sarcoplasmic reticulum (Schmidt *et al.*, 2000; Lompre, 1998), and an increase in the expression of slow:fast myosin heavy chains (Lakatta, 1999). This slower function of the healthy older human heart and its decreased compliance results in an increase in left ventricular end-diastolic pressure. This in-turn leads to a reduction in the early-passive phase of diastolic filling, such that the heart increases its reliance on atrial contraction to augment the late-phase of diastolic filling to maintain left ventricle end-diastolic volume. This is illustrated by an increase of up to 40% in the time between the aortic valve closing and the mitral valve opening, and also a decrease of up to 50% in the peak rate at which blood fills the left ventricle in early diastole between twenty and eighty-years of age in both men and women (Lakatta, 1993). Overall the heart becomes shorter base-to-apex (Henry *et al.*, 1980), as the left atrium dilates, while the left ventricle becomes more spherical in shape (Hees *et al.*, 2002).

1.8.1 Age-Related Changes in Resting Cardiac Function

At rest the ageing heart adapts well to maintain its function (Pugh and Wei, 2001). In terms of what effect healthy ageing has on the generation of resting blood flow the published research is somewhat equivocal. Some studies have

documented a reduction in resting cardiac output (\dot{Q}_{rest}) equal to 1% per year (Brandfonbrener *et al.*, 1955), while others have documented no change (Lakatta, 1999; Rodeheffer *et al.*, 1984). The reason for these different conclusions can be attributed to different subject inclusion criteria, differences in body posture during the measurements and the methods employed to measure \dot{Q}_{rest} .

Cardiac output is the product of stroke volume and heart rate. Again there is some disagreement regarding what impact, if any, healthy ageing has on resting stroke volume (SV_{rest}). The study by Rodeheffer *et al.* (1984) reported a decrease from 85ml for men in their twenties to 60ml for men in their eighties. Other more recent studies have reported no change in SV_{rest} (Lakatta, 1993). Again these discrepancies are the result of the same methodological differences that caused different conclusion relating to \dot{Q}_{rest} . Resting heart rate (HR_{rest}) also appears to remain largely unchanged with the progression of healthy ageing (Fleg *et al.*, 1990). There have been reports of decreases in HR_{rest} in both men and women when it has been measured in a seated position (Schwartz *et al.*, 1991). This is the result of a prolonged P-R interval which reflects the delay at the atrioventricular junction resulting from the previously detailed age-related accumulation of fat and collagenous tissue (Lakatta, 1993), and secondly from the reduction in the number of pacemaker cells in the sinoatrial node (Lev, 1954).

In the Framington study reported by Kannell *et al.* (1981) ageing in humans was associated with increases in resting systolic blood pressure (SBP_{rest}) in both men and women. Between the forth and eight decades the increase was

25 mmHg in men and 35 mmHg in women. Diastolic blood pressure (DBP_{rest}) was reported to plateau by the sixth decade, and then showed a slight decrease thereafter.

Resting cardiac function in healthy humans therefore appears to be well maintained in spite of advancing age, given the absence of any pathological disease processes. But, at rest the cardiovascular system is operating at only a small percentage of its potential. To accurately measure any functional changes that are elicited in cardiovascular performance tests must be conducted when it is maximally stressed. In healthy humans exercise is the most appropriate research tool, and therefore the most widely used technique to evoke a maximal response.

1.8.2 Age-Related Changes in Maximum Cardiac Function

As previously detailed it has been recognised for many years that ageing results in a decrease in $\dot{V}O_{2max}$. This decrease is generally regarded to start in the third decade of life, and the rate of the decline is between 5 and 10% per decade (Dehn and Bruce, 1972). The decrease in $\dot{V}O_{2max}$ is paralleled by a decrease in work capacity, and at sub-maximal work loads the elderly often achieve a higher level of oxygen consumption. A major factor which has been recognised to contribute towards the age-associated decrease in $\dot{V}O_{2max}$ is a decline in maximum cardiac output (\dot{Q}_{max}).

Many investigators have demonstrated age-related decreases in \dot{Q}_{max} (Ehsani *et al*, 1991; Fleg *et al.*, 1995; Ogawa *et al.*, 1992). However some recent studies have cast doubt on this observation, showing \dot{Q}_{max} to be maintained in

the face of healthy ageing (Rodeheffer *et al.*, 1984; Fleg, 1986). These reports have attributed the decreases observed in other studies to be the result of less rigorous inclusion criteria which failed to exclude subjects who were suffering from covert coronary artery disease, and secondly the invasive methods used.

Maximum blood flow generation is the product of stroke volume (SV_{\max}) and heart rate (HR_{\max}). The investigators who have found \dot{Q}_{\max} to be effectively maintained throughout ageing have attributed it to an age-related increase in SV_{\max} or stroke volume index (SVI_{\max}) (Lakatta, 1993). Whilst not surprisingly, those who have reported \dot{Q}_{\max} to decrease have also reported SV_{\max} and SVI_{\max} to be maintained or to decrease with ageing (Bogaard *et al.*, 1997; Fleg *et al.*, 1995; Ogawa *et al.*, 1992).

All the studies agree that ageing results in a significant reduction in HR_{\max} , which accounts for the majority of the decrease in \dot{Q}_{\max} . Between the third and seventh decade of life Julius *et al.* (1967) reported HR_{\max} to decrease by 18% (170 to 140 beats per minute), while SV_{\max} fell only 9% (95 to 86 ml). As with the age-related decline HR_{rest} the decline in HR_{\max} has been attributed to the loss of pacemaker cell within the sinus node (Lev, 1954), but also to a reduced responsiveness of the older heart to circulating catecholamines (Fleg *et al.*, 1985; Kitzman and Edwards, 1990), or possibly to some other intrinsic age-related mechanism as yet ill defined (Tanaka *et al.*, 2001). It is generally concluded that \dot{Q}_{\max} declines with ageing, with the majority of this decrease attributed to the age-related decline in HR_{\max} , although some studies have also shown SV_{\max} to decrease but to a lesser extent. With advancing age,

therefore, there is an unequivocal increased reliance on the Frank-Starling mechanism in the absence of decreased cardio-acceleration.

Significantly less research has been carried out investigating the age-related changes that occur in the generation blood pressure during maximal aerobic exercise. Clearly arterial pressures under these conditions will be lower than the pressures generated when subjects perform heavy weight-lifting exercise. Under these conditions systolic blood pressure can rise to in excess of 480 mmHg, and diastolic to over 350 mmHg (MacDougall *et al.*, 1985). This is due the mechanical compression of the blood vessels, combined with the potent pressor and Valsalva responses.

At $\dot{V}O_{2\max}$ Ogawa *et al.* (1992) reported significant age-related increases in maximal systolic (SBP_{\max}), diastolic (DBP_{\max}) and mean arterial (MAP_{\max}) blood pressures. Furthermore the age-related increases in blood pressure were greater in women. In their twenties women had a lower SBP_{\max} and MAP_{\max} than their male counterparts, while the trend was reversed above sixty years of age. Stratton *et al.* (1994) reported that SBP_{\max} , DBP_{\max} and MAP_{\max} were all higher in men who were over sixty years of age, when compared to healthy men who were under thirty-two years of age. In contrast, work reported by Rodeheffer *et al.* (1984) found no significant age-related increases in any of the measures of blood pressure at $\dot{V}O_{2\max}$.

There appears to be much conflicting evidence pertaining to what impact ageing has on cardiac function. This is especially true when concentrating on maximum cardiac function. Many of these contradictions result from differing

subject populations, their inclusion or exclusion criteria, and the methods employed. This includes the emphasis on measuring blood flow and not overall cardiac function (i.e. cardiac power output; CPO).

1.9 Effects of Exercise on Cardiac Function

As previously described (section 1.3) engaging in long-term endurance exercise can have a beneficial effect of $\dot{V}O_{2\max}$. Importantly, in a society which is becoming increasingly sedentary it appears the ability to increase $\dot{V}O_{2\max}$ is not blunted with age. Although the upper ceiling of adaptation is reduced, the rate of improvement in response to a sufficient stimulus does not decrease with advancing age (Paterson, 1992). This applies to both men and women (Seals *et al.*, 1984).

There is some debate though surrounding whether the mechanisms which adapt and contribute towards an increased $\dot{V}O_{2\max}$ are sex specific. Stratton *et al.* (1994) reported that previously sedentary young and older men retain their capacity to improve cardiac function. This has been supported by numerous studies which have concluded that men have the ability to adapt cardiac function in response to endurance exercise. Specifically, improvements in left ventricular systolic function (Ehsani *et al.*, 1991) and left ventricular filling rate (Spina *et al.*, 1996) have been reported. It has also been reported that men also increase their maximum arteriovenous oxygen difference ($a - \bar{v} O_{2\text{diff}_{\max}}$). While some studies have found women have a similar capacity to improve their cardiac function (McCole *et al.*, 1999; Sullivan *et al.*, 1991), others have found that women in contrast to men exhibit no improvements in either \dot{Q}_{\max} or

SV_{\max} . Their ability to improve $\dot{V}O_{2\max}$ in response to endurance exercise is therefore solely attributable to an improved $a - \bar{v} O_{2\text{diff}\max}$ (Ehsani *et al.*, 2003; Spina *et al.*, 2000; Spina *et al.*, 1993). But the question of what impact long-term endurance training has on CPO has not yet been addressed.

As well as inducing $\dot{V}O_{2\max}$ values which can be twice that of their sedentary counterparts, master athletes also have reduced levels of subcutaneous fat. The increased levels of peripheral oxygen extraction are the result of greater Type I muscle fibre hypertrophy and the augmentation of oxidative muscle enzymes (Lakatta, 1993). But, several studies have attributed the endurance exercise-induced improvements in aerobic power mainly to increases in \dot{Q}_{\max} (Lakatta, 1994). For example, Ogawa *et al.* (1992) estimated that 88 to 99% of the training-induced increase in $\dot{V}O_{2\max}$ was the direct result of increases in \dot{Q}_{\max} .

An augmentation in SV_{\max} is the major cause for increases in \dot{Q}_{\max} , because exercise training has been found to have no significant effect on the age-related decline in HR_{\max} . Stratton *et al.* (1994) reported a 17% increase in SV_{\max} in men aged between twenty-four and eighty-two years of age after only six months of exercise training. Gledhill *et al.* (1994) and Zhou *et al.* (2001) found similar increases in SV_{\max} which were the result of increases in ventricular filling and emptying in endurance trained athletes. Furthermore, Stratton *et al.* (1994) also found that an increase in ejection fraction occurred in spite of an exercise-induced increase in SBP_{\max} . They concluded this increase in blood pressure could be the result of an increase in myocardial

contractility. This increase in contractility has been contested by other researchers (Ehsani, 1987), but several echocardiography studies have found exercise-induced increases in left ventricular hypertrophy and chamber size in both old (Heath *et al.*, 1981; Douglas and O'Toole, 1992) and young (George *et al.*, 1999; Whyte *et al.*, 2004) males and females. However, these echocardiography measurements were conducted under resting conditions, and as a result do not directly relate to contractility, and are poor reflections of what happens in the dynamic state i.e. during exercise.

Another mechanism which could explain the exercise-induced augmentation in SV_{max} is a decrease in arterial stiffness. Exercise has been shown to blunt the age-associated increases in carotid pulse pressure and pulse wave velocity in older endurance-trained athletes (Vaitkevicius *et al.*, 1993). From a structural standpoint exercise has been shown to increase the elastin content, and reduce the calcium content of the elastin in the walls elastic arteries. From a non-structural context exercise has been shown to be effective at increasing vascular-endothelial-dependant vasodilatation (Seals, 2003) thus decreasing systemic vascular resistance (SVR) and allowing increases in \dot{Q}_{max} and SV_{max} to be achieved more easily.

Finally, if individuals have participated in endurance based training, and as a result have augmented their aerobic and cardiovascular function, it is critical that they maintain the same levels of activity if they wish to maintain these beneficial adaptations. Studies by Pimentel *et al.* (2003) and Tanaka and Seals (2003) have found that as with $\dot{V}O_{2max}$ endurance-trained individuals have higher cardiac functional capacities. But, if the exercise stimulus is

withdrawn the rate of decline is greater than that which is associated with ageing alone. As a result of this detraining effect, previously trained individuals quickly lose all of the cardiac and aerobic benefits, and become indistinguishable from their long-term sedentary contemporaries.

1.10 Effects of Heart Failure

Heart failure is one of the cardiology's most difficult concepts to grasp (Williams *et al.*, 2005). Often the term is used to characterise a heart that is failing, but its symptoms are not uniform. Most commonly, from a cardiac perspective individuals who are suffering from heart failure have a dyssynchronous myocardial contraction. As a result, the heart fails to produce sufficient hydraulic power to supply the tissues of the body with oxygen, and therefore normal levels of function cannot be maintained.

Early classical symptoms of heart failure include breathlessness (dyspnoea) and fatigue (Ekman *et al.*, 2005). A key manifestation and principal symptom of heart failure is exercise intolerance which is often the cause of many patients seeking medical care; the degree to which exercise tolerance is limited is a key prognostic indicator (Francis *et al.*, 2001).

In severe cases the functional impairment which results from heart failure may be manifested at rest. But to fully appreciate the impact of heart failure as with ageing and exercise the effects must be measured accurately and under conditions of maximal stress. It is here that the inadequacy of the heart's reserve capacity is only fully exposed and truly quantifiable.

Heart failure patients have a much lower aerobic power than healthy individuals. Middle aged patients typically achieve a $\dot{V}O_{2\max}$ of 10 to 20 ml/kg/min, in comparison to the 30 to 40 ml/kg/min achieved by healthy age-matched individuals. This is the result of inadequate blood flow reaching the skeletal muscles, and muscle wasting through inactivity (Wilson *et al.*, 1984). The cardiac output of heart failure patients has been reported to be only one-half of that of a healthy but sedentary individual when measured at maximal exertion. This is the result of both a stroke volume which as well as being decreased at rest can only be increased moderately up to between 50 and 65 ml, compared with the 100 ml that is achieved by healthy subjects (Piña *et al.*, 2003).

The reduced ability of heart failure patients to increase their stroke volume is the result of a left ventricle that is already dilated at rest, and has no remaining capacity to augment preload or ejection fraction in response to the exercise stimulus (Sullivan and Cobb, 1992). The failure to increase left ventricle ejection fraction results from a combination of impaired intrinsic contractility, reduced β -adrenergic responsiveness, and elevated systemic vascular resistance (Piña *et al.*, 2003; Fig. 2).

As a result heart failure patients rely on increases in heart rate to enhance cardiac output in response to an exercise stimulus. Although the initial increases in heart rate in response to exercise are often very similar to those seen in healthy individuals (Sullivan and Cobb, 1992) the heart rate reserve capacity is vastly decreased. This is because typically the resting heart rate of a heart failure patient is already elevated.

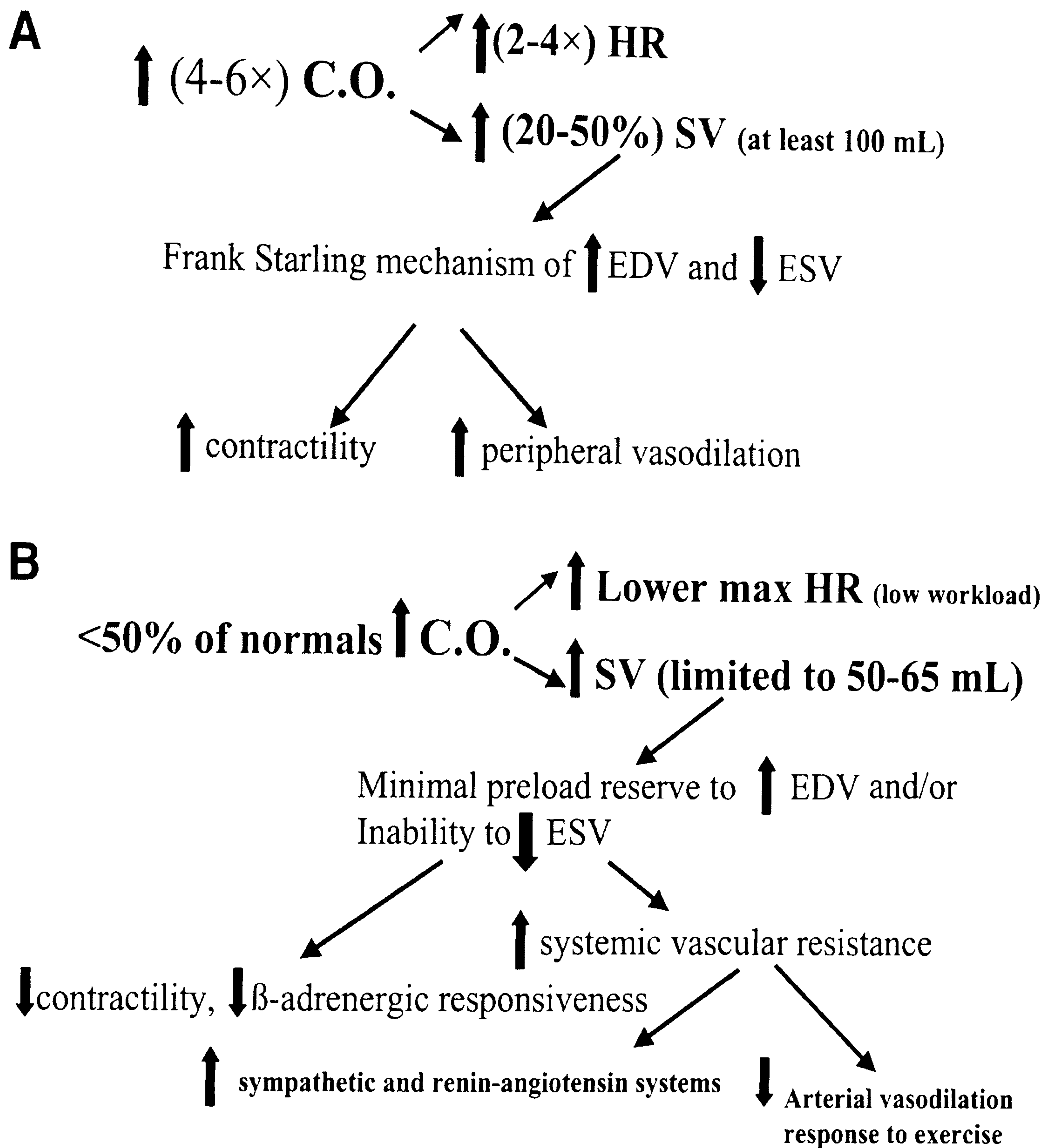


Figure 2 – Mechanisms that augment cardiac output in healthy humans and heart failure patients

Flow diagram showing how healthy people (A) without heart failure, and patients (B) with heart failure increase cardiac output.

C.O indicates cardiac output; HR, heart rate; SV, stroke volume; EDV, end-diastolic volume; and ESV, end-systolic volume.

Figure adapted from Piña *et al.* (2003).

In the United Kingdom approximately one in every five deaths in men and one in every six in women is the result of heart failure. The economic cost exceeds £7.9 billion per year. Heart failure therefore has numerous negative cardiovascular, aerobic and economic implications. It was for these reasons that the investigators decided to study individuals who were suffering from the condition. It represents the negative end of the spectrum in terms of its cardiovascular and activity implications, and therefore makes a good contrast to the effects of healthy ageing, and long-term endurance training.

1.11 Cardiac Power Output

It is apparent that numerous studies have been conducted on the effects of ageing, exercise, or heart failure on the individual indices of cardiac function, such as \dot{Q} , SV, blood pressure and or ventricular dynamics. Furthermore, some investigators have correctly recognised the validity of measuring cardiac reserve capacities by testing cardiac function at both rest and when maximally stimulated (Lakatta, 1993). But none of these studies have reported changes which occur in overall cardiac function.

The major function of the heart is to operate as a hydraulic pump. It converts adenosine triphosphate (ATP) into kinetic energy to maintain the circulation of blood (Tan, 1991). Without this energy the circulation would cease and hypoxia would quickly occur in all the tissues of the human body. The potential of the heart to generate external work depends on its ability to create blood flow and blood pressure. Both are equally important in maintaining the circulation of blood. It was the recognition of this fact that lead Tan (1987) to develop the term cardiac power output (CPO), and develop its measurement.

Furthermore, it illustrates that when previous studies have only measured either the blood flow or blood pressure generation they have failed to measure overall cardiac function.

The measurement of CPO was developed within clinical cardiology (Tan, 1986). It is calculated as:

$$\text{CPO (Watts)} = (\dot{Q} \times \text{MAP}) \times K,$$

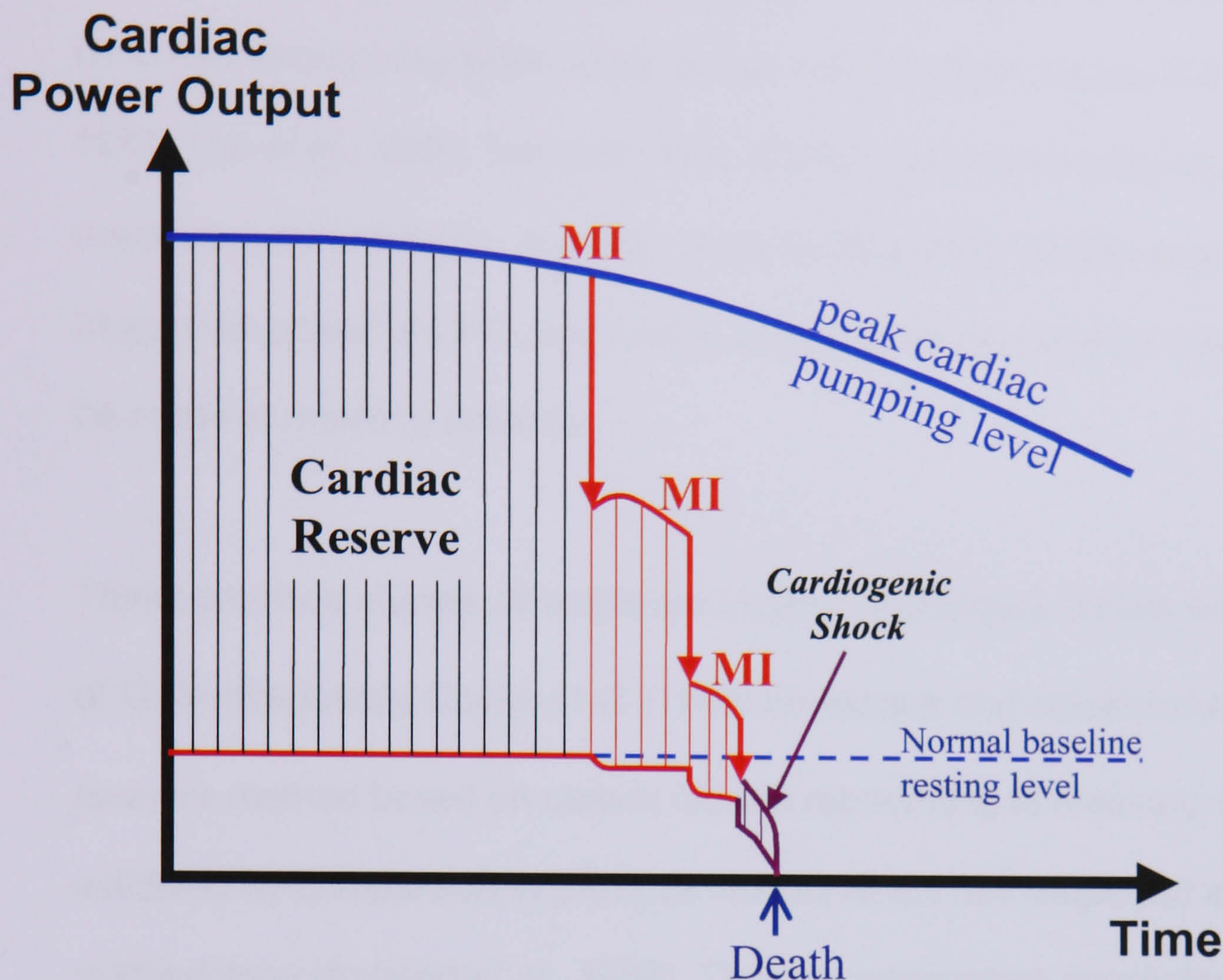
where \dot{Q} is cardiac output (l/min), MAP is mean arterial pressure (mmHg), and K the constant conversion factor (2.22×10^{-3}) into watts.

Furthermore, CPO can be measured at rest (CPO_{rest}), and when the heart is maximally stressed (CPO_{max}). The functional cardiac reserve (CR) can then be calculated from the following equation,

$$\text{CR} = \text{CPO}_{\text{max}} - \text{CPO}_{\text{rest}}.$$

The technique was first applied when assessing the prognosis of heart failure patients. Invasive measurement methods were employed, and dobutamine infusion was used to illicit maximal cardiac stress (Tan, 1986). It was concluded that patients who had a CPO_{max} of less than one watt, and hence a small CR, had a poor chance of surviving more than one year.

A further study by Tan and Littler (1990), again using invasive measurement techniques and dobutamine induced stress, also supported the use of CPO as a prognostic tool in patients who were suffering from acute cardiogenic shock, the majority of whom had suffered myocardial infarctions (MI). The effect of one or more MI on CPO and CR is illustrated in figure 3.



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Figure 3 – Schematic diagram illustrating the changes in cardiac power output as a result of ageing and ischaemic damage.

The dashed blue line represents resting cardiac power output (CPO_{rest}) and the solid blue line represents predicted maximal cardiac power output (CPO_{max}). Cardiac functional reserve (CR) is the difference between the two lines and is represented by the hatched area.

Cardiac reserve can be negatively affected by ageing, or more dramatically by a myocardial infarction (MI) and damage to the myocardium.

When CPO_{max} and CPO_{rest} become indistinguishable the long-term prognosis of the heart failure patient is very poor. In extreme conditions when CPO_{max} falls below the previous basal CPO_{rest} value a state of cardiogenic shock ensues, which is rapidly followed by death unless drastic interventions (e.g. surgery) are successful.

Figure adapted from Goldspink *et al.* (2003).

Roul *et al.* (1995) were the first to employ CPO when inducing stress through exercise rather than a pharmacological approach. Again they concluded that CPO had strong prognostic value, but as with previous studies (Tan, 1986 and 1987; Tan *et al.*, 1989; Tan and Littler, 1990) they were employing an invasive measurement technique. A further study by Bain *et al.* (1990) supported the prognostic power of CPO, and further emphasised the need for measures to be made at maximal exertion.

These previous studies all employed invasive techniques for the measurement of \dot{Q} . Subsequently Cooke *et al.* (1998) developed and employed a non-invasive method based on carbon dioxide rebreathing to measure \dot{Q} . This was validated by comparison to previous studies which had employed an invasive methodology (Åstrand *et al.*, 1964). These investigators concluded that CPO, and the subsequent calculation of CR, was the best objective indicator of overall cardiac function. Furthermore, they found that CPO could be measured reproducibly during peak exercise and that it was strongly correlated to $\dot{V}O_{2\max}$ and exercise capacity.

Recently CPO (Tan, 1991) has been described as the best overall indicator of cardiac performance, and its prognostic power in terms of measuring cardiac function has shown to be greater than that of $\dot{V}O_{2\max}$ (Nicholls and Reilly, 2001). Yet the application of CPO is still mainly confined to use in the clinical environment, where it is used as a prognostic tool in the diagnosis (Cotter *et al.*, 2003) and treatment (Marshall *et al.*, 2001) of patients with impaired cardiac function.

1.12 Aims of the Study

The overall aim of these studies was to use CPO for the first time to measure what impact healthy ageing, long-term endurance exercise and heart failure have on overall cardiac function in a large number of both men and women. These subjects represent a cross-section of the community, and enable sex-related comparisons to be made with ageing and exercise training.

Given the cross-sectional nature of the studies, a number of preliminary studies had to be conducted first to ensure the data collected was accurate and meaningful.

The objectives of the preliminary studies were:

1. The validation of the automated equipment to be used to analyse respiratory gases.
2. Test the reproducibility of the measurements of cardiac function to ensure that they were reliable.
3. Determine what the recovery period must be between multiple bouts of maximal exercise, to ensure a true maximal state is elicited for meaningful measurements of CPO.
4. Investigate whether circadian rhythm affects the measurement of CPO, and if it does determine what the most appropriate time of day is to conduct the measurements.

After these preliminary studies had been concluded, focus moved to the collection of physiological data for interpretation. A large number of subjects were carefully recruited, screened and selected to ensure any conclusions

drawn from the data were meaningful and accurate. The studies were carefully designed with the following objectives in mind:

1. Measure the effects of ageing on $\dot{V}O_{2\max}$, CPO_{rest} and CPO_{\max} in healthy sedentary men and women.
2. Make a meaningful body size and composition independent comparison between men and women to determine if healthy ageing similarly affected $\dot{V}O_{2\max}$, CPO and CR in the two sexes.
3. Measure and compare what impact engaging in endurance exercise has on $\dot{V}O_{2\max}$, CPO and CR in long-term endurance trained men and women.
4. Determine what quantifiable effect NYHA class III and IV heart failure has on $\dot{V}O_{2\max}$, CPO and CR when measured non-invasively.

Chapter 2

Methods

2.0 Pre-Test Screening and Subject Recruitment

Before beginning the study ethical approval was granted from Liverpool John Moores University ethics committee for all the procedures involved.

Subjects were recruited from Merseyside and the surrounding area. After expressing an interest in taking part in the study, subjects completed a questionnaire initially detailing their health status and medical history (App. 1). Completed questionnaires were examined, and subjects were rejected based on the following medical criteria; any history of cardiovascular disease, including coronary heart and coronary artery disease, a history of hypertension [defined as a resting blood pressure $> 140/89$ mmHg (Williams *et al.*, 2004)], diabetes mellitus, or significant clinical obesity as defined by a body mass index (BMI) above 35 kg/m^2 . Individuals who were consuming any prescribed medication or food supplements known to affect cardiovascular or respiratory function were also refused entry into the study, as were all tobacco smokers.

The second part of the questionnaire addressed the volunteers past and current activity levels. Individuals were asked to detail the frequency, duration and intensity of all activities that they participated in, including all recreational and structured exercise. If any discrepancies were found, or questions were not satisfactorily answered a further interview was used for clarification. Any individual who reported doing less than ninety minutes of exercise per week (none of which was structured) was regarded as having a sedentary lifestyle based on this self-reporting basis.

The female version of the questionnaire contained a section relating to the volunteers hormonal status, e.g. menstrual cycle where applicable, and all forms of contraception and hormone replacement therapy.

Finally, a group of patients with heart failure were studied. From an initial medical assessment it was determined that all were suffering from NYHA class III and IV heart failure. Class III or moderate heart failure patients are comfortable at rest, but less than ordinary physical activity in these patients causes fatigue, palpitations, dyspnoea, or angina pectoris. Class IV patients are suffering severe heart failure and have an inability to carry out any physical activity without discomfort. They exhibit symptoms of cardiac insufficiency at rest, and if any physical activity is undertaken, discomfort is increased (Bennett *et al.*, 2002). Following completion of the tests all of these patients were scheduled to undergo surgery at Liverpool Cardiothoracic Centre to install bio-ventricular pacemakers. Due to their medical condition all of these patients were being treated with various beta-blockers, diuretics, spiro-lactones, and ACE-inhibitors to help maintain their heart function. Hence, they were treated as an entirely separate group as they did not adhere to the strict health criteria of the earlier populations.

2.1 Evaluation Procedures

All of the performance tests were conducted in the exercise laboratories at Liverpool John Moores University. The temperature of the laboratories was maintained around 20°C, and humidity between 40 and 60%. Subjects reported for each test at least three-hours postprandial, having avoided the

consumption of caffeine for at least three-hours, and having abstained from all strenuous physical exertion for twenty-four-hours.

Before arriving at the university all the volunteers were sent a full description of the test battery. On arrival a further verbal explanation was given of all the procedures and any questions were answered. Each individual then signed a consent form (App. 2) and testing began.

2.2 Measurement of Body Composition

First, height and weight were measured using a Harpenden stadiometer and Avery balance beam scales, respectively.

Whole, and regional, body composition was measured using Dual-Energy X-ray Absorptiometry (DEXA). Previous validation has proven this technique to be accurate in both sexes and across a wide age range (Kohrt, 1998). Its accuracy is unaffected by race, athletic status or musculoskeletal development (Prior *et al.*, 1997).

The DEXA unit (Hologic Inc, Horizon Park, Levensesteenweg, Belgium) consists of a bed, underneath which a collimated two-dimensional X-ray fan beam originates. Above the bed are detectors that measure the transmitted beams after attenuation by the different constituents of the human body (Fig. 4). The scanner and bed is controlled by a dedicated computer and software (Delphi A S/N 70719) which also allows the subject's body to be divided into various sub regions via the identification of anatomical landmarks (Fig. 5).

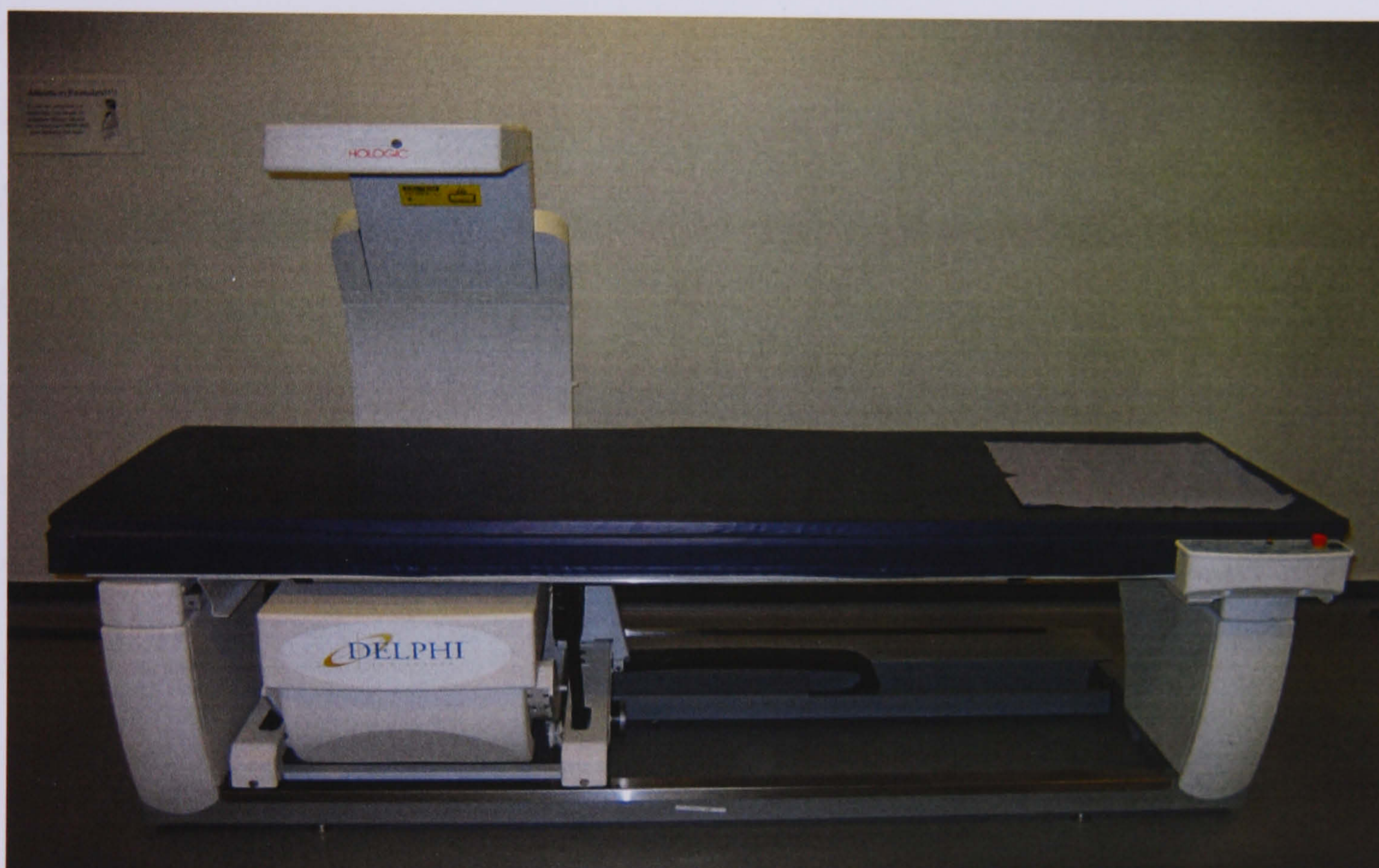


Figure – 4 Dual-energy X-ray absorptiometry unit (DEXA).

Before measuring the body composition of each subject the DEXA was calibrated. Firstly a phantom spine was scanned; this ensured the accuracy of the system when measuring bone content, and the clarity of the captured images. Secondly, a synthetic phantom containing known quantities of lean and soft tissue was scanned; this was used to guarantee the accuracy of the system with respect to these constituents.

Each subject was instructed to remove all metal appendages (jewellery, under-wired bras, clothes with zips etc) before lying on the bed. The subjects were positioned, and secured with non-reflective polystyrene blocks to ensure they did not move during scanning. Once initiated the bed and the source of the X-ray fan beam move in opposite directions in unison, scanning the entire subject area in three minutes. The degree of the X-ray attenuated by the subject's body is recorded. Within each region, as well as the whole body, DEXA can quantify total body mass (TBM), fat mass (FM), bone mineral content (BMC), and lean body mass (LBM). These can subsequently be calculated as percentages of body mass (Fig. 6).



Figure 5 – DEXA scan.

The scan illustrates the image used to identify the anatomical landmarks, and subdivide the regions of the body.

DEXA Results Summary:

Region	BMC (g)	Fat (g)	Lean (g)	Lean+BMC (g)	Total Mass (g)	% Fat
L Arm	237.57	911.0	3775.0	4012.6	4923.6	18.5
R Arm	249.90	936.2	3989.6	4239.5	5175.7	18.1
Trunk	948.62	5802.0	34016.1	34964.7	40766.7	14.2
L Leg	606.32	2632.1	11255.1	11861.5	14493.5	18.2
R Leg	636.25	2649.5	11864.1	12500.3	15149.9	17.5
Subtotal	2678.67	12930.8	64899.8	67578.5	80509.3	16.1
Head	627.09	1090.5	3779.6	4406.7	5497.2	19.8
Total	3305.76	14021.3	68679.5	71985.2	86006.5	16.3

TBAR2460

Figure 6 – DEXA results from a typical healthy male subject.

The DEXA quantifies the compositional elements of the whole body and its sub-regions.

2.3 Measurement of Aerobic Power and Cardiac Power

Output

The practical testing of maximal aerobic power ($\dot{V}O_{2\max}$) and cardiac power output (CPO) was separated into three distinct stages to ensure that accurate and representative results were recorded. The stages were:

1. An incremental treadmill exercise test to exhaustion to determine $\dot{V}O_{2\max}$.
2. The measurement of resting CPO.
3. The measurement of maximal CPO.

Subjects were fitted with a 12-lead electrocardiogram (ECG; Cardio-Perfect, Welch Allyn, Skaneateles Falls, NY, USA) for the duration of all three stages. Respiratory gases were measured continuously on a breath-by-breath basis using a Medgraphics® CPX/D system (Medgraphics corporation, St. Paul, Minnesota, USA).

The CPX/D system consists of a flow analyser, and a gas concentration analyser, these are fully integrated with the 12-lead ECG via a standalone personal computer using *BREEZEX™* software. The reported accuracy of the system is $\pm 0.1\%$, with a response time of less than less than 100 milliseconds.

The flow analyser draws gas via a pneumotachograph (preVent™) and a double lumen umbilical cord fitted directly to a mouthpiece. One lumen of the umbilical cord houses a small resistive element which generates a pressure drop as gas flow passes across it. The pressure differential across the

resistive element is proportional to the flow of gas in the pneumotachograph, thus flow volume is measured.

The gas analyser uses a vacuum to draw a respiratory gas sample through a sample line that is also fitted to the mouthpiece. The gas sample passes through a drying cartridge and into the analyser. Oxygen concentrations are measured using an electrical voltage, this causes movement of the O₂ molecules. The molecules are then measured as they pass a patent zirconia fuel cell, and are compared to a reference gas sample.

The carbon dioxide (CO₂) concentration of the same respiratory gas sample is also measured using an infrared analyser. Carbon dioxide absorbs more 4.3 μ m wavelength infrared light than any other gas. The amount of light absorbed by the sample is again compared to a reference sample, and the amount of CO₂ contained within was quantified.

From these measures we derived oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation (\dot{V}_E), tidal volume (V_T), and end tidal pressure of carbon dioxide (P_{ETCO_2}).

Prior to each test the flow and gas modules were calibrated. Ambient temperature, barometric pressure, and relative humidity were recorded. A three-litre syringe was used to replicate five full respiratory cycles, these cycles were performed at varying rates to test the accuracy of the flow module. The gas module was then calibrated using both reference (21% O₂, and balance N₂) and calibration (12% O₂, 5% CO₂, balance N₂) gases.

2.3.1 The Measurement of $\dot{V}O_{2\max}$

The main objectives of this first stage were to accurately measure the subject's $\dot{V}O_{2\max}$, their ability to generate blood pressure, and their exercise tolerance. It also provided a quantitative measure of their health status, and confirmed the information gathered from the questionnaire.

Subjects completed an incremental treadmill exercise test. The protocol was a further modified version of the Bruce protocol (Bruce, 1971). The first two minutes acted as a warm-up and familiarisation period for those subjects who were unaccustomed to using treadmills. The speed for the first minute was 2.2 kilometres per hour (km/h), and the gradient was 5°. This increased to 2.7 km/h and 10° gradient in the second minute. After the warm-up period increments of 0.5 km/h and 1° gradient occurred at regular one minute intervals until volitional exhaustion (Table 1). The decision to employ intermediate increments in both speed and gradient with increased regularity was based on the findings of Porszazs *et al.* (2003) and Myers *et al.* (2000). This research recommended these modifications be made to the standard Bruce protocol to elicit a linear increase in $\dot{V}O_2$, to ensure the accurate measurement of $\dot{V}O_{2\max}$, and to guarantee the test lasts an appropriate duration. This protocol was employed for all subjects.

The subject's respiratory gases were sampled continuously throughout the test. Subjects were considered to have achieved $\dot{V}O_{2\max}$ when two of the following three criteria were met:

1. A plateau in $\dot{V}O_2$, despite a further increase in workload.

Stage	Duration (minutes)	Speed (km/h)	Incline (°)
1	0:00 – 1:00	2.2	0
2	1:00 – 2:00	2.2	0
3	2:00 – 3:00	2.7	5
4	3:00 – 4:00	2.7	10
5	4:00 – 5:00	3.3	11
6	5:00 – 6:00	4	12
7	6:00 – 7:00	4.8	13
8	7:00 – 8:00	5.5	14
9	8:00 – 9:00	6.2	15
10	9:00 – 10:00	6.8	16
11	10:00 – 11:00	7.4	17
12	11:00 – 12:00	8	18
13	12:00 – 13:00	8.4	19
14	13:00 – 14:00	8.8	20
15	14:00 – 15:00	9.2	21
16	15:00 – 16:00	9.6	22

Table 1 – Treadmill Protocol.

2. A heart rate within 10 beats per minute of their age predicted maximum (i.e. $220 - \text{age}$).
3. An respiratory exchange ratio (RER) equal or greater than 1.10.

Heart rate was derived from the ECG, which was monitored throughout the test by a qualified cardiologist. Any exercise-induced ischaemia or arrhythmia indicating abnormal cardiac function was considered grounds for the early termination of the test, and subsequent exclusion of the subject from further testing.

Blood pressure was taken manually from the brachial artery using a mercury sphygmomanometer and stethoscope. The subject's arm was raised and supported at the level of the heart during each recording (Fig. 7). The first measurement was taken before beginning the test. During the exercise blood pressure was taken initially at two minute intervals, the frequency of the measurement increased towards volitional exhaustion to ensure maximal blood pressure was recorded. A final recording was taken immediately post exercise. If any abnormal changes in blood pressure were detected, once again the test was terminated and the subject excluded from further analysis. Abnormal changes in blood pressure are for example, a failure of systolic blood pressure to increase with increasing workload, or an excessive increase in response to exercise (American College of Sports Medicine, 2000).

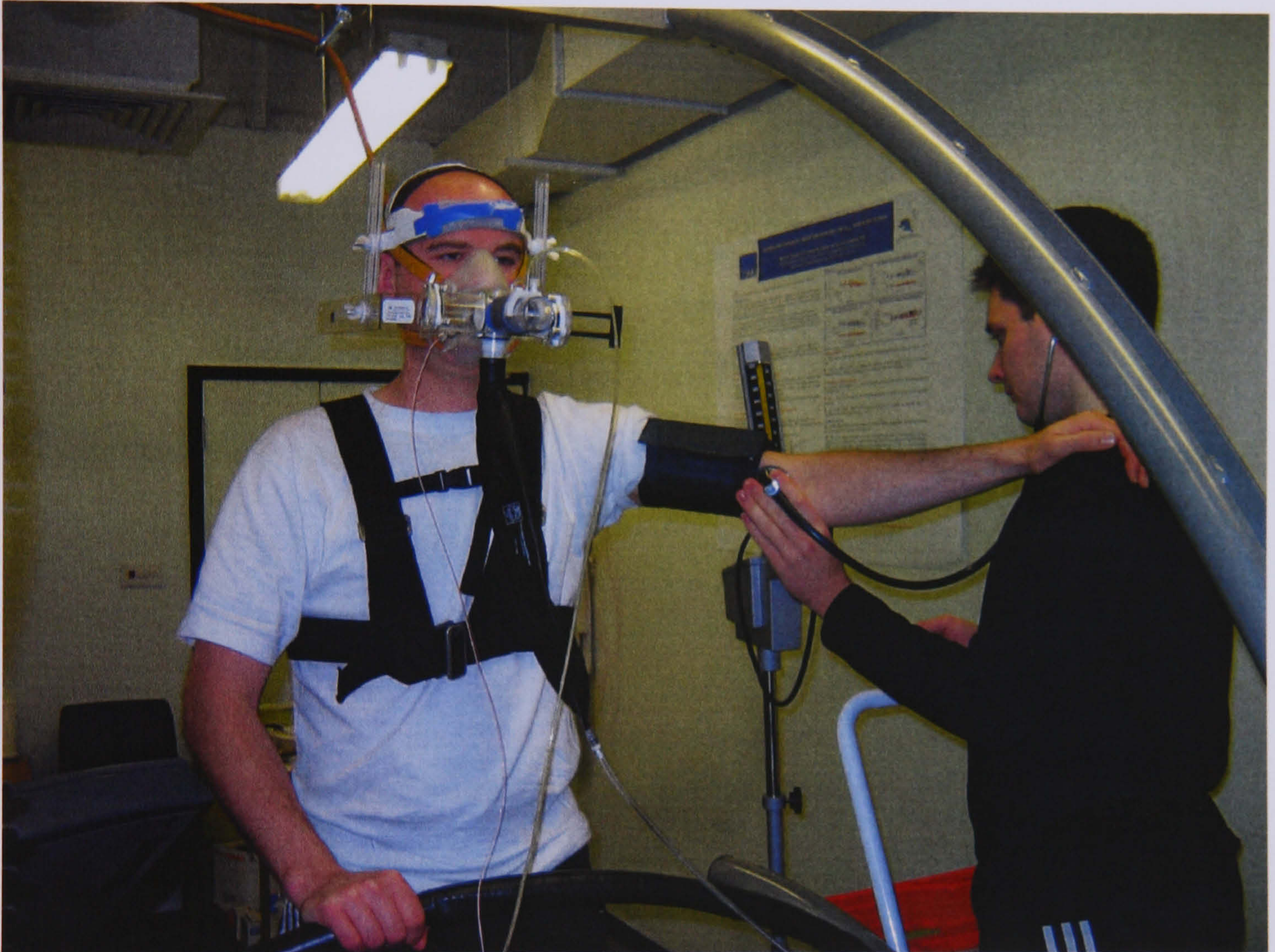


Figure 7 – Measurement of blood pressure using auscultation method during incremental exercise.

2.3.2 The Measurement of Resting Cardiac Function

The purpose of this second stage was to measure resting cardiac output (\dot{Q}_{rest}) and mean arterial blood pressure (MAP_{rest}). The Collier (1956) method was implemented to measure end venous pressure of carbon dioxide ($P_{\bar{v}\text{CO}_2}$).

Previous research has proved this method to be most accurate CO_2 rebreathing technique for measuring \dot{Q}_{rest} (Auchinloss *et al.*, 1980, Franciosa *et al.*, 1976, Zeidifard *et al.*, 1972).

Subjects reported to the laboratory and the 12-lead ECG was re-attached, they sat down and were fitted with a mouthpiece and nose-clip. The subject stayed in this relaxed position for a minimum of five minutes, during which respiratory gases and the ECG were monitored continuously.

Attached to the mouthpiece were the respiratory gas sample lines, and a Hans Rudolph three-way rebreathing valve (Model 2870 series). A preVent™ pneumotachograph was attached to the outflow route of the valve, while a five-litre anaesthesia bag, which acted as a CO_2 rebreathing bag was attached to the remaining channel. The valve allowed the researcher to manual redirect the subjects breathing from atmospheric air, to breathing the gas mixture in the bag. The weight of this equipment was fully supported from the treadmill structure (Fig. 8). The mouthpiece was used in preference to the face mask as it is less cumbersome for the subject, and could be more quickly fitted and removed.

When a stable baseline was achieved, blood pressure was measured using

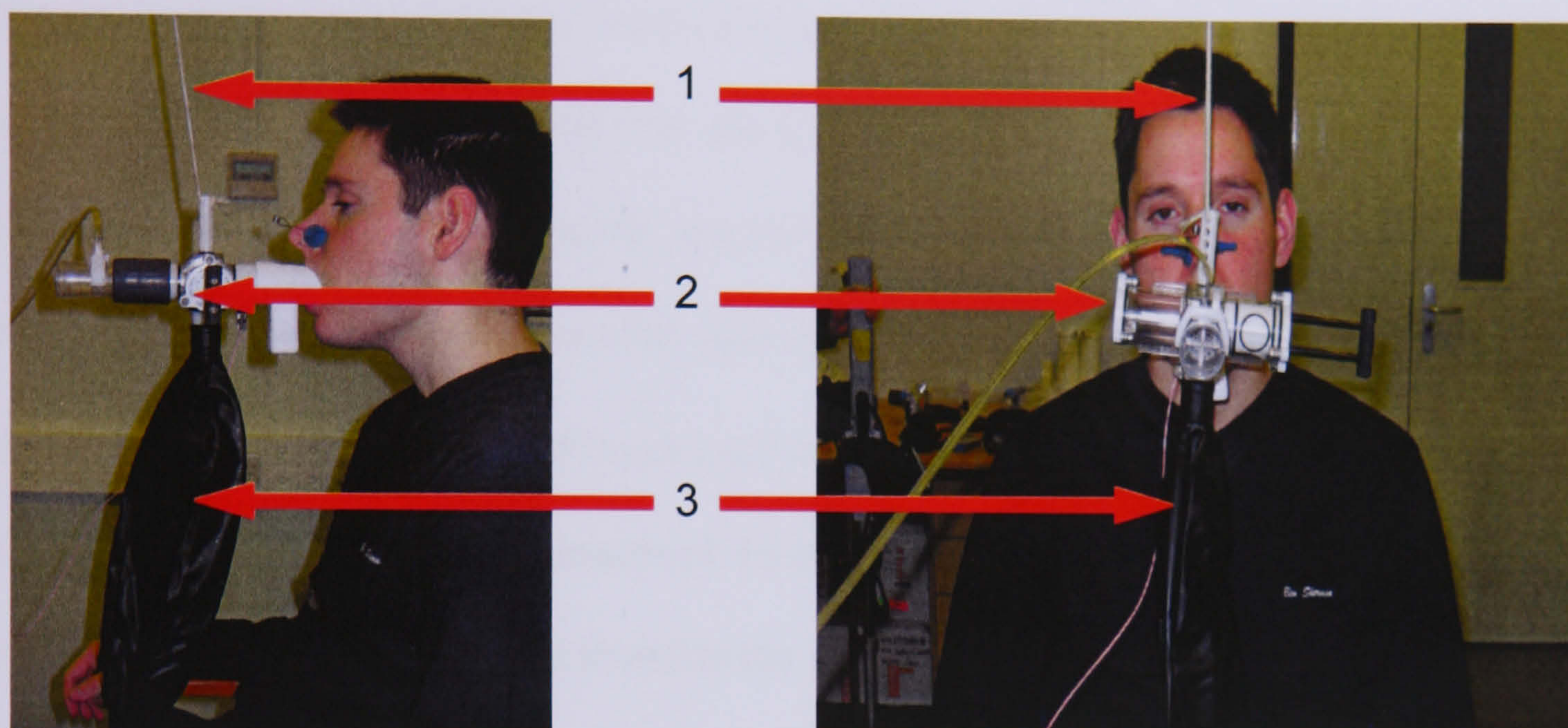


Figure – 8 Resting rebreathing valve.

Key

1. Cord supporting weight of the equipment.
2. Three-way rebreathing valve.
3. Five-litre anaesthesia rebreathing bag.

the manual auscultation method. The anaesthesia bag was filled with a medical grade mixture of 10% CO₂, 35% O₂ and balance N₂; the volume corresponding to double the subjects V_T.

After another brief moment to allow the respiration and heart rate to stabilise the investigator switched the rebreathing valve at the end of a tidal breath, this redirected the air flow towards the rebreathing bag. The subject was instructed to take a deep inspiratory breath, inhaling the full volume of gas from the rebreathing bag. This ensured the gas mixed well with the alveolar gas. The rebreathing manoeuvre continued until a plateau in \dot{V}_{CO_2} was observed on the CPX/D screen, or for a maximum of 15 seconds. After this time recirculation of CO₂ in the blood occurs and invalidates any further results. Once complete, the valve is retracted so the subject could inhale atmospheric air once again.

A satisfactory capnograph plot (Fig. 9) would clearly illustrate:

- Good mixing of the rebreathing gas with the alveolar gas.
- A CO₂ equilibrium occurring after 3 respiratory cycles, and within 15 seconds.
- The CO₂ equilibrium lasting for a minimum of 2 additional respiratory cycles.
- Appropriate volume of the rebreathing gas mixture.
- Appropriate breathing rate of circa 30 breaths per minute.

If these criteria were not met the measure was discarded and the cause of any error remedied.

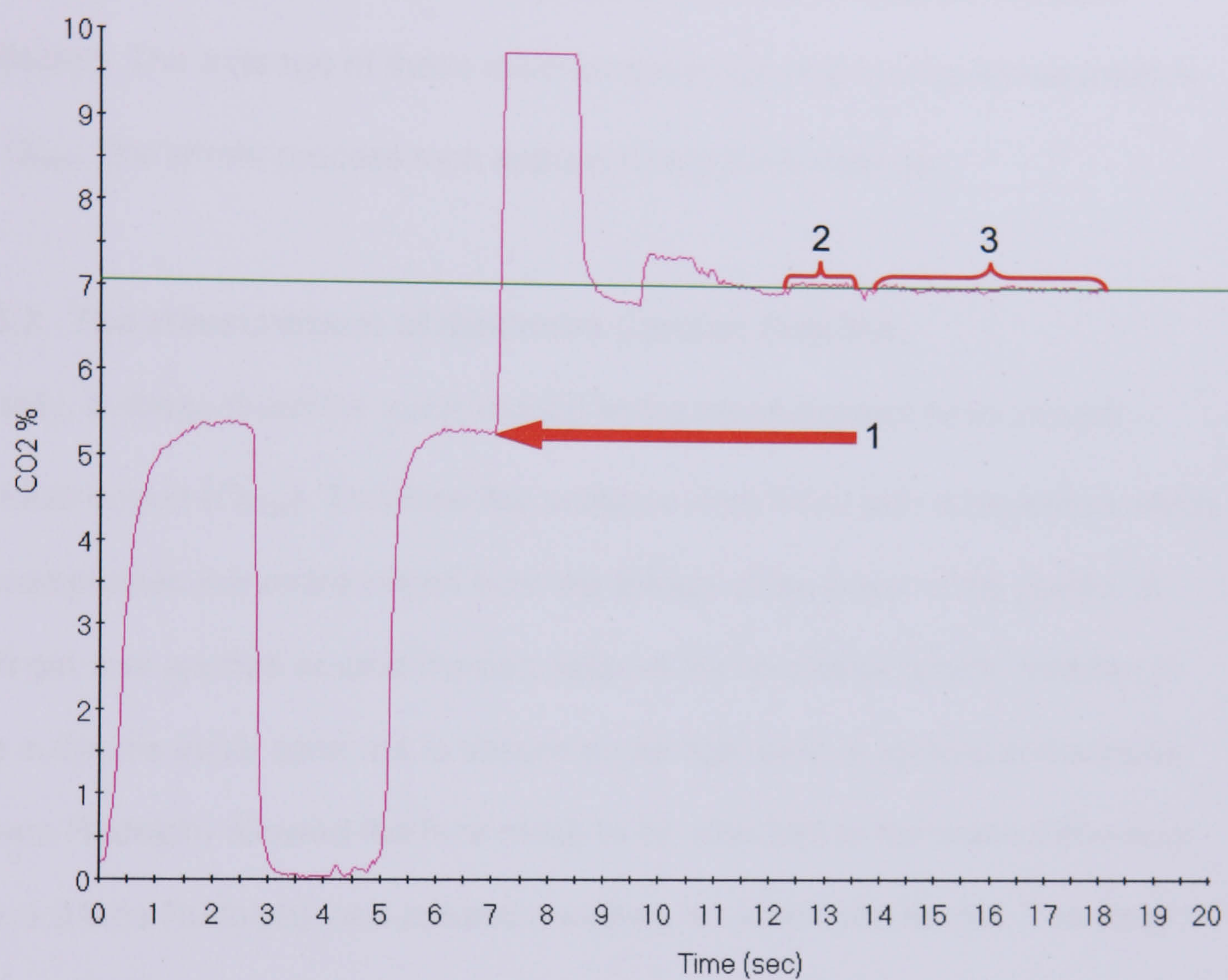


Figure 9 – An example of a satisfactory resting capnograph.

Key

1. Start of rebreathing.
2. Third breath after start of rebreathing.
3. Plateau in the inspired and expired CO₂.

A minimum of three minutes was allowed to pass between each measurement, this ensured that the subject had washed out any residual CO₂ from the previous rebreathing manoeuvre. Once the subjects heart rate and respiratory gases had returned to the predetermined baseline values, the procedure was repeated until at least three accurate measures had been collected. The average of these measures was taken as being representative of \dot{Q}_{rest} . The whole process took approximately thirty minutes.

2.3.3 The Measurement of Maximum Cardiac Function

Finally, in stage three the focus moved to the measurement of maximum cardiac output (\dot{Q}_{max}). This time the subjects were fitted with a facemask which encompassed the entire region from the bridge of the nose to the jawline. A soft gel was applied around the perimeter of the facemask which moulded to the subject's facial contours to ensure an air tight seal. A specialised adaptor (Hans Rudolph) allowed the face mask to be attached to the same three-way valve (Hans Rudolph), and anaesthesia bag, as employed at rest. The weight of the mask and rebreathing valve was now supported by a perspex head gear (Hans Rudolph, Model 2785 Series; Fig. 10). This lightweight structure allowed the subject to exercise freely, without it the weight of the rebreathing valve would have dislodged the facemask during exercise.

Subjects completed a two minute warm-up period, thereafter increments were made in both speed and gradient until the subject once again achieved their $\dot{V}O_{2max}$, as determined during stage one. The frequency and magnitude of the increments was tailored slightly for each subject to ensure that the test lasted an appropriate duration to elicit their maximal oxygen consumption (Myers *et*

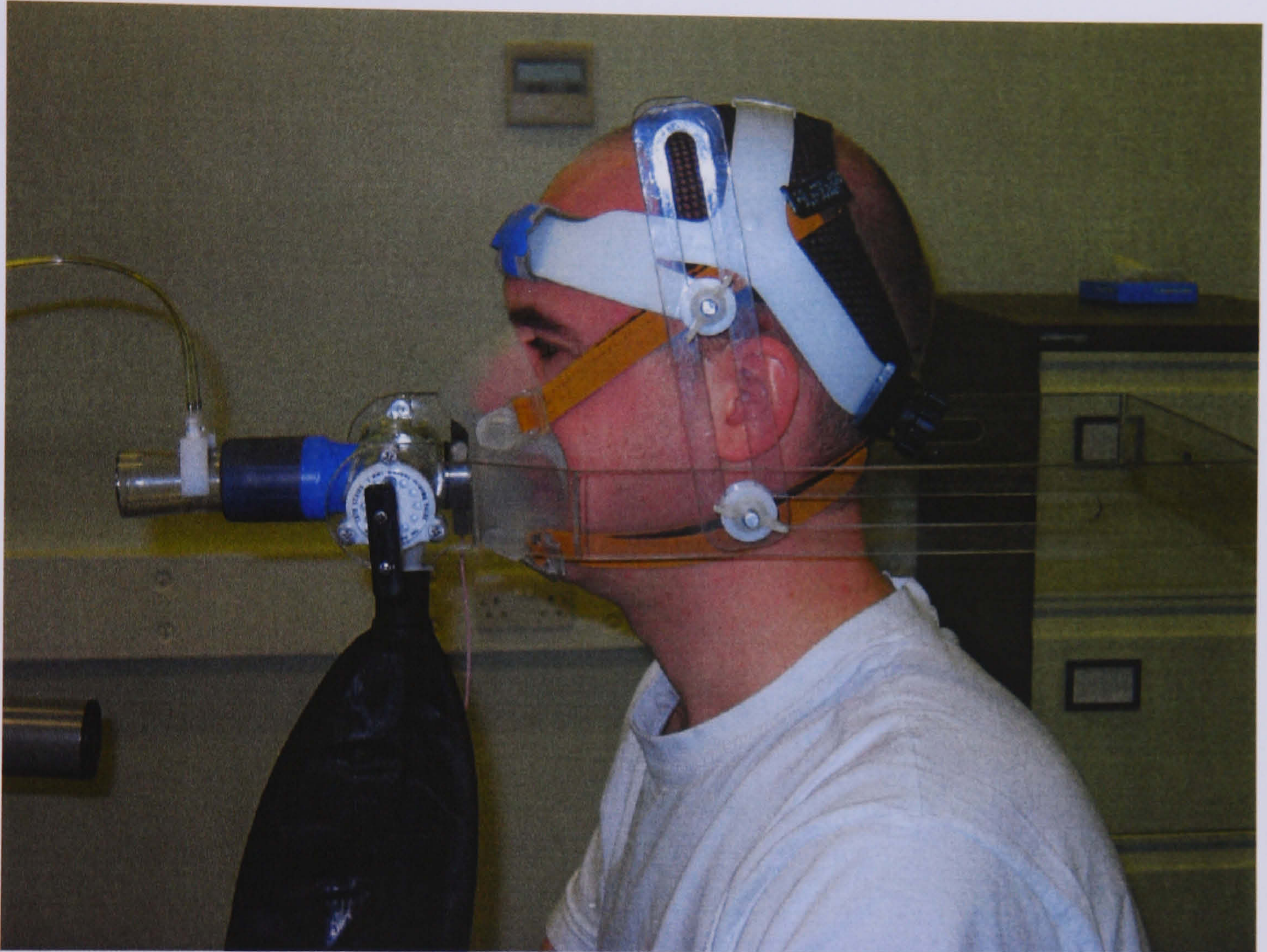


Figure – 10 Headgear used to support the weight of rebreathing valve and bag during exercise.

al., 1991) and cardiac output (McCole *et al.*, 2001).

This time the Defares (1958) exponential method of CO₂ rebreathing was employed to measure maximal cardiac output. This method uses the exponential rise of Pco₂ towards asymptote to calculate \bar{P}_{vco_2} , and the Fick (1870) equation to calculate \dot{Q}_{max} (Fig. 11). The Defares method was chosen because it provides an accurate and reliable measure of \dot{Q}_{max} under conditions of exercise stress (Ferguson *et al.*, 1968). It has proven to be highly reproducible (Cade *et al.*, 2004), and is applicable to individuals of all ages (Beekman *et al.*, 1984). Importantly it causes less distress to the individual at the point of maximal exertion than alternative methods (Jones, 1988).

The rebreathing gas mixture in the anaesthesia bag was 4% CO₂, 35% O₂ and balance N₂ on this occasion, the volume was equal to the subjects maximal V_T as determined during stage one. When the subject achieved their $\dot{V}_{\text{O}_{2\text{max}}}$, the directional valve was manually switched at the end of a respiratory cycle. This ensured that the subject inhaled the full volume of rebreathing gas. The rebreathing manoeuvre took a maximum of ten seconds, during which the subject continued to exercise. The valve was then retracted, and the subject was allowed to breath atmospheric air whilst the exercise intensity was reduced. A minimum of three minutes recovery time was then allowed to ensure the elimination of all the inhaled gases. During this time, subjects were encouraged to continue exercising but at a reduced intensity to facilitate the recovery process. Once the washout process had been completed the process was then repeated. If a discrepancy of more than one litre per minute was

present between the first two measure of \dot{Q}_{\max} the process would be repeated a third time.

A satisfactory maximum capnograph (Fig. 11) clearly illustrates:

- The systematic discarding of the P_{ETCO_2} recorded at the end of the first breath. This is done as there is insufficient time for the adequate mixing of alveolar gas and the mixture from the anaesthesia bag (da Silva *et al.*, 1985)
- A minimum of three respiratory cycles within eight seconds.
- The discarding of any breaths recorded after eight seconds, i.e. after this time recirculation of CO_2 invalidates any measurement (Laszlo, 2004).

The P_{ETCO_2} from the remaining breaths is then analysed using the iterative technique of Heigenhauser *et al.* (1978). This procedure minimizes the variance of the points around the least squares regression line, and plots the \dot{Q}_{\max} after twenty seconds.

2.4 Calculations

Cardiac power output (expressed in Watts) is the only non-invasive method that can be used to test overall cardiac function at rest (CPO_{rest}) and maximal (CPO_{\max}) exertion in humans *in vivo*. It integrates both blood flow and blood pressure, and is calculated from the equation described by Cooke *et al.* (1998),

$$CPO = (\dot{Q} \times MAP) \times K,$$

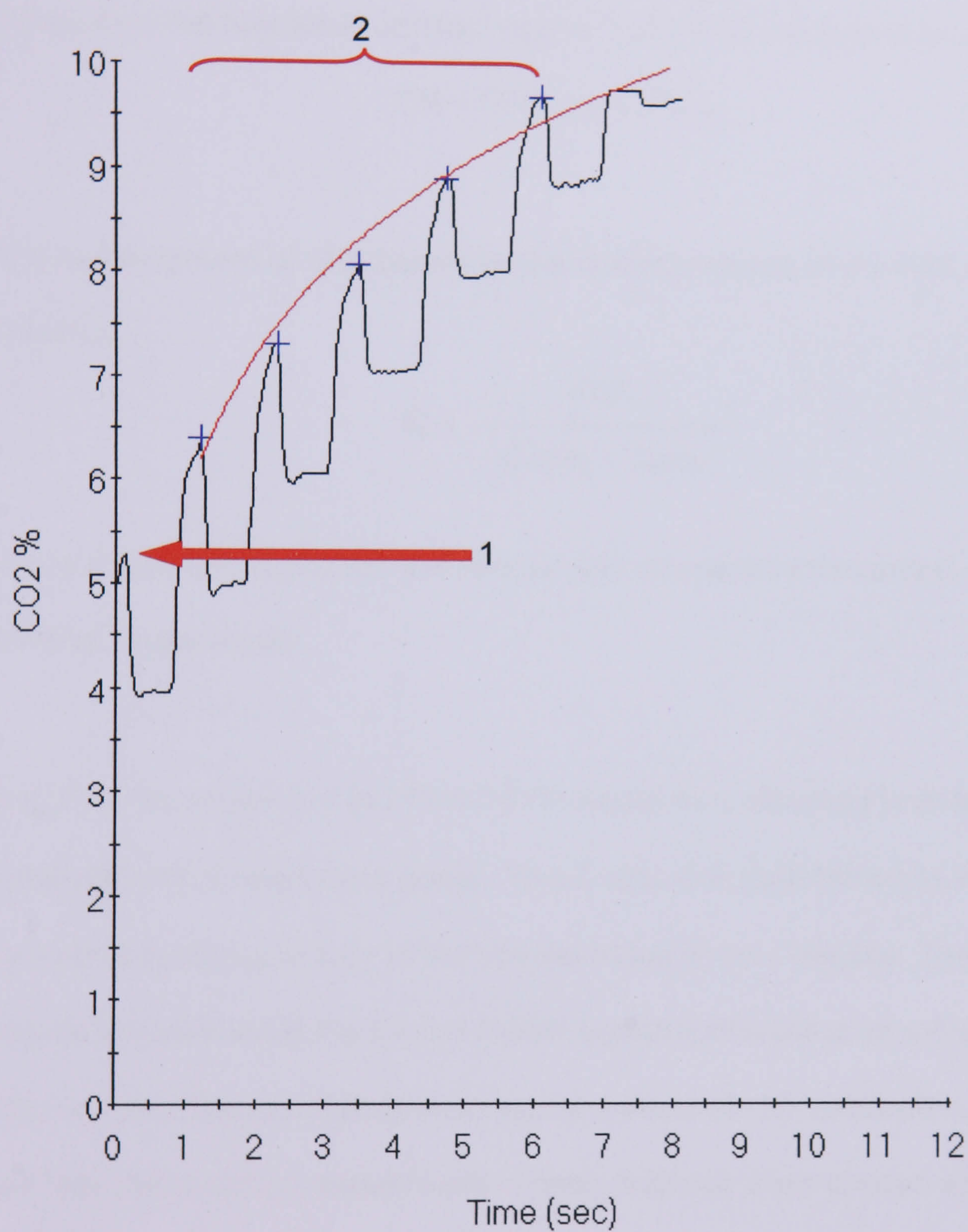


Figure 11 – An example of a satisfactory maximum capnograph.

Key

1. Discarded P_{ETCO_2} recorded at the end of the first breath.
2. Respiratory cycles occurring within eight seconds.

where \dot{Q} is cardiac output (l/min), MAP is mean arterial pressure (mmHg), and K the constant conversion factor (2.22×10^{-3}) into watts.

When CPO has been measured at rest and at maximal exertion it is possible to calculate the functional cardiac reserve (CR) from the following equation,

$$CR = CPO_{\max} - CPO_{\text{rest}}.$$

The measurement of \dot{Q} is based on the indirect version of the Fick (1870) equation,

$$\dot{Q} = \frac{\dot{V}_{\text{CO}_2}}{C_{\bar{v}\text{CO}_2} - C_{a\text{CO}_2}}$$

where $C_{\bar{v}\text{CO}_2}$ and $C_{a\text{CO}_2}$ are the venous and arterial concentrations of CO_2 (mmHg), respectively.

The \dot{V}_{CO_2} component of the Fick (1870) equation is obtained from the measurement of respiratory gases. The $C_{\bar{v}\text{CO}_2}$ was determined by measuring the partial pressure of CO_2 in the venous blood ($P_{\bar{v}\text{CO}_2}$ mmHg). The $P_{\bar{v}\text{CO}_2}$ was determined using the Collier (1956) equilibrium method of rebreathing CO_2 , and the Defares (1958) exponential method of CO_2 rebreathing at rest and maximal exertion, respectively. These methods were chosen as they minimise the effect of ventilation heterogeneity, and required less subject co-operation than alternative non-invasive rebreathing techniques (Barazanji *et al.*, 1996).

The C_{aCO_2} was derived from the partial pressure of CO_2 in the arterial blood. This was estimated from the end-tidal P_{CO_2} (P_{ETCO_2}), assuming normal lung function using the equation of Jones (1988),

$$P_{aCO_2} = 5.5 + 0.90 P_{ETCO_2} - 0.0021 V_T,$$

where V_T is tidal volume (ml BTPS), and P_{ETCO_2} is the average of the last 30 seconds measured from the expired gases prior to performing the rebreathing manoeuvre.

When converting partial pressures to content, two assumptions are made.

First the haemoglobin concentration is 15 g/100ml, and second that the arterial oxygen saturation is greater than 95% during rebreathing (Jones, 1988).

To ensure an accurate measure of \bar{P}_{vCO_2} from the equilibrium of P_{CO_2} , Jones (1988) recommends the use of a “downstream correction” factor. This accounts for the lung-to-artery circulation time (Jones *et al.*, 1969), and was integrated within the *BREEZEX*TM software as follows:

$$\bar{P}_{vCO_2} \text{ (mm Hg)} = P_{eqCO_2} - (0.24 \times P_{eqCO_2} - 11)$$

where P_{eqCO_2} is the equilibrium P_{CO_2} before correction.

Both the Fick (1870) equation and the Jones (1988) conversion equations were incorporated in the CPX/D system. The system also has the capability to perform both Collier (1956) and Defares (1958) manoeuvres for CO_2 rebreathing, and integrating the measures with the continuous respiratory gas analysis and ECG.

Mean arterial pressure is used in the calculation of CPO because it represents the average pressure throughout the entire cardiac cycle. It is calculated using the equation of Meaney *et al.* (2000),

$$\text{MAP} = \text{DBP} + 0.412 (\text{SBP} - \text{DBP}),$$

where SBP is systolic and DBP diastolic blood pressure, measured in mmHg.

In 1846 Poiseuille described the factors which govern pulsatile flow (Smith and Kampine, 1990). By transposing Poiseuille's original equation an equation for calculating systemic vascular resistance (SVR) was derived,

$$\text{SVR} = (80 \times \text{MAP}) / \dot{Q},$$

where MAP is mean arterial pressure in mmHg, \dot{Q} is cardiac output in l/min, and 80 is the conversion factor to dynes/sec/cm⁵.

Finally, after measuring \dot{Q} and $\dot{V}\text{O}_2$ it is possible to rearrange the Fick equation, and calculate arteriovenous oxygen difference ($a - \bar{v}\text{O}_2$ diff),

$$a - \bar{v}\text{O}_2 \text{ diff} = \frac{\dot{V}\text{O}_2}{\dot{Q}},$$

where $\dot{V}\text{O}_2$ is oxygen consumption measured in ml/min, and \dot{Q} is cardiac output in l/min, the resultant $a - \bar{v}\text{O}_2$ diff is millilitres of oxygen per litre of blood (ml/l).

2.5 Scaling

It has been established that body size significantly affects some aspects of cardiac function (Collis *et al.*, 2001). Therefore, to accurately allow direct comparisons of cardiac function between different groups (e.g. male versus

female, athletic versus sedentary) the effects of body size must be allowed for. The most appropriate way is to implement a curvilinear allometric scaling technique (Batterham *et al.*, 1999).

First a Pearson's product correlation is conducted to establish measure of body dimension (e.g. height, weight, BMI etc) has the strongest impact on the measurement of cardiac function. The two variables are then transformed using natural logarithms (base ε) to account for any deviations from a linear relationship.

The basic linear relationship equation is,

$$y = a + bx + \varepsilon,$$

where b is the gradient of the line of best fit, a the y-axis intercept, and ε the additive residual error.

The allometric equation is,

$$y = a x^b \varepsilon,$$

where y is the value of physiological interest (e.g. cardiac output), x is the measure of body dimension (e.g. weight), a is the proportional coefficient, and b is the power function.

This allometric equation can be logarithmically transformed and the data can then be entered into the following equation:

$$\log y = \log a + x \log b + \log \varepsilon$$

The equation is then solved and the b exponent derived by removing the interaction term. If the relationship between the physiological variable and the measure of body dimension were perfectly linear then $b = 1.0$. The physiological variable is then powered to the derived b exponent and becomes a measurement that is independent of body size.

Once any two populations of interest have been analysed the resultant cardiac measurement can then be plotted over the range of ages. If two populations are plotted alongside each other, significant differences in the slope of the regression lines can be sought, and any residual differences will be the result of ageing, and are not confounded by differences in body size.

2.6 Statistical Analysis

The male and female sedentary subjects were independently separated into decade age groups, 20 – 29, 30 – 39 years etc. The American College of Sports Medicine (2000) publishes percentiles for the $\dot{V}O_{2\max}$ for each group, and categorizes fitness accordingly. Rather than arbitrarily applying these criteria to our population, percentiles were calculated based on the data that was collected. Any individual who achieved a $\dot{V}O_{2\max}$ in the top twenty-five percent, when compared to their age-matched peers, was excluded from further analysis. This ensured that when the affects of healthy ageing were the focus, only healthy sedentary subjects were included in the analysis.

The normality of the distribution of the data was initially tested using Kolmogorov-Smirnov test. Thereafter, normally distributed data was then analysed using parametric tests.

To compare data between specified groups one-way and multi-way analysis of variance (ANOVA) was employed. When using a one-way ANOVA, a Tukey HSD *post-hoc* test was used to identify significant differences. Where a multi-way ANOVA was employed, Bonferroni's *post-hoc* test was used.

Pearson's product-moment correlation coefficient was used to test for relationships between variables. Where a relationship was confirmed, linear regression analysis was used to measure the change in the dependent variable per unit change in the independent variable. On graphs the r values and the equations from which they are derived are presented. In the caption the F ratio is given, with the associated degrees of freedom and level of significance.

Linear regression was also employed to test for differences in relationships. Where more than one dependent variable was measured using the same units (i.e. resting and maximal cardiac output), the variables are plotted against a single independent variable (e.g. age). A linear line of best fit was then applied to each data set. If the r values are significant, and there is no overlap in the confidence intervals associated with each regression line, it was concluded that the slopes of the lines, and consequently the relationships, are significantly different.

The level of statistical significance was arbitrarily set at $P < 0.05$, but where a stronger significant difference was found the resulting P value is shown.

Chapter 3

Results

Validity and Reliability of the
Equipment and Techniques

3.0 Preliminary Studies

Before beginning the collection of data to measure the physiological impacts of ageing, exercise, and heart failure three preliminary studies were conducted.

These studies were designed to test the validity and reliability of the equipment, and the reproducibility of the proposed techniques to be used throughout these large projects.

3.1 The Reproducibility of Measurements of Aerobic Power and Cardiac Function

To conduct a cross-sectional study and accurately examine changes in any given physiological function it is critical that the measurements made are not subject to excessive variation that might lead to inaccurate conclusions being drawn. Previous research has reported intra-individual day-to-day variations in the measurement of $\dot{V}O_2$ by automated gas analysis systems. These variations range from 3% (Miles *et al.*, 1994) to as high as 12% (Versteeg and Kippersluis, 1989). Macfarlane (2001) highlighted the importance of recognising that such variations include both biological and technical variability.

Twenty-five subjects (seventeen males, and seven females) were recruited to test the variability within the chosen measurement techniques. They represented a broad cross-section of the subjects to be tested in the principle projects, e.g. the effects of healthy ageing and long-term endurance exercise. All were aged between twenty-three and sixty-nine years, and ranged from healthy sedentary individuals to elite veteran athletes. The subjects completed

stage one of the protocol to measure $\dot{V}O_{2\max}$ (see Methods section 2.3.1). Stages two and three to measure CPO_{rest} (see Methods section 2.3.2) and CPO_{\max} (see Methods section 2.3.3) were repeated on two occasions, separated by a minimum of seven days.

The coefficients of variation for the measurements of $\dot{V}O_2$, CPO and \dot{Q} , both at rest and during maximal exercise, are shown in Table 2.

The total day-to-day and subject-to-subject variability in the measurements of $\dot{V}O_2$, CPO, and \dot{Q} were all less than five percent both at rest and at maximal exercise. These are significantly less than the commonly accepted level of 10% total variation. They also signify that the chosen techniques were highly reproducible. Consequently, any recorded differences greater than these variations could confidently be attributed to significant changes in physiological mechanisms.

3.2 The Impact of Recovery Time between Repeated Bouts of Maximal Exercise

Once the validation of the equipment had been completed, the focus moved to the design of the protocol. This protocol was originally devised for measuring cardiac performance in heart failure patients where it was necessary to complete all the measurements i.e. $\dot{V}O_{2\max}$, CPO_{rest} and CPO_{\max} , in a single visit to the hospital laboratory. This necessitated a recovery period of only thirty minutes between the bouts of exhaustive exercise. Although the measurements of blood pressure returned to baseline values within this time

	Coefficient of Variability (%)
Resting Measures	
Oxygen Consumption	2.46
Cardiac Power Output	4.46
Cardiac Output	4.15
Maximal Measures	
Oxygen Consumption	3.47
Cardiac Power Output	2.20
Cardiac Output	2.33

Table 2 – The coefficients of variability in resting and maximal measurements of aerobic power and cardiac function.

interval changes in other factors such as respiratory gases, which could conceivably affect the measurement of CPO, were not measured.

Previous research has concluded that successive bouts of heavy aerobic exercise causes hypoxaemia and disturbs the exchange of pulmonary gases for at least thirty minutes after the cessation of exercise (Caillaud *et al.*, 1996). Although a prior bout of heavy exercise has no effect on $\dot{V}O_2$ kinetics, it is associated with a suppression of the $\dot{V}O_2$ slow component and $\dot{V}CO_2$ (Burnley *et al.*, 2000). The impact of an acute prior bout of heavy exercise on overall cardiac function is not known. If the impact is not significant, then it would be preferable from a purely practical standpoint to continue completing all stages of the testing protocol in a one visit to the laboratory. If a significant impact does occur then an appropriate recovery time will need to be incorporated into the protocol.

To examine the effects of different recovery periods on the measurements of respiratory gases, haemodynamics and CPO, thirteen male subjects with a mean age of 21.8 ± 0.7 years were recruited. First CPO_{rest} was measured, this was followed by the standard $\dot{V}O_{2max}$ test. The measurement of CPO_{max} was then conducted twice, first after a thirty minute recovery period, then again after a twenty-four hour recovery period.

Resting CPO for this group of males was 1.26 ± 0.1 Watts. The values for the respiratory gases analysed during the three bouts of maximal exercise are presented in Table 3. All of the gas values measured after the thirty minute recovery period were significantly suppressed, with the exception of $P_{ETCO_{2max}}$.

	$\dot{V}O_{2\max}$ Test	Recovery Time	
		30 minutes	24 Hours
$\dot{V}O_{2\max}$ (l/min)	4.1 ± 0.2	3.9 ± 0.2 *	4.0 ± 0.2
$\dot{V}O_{2\max}$ (ml/kg/min)	52.8 ± 2.5	49.5 ± 2.0 *	51.4 ± 2.6
$\dot{V}CO_{2\max}$ (l/min)	4.9 ± 0.2	3.9 ± 0.2 *	4.3 ± 0.2 *†
RER_{\max}	1.2 ± 0.03	1.0 ± 0.02 *	1.1 ± 0.02 *
$V_{T\max}$ (l/min)	2.9 ± 0.1	2.4 ± 0.1 *	2.6 ± 0.1
$P_{ETCO_{2\max}}$	38.0 ± 1.0	35.4 ± 1.1	37.2 ± 1.2

Table 3 – Respiratory gas values during three maximal exercise tests, with different length of recovery intervals.

Data are presented as means \pm standard error of the mean.

Significant differences between the values were tested using an ANOVA with repeated measures and Bonferroni *post-hoc* test, where appropriate.

* $P < 0.05$ significant difference when compared to initial $\dot{V}O_{2\max}$ test.
† $P < 0.05$ significant difference when compared to the test conducted after a thirty minute recovery period.

This illustrates that a thirty minute rest period is insufficient to accurately measure aerobic power after a previous acute bout of heavy aerobic exercise.

However, following a twenty-four recovery period there were no significant difference in $\dot{V}O_{2\max}$, $V_{T\max}$, or $P_{ETCO_{2\max}}$, when compared to the initial test.

Although a significant suppression in $\dot{V}CO_{2\max}$ remained in comparison to the first $\dot{V}O_{2\max}$ test, this difference was reduced as a consequence of the prolonged recovery period.

When maximal overall cardiac function was measured, there were no significant differences irrespective of the rest period between the bouts of maximal exercise (Table 4). This was also true of the individual components of blood flow (i.e. SV_{\max} and HR_{\max}) and blood pressure (SBP_{\max} and DBP_{\max} ; Table 4).

The overall trend for higher values to be attained following a twenty-four hour recovery period after an acute bout of maximal exercise, coupled with the feedback from the subjects who found completing two bouts of maximal exercise in close succession particularly difficult, convinced us of the merits of a prolonged recovery period. Therefore, a minimum twenty-four hour recovery period was integrated between stages one ($\dot{V}O_{2\max}$ test) and three (the measurement of CPO_{\max}). We believe this improves the original protocol, which was designed for diagnosing heart failure.

	$\dot{V}O_{2\max}$ Test	Recovery Time	
		30 minutes	24 Hours
CPO_{\max} (Watts)		6.0 ± 0.3	6.2 ± 0.3
\dot{Q}_{\max} (l/min)		23.6 ± 0.9	24.9 ± 1.0
SV_{\max} (ml/beat)		123.3 ± 4.5	131.1 ± 5.4
HR_{\max} (bpm)	188.2 ± 2.4	191.9 ± 2.8	190.2 ± 2.6
MAP_{\max} (mmHg)	113.2 ± 2.4	111.9 ± 2.3	112.2 ± 2.3
SBP_{\max} (mmHg)	197.1 ± 6.7	197.2 ± 6.2	198 ± 5.9
DBP_{\max} (mmHg)	52.1 ± 2.6	52.2 ± 2.8	52.2 ± 2.8
CR (Watts)		4.7 ± 0.2	5.0 ± 0.3

Table 4 – Measures of overall cardiac function, blood flow and blood pressure generation during three maximal exercise tests, with different length of recovery interval.

Data are presented as means \pm standard error of the mean.

Significant differences between the values were tested using an ANOVA, with repeated measures where appropriate.

There were no statistically significant differences between any of the measures when compared to the initial $\dot{V}O_{2\max}$ test, or as a result of different recovery periods between the bouts of acute exercise.

3.3 The Possible Effects of Circadian Rhythms on Cardiac Power Output

The variations that occur over twenty-four hours in circadian rhythm are known to be reflected by changes in core body temperature, the peak occurring at 16:30, and the lowest point at 04:30 (Reilly *et al.*, 1997). Previous research has suggested that variations include changes in resting cardiac output (Cugini *et al.*, 1991), heart rate (Reilly *et al.*, 1984) and diastolic blood pressure (Deschenes *et al.*, 1998). It has also been suggested that these variations persist following bouts of intense and exhaustive exercise (Cabri *et al.*, 1988). Similarly a time-related variation in the occurrence of cardiovascular events that require clinical interventions has been established (Muller, 1999).

Such time of day variations in \dot{Q} and blood pressure could conceivably affect measurements of CPO, because they are integral components of overall cardiac function. However, the previously reported changes were measured either at rest, or following bouts of exercise, and the variables were not measured at maximal exertion. Therefore, it was important to establish if circadian rhythms have a significant effect on both CPO_{rest} and CPO_{max} . If a significant impact of time of day occurs then it will be necessary to remove any confounding effects by standardising the time at which tests are conducted on each individual.

Ten male subjects, with a mean age of 21.5 ± 1.2 years, were recruited to determine if circadian rhythms effected the measurement of CPO. Stage one of the standard protocol was initially conducted to measure $\dot{V}O_{2max}$. Following a break of a week the subjects returned to perform stages two and three, i.e.

to measure CPO_{rest} and CPO_{max} at two different times of day. The first of these tests was performed at 04:30, and the second at 16:30. These times were selected to reflect the trough and peak of circadian rhythm. The order in which the tests were performed was randomly assigned to the subjects, and the appointments were separated by a minimum of forty-eight hours.

The measurements of CPO were made following the standard protocol with one minor addition. Rectal probes were used to record the core body temperature as this is known to reflect circadian variations.

Indeed core temperature was $37.0^{\circ}\text{C} \pm 0.01$ and $37.5^{\circ}\text{C} \pm 0.01$ in the morning and afternoon respectively; the difference between these values was highly significant ($P < 0.01$). This difference of approximately 0.5°C remained following a bout of maximal exercise, i.e. $37.5^{\circ}\text{C} \pm 0.1$ in the morning compared to $37.9^{\circ}\text{C} \pm 0.01$ in the afternoon ($P < 0.01$).

Maximal aerobic power was unaffected by the time of day at which it was measured. This is clearly illustrated by the lack of any significant differences when comparing the mean $\dot{V}O_{2max}$ attained at 04:30 (i.e. 41.6 ± 3.5 ml/kg/min) and 16:30 (i.e. 44.9 ± 1.7 ml/kg/min). In addition, neither of these values differed significantly from the $\dot{V}O_{2max}$ measured a week earlier (i.e. 45.0 ± 1 ml/kg/min).

Despite the significant differences in core body temperature which confirmed the impact of a circadian rhythm, no significant differences were found in any

of the measures of cardiac function. A lack of change was evident in both the resting and maximal measures (Table 5).

None of the measures were close to approaching significance levels shown by the high *P* values in Table 5. These results indicate that CPO was not affected by circadian rhythms, and could therefore be measured with confidence at any time of day. This has obvious practical implications, especially given the large number of subjects involved in the forthcoming studies investigating the effects of healthy ageing, exercise training and heart failure on overall cardiac function.

	Time Of Day		
	04:30	16:30	<i>P</i> value
Cardiac Power Output (Watts)			
Resting	0.97 ± 0.1	1.1 ± 0.0	0.24
Maximum	5.6 ± 0.5	5.8 ± 0.3	0.73
Cardiac Output (l/min)			
Resting	4.7 ± 0.3	5.6 ± 0.3	0.52
Maximum	22.8 ± 1.1	22.9 ± 1.0	0.94
Heart Rate (bpm)			
Resting	62.8 ± 2.9	67.2 ± 3.2	0.31
Maximum	185.6 ± 2.3	189.8 ± 2.7	0.25
Stroke Volume (ml/beat)			
Resting	76.4 ± 5.6	84.2 ± 3.5	0.26
Maximum	123.3 ± 6.5	121.2 ± 5.9	0.81
Mean Arterial Pressure (mmHg)			
Resting	91.4 ± 2.9	88.5 ± 1.8	0.40
Maximum	113.7 ± 3.0	113.3 ± 2.9	0.92
Systolic Blood Pressure (mmHg)			
Resting	116.1 ± 3.8	117.9 ± 2.3	0.70
Maximum	194.7 ± 5.4	194.6 ± 5.2	1.00
Diastolic Blood Pressure (mmHg)			
Resting	74.1 ± 2.8	67.9 ± 2.7	0.13
Maximum	57.1 ± 2.7	56.4 ± 2.3	0.86
Cardiac Reserve (Watts)	4.6 ± 0.5	4.7 ± 0.3	0.88

Table 5 – Measurement of CPO, blood flow and blood pressure at rest and maximal exercise in the morning and afternoon.

Data are presented as means ± standard error of the mean.

There were no statistically significant differences in any of the physiological variables as a result of the time of day, as determined by the two extreme times of 04:30 and 16:30.

Chapter 4

Results

The Effects of Healthy Ageing on
Aerobic and Cardiac function in Men

4.0 The Effects of Healthy Ageing on Cardiac Power Output in Sedentary Men

After completing the questionnaire (App. 1), stress test and screening process, sixty-nine healthy sedentary males, ranging in age from nineteen to seventy-six years were included in the subsequent analysis, investigating the impact of healthy ageing on overall cardiac function.

4.1 Changes in Body Mass and Aerobic Function in Sedentary Men

Total body mass (TBM), body mass index (BMI) and body surface area (BSA) were 82.0 ± 1.3 kg, 26.4 ± 0.4 kg/m² and 2.0 ± 0.0 m² respectively. There were no significant changes ($P > 0.1$) in any of these measures in men over the course of healthy ageing.

Resting oxygen consumption ($\dot{V}O_{2\text{rest}}$) showed a significant ($P < 0.01$) linear decrease in over this age range. This decrease was equivalent to 16% in both absolute (Fig. 12a), and relative terms (Fig. 12b) after normalisation for total body mass.

Maximal aerobic power showed a much stronger correlation, and a greater decrease as a consequence of healthy ageing than $\dot{V}O_{2\text{rest}}$. In absolute terms $\dot{V}O_{2\text{max}}$ declined significantly ($P < 0.0001$) by 1834 ml/min (49%) over the fifty-seven years studied (Fig. 12a). Neither the rate of decline, nor the strength of the correlation changed if this measure was reported relative to total body mass (Fig. 12b).

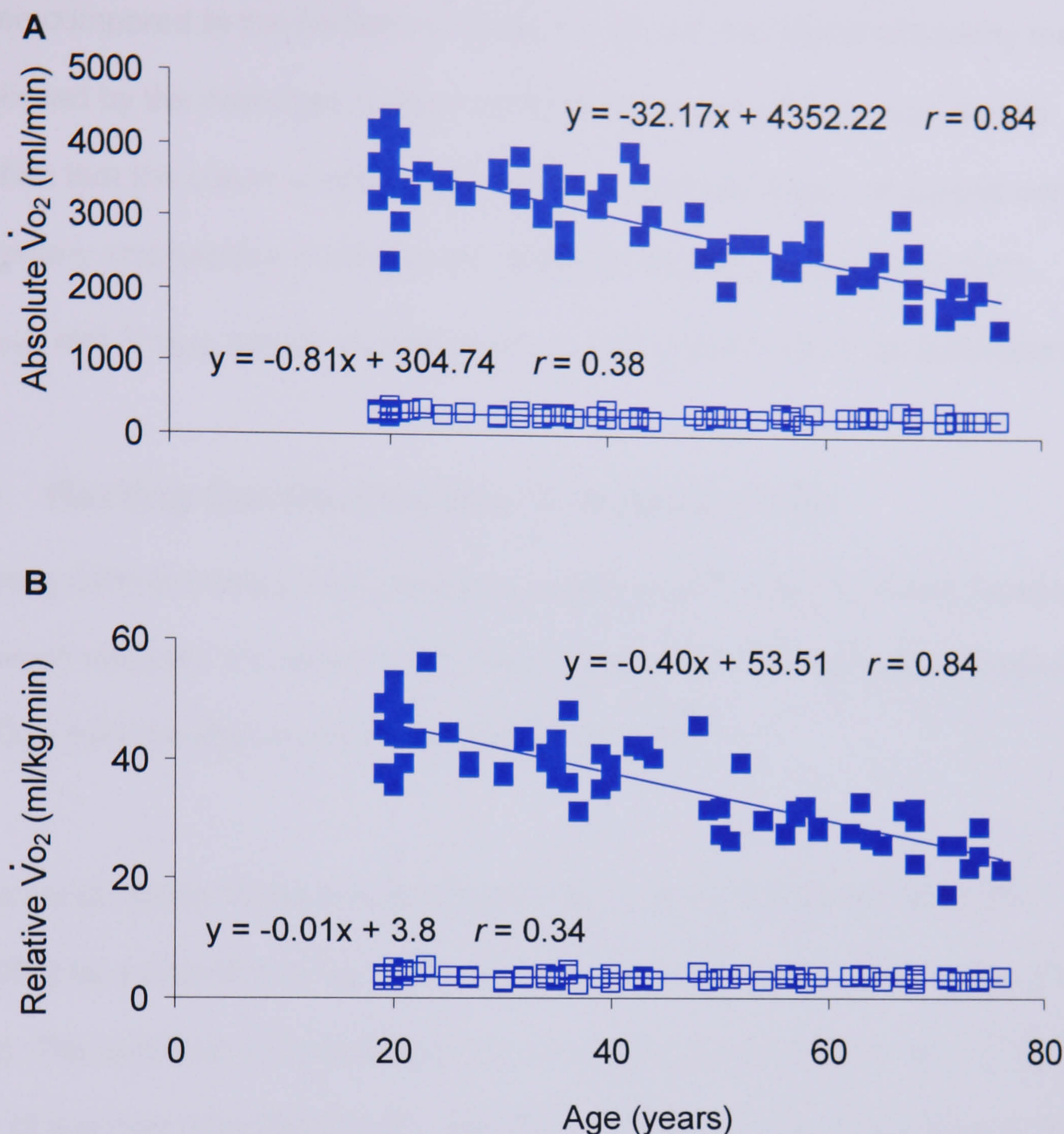


Figure 12 – Changes in aerobic function in men as a consequence of healthy ageing.

Resting $\dot{V}O_2$ (□) expressed in (A) absolute terms ($F(1, 67) = 11.1$, $P < 0.001$), and (B) relative to total body mass ($F(1, 67) = 8.5$, $P < 0.01$) were both significantly correlated to age.

Maximum $\dot{V}O_2$ (■) expressed in (A) absolute terms ($F(1, 67) = 163.4$, $P < 0.0001$), and (B) relative to total body mass ($F(1, 67) = 162.4$, $P < 0.0001$) were also significantly correlated to age.

The strength of the correlation and the rate of decrease were both significantly greater in the maximum measures, as opposed to the resting measures.

When compared to the normative values for the aerobic power of healthy men published by the American College of Sports Medicine (2000) these results confirm that the cohort used in this study to assess the impact of ageing were sedentary and healthy. Furthermore, given the significant declines in both $\dot{V}O_{2\text{rest}}$ and $\dot{V}O_{2\text{max}}$ similar decreases in cardiac function would be anticipated.

4.2 Resting Cardiac Function in Sedentary Men

Resting CPO in healthy men showed a significant ($P < 0.0001$) linear decline between nineteen and seventy-six years of age (Fig. 13). The total decrease in CPO_{rest} over the fifty-seven years studied was 27%.

In terms of resting blood flow generation, \dot{Q}_{rest} decreased significantly ($P < 0.0001$) by a total of 41% between nineteen and seventy-six years of age (Fig. 14a). The decrease in resting stroke volume was also significant ($P < 0.0001$), and of a similar magnitude (38%; Fig 14b). The mean resting heart rate for the entire group was 68 ± 1.3 bpm, and did not change significantly ($P > 0.07$; Fig. 14c). Therefore, it appears that the reduced resting stroke volume was solely responsible for the decrease measured in cardiac output.

The changes in resting blood pressure generation measured over the course of healthy ageing were in the opposite direction to the changes that were measured in blood flow generation. There were significant 10% increases in MAP_{rest} ($P < 0.01$), SBP_{rest} ($P < 0.001$) and DBP_{rest} ($P < 0.05$) between nineteen and seventy-six years of age (Fig. 15).

Resting systemic vascular resistance (SVR_{rest}) also increased significantly

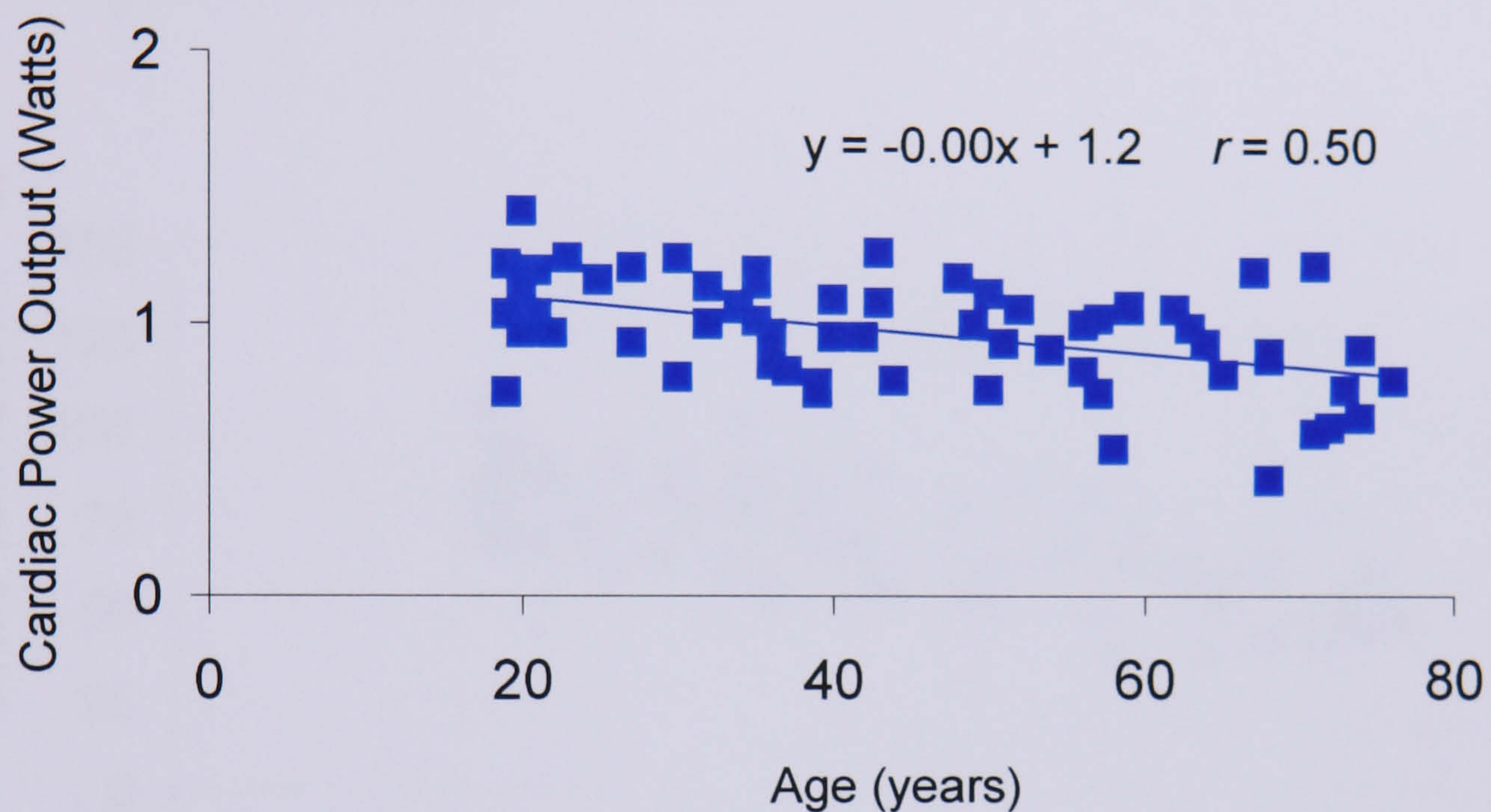


Figure 13 – The effect of healthy ageing on resting overall cardiac function in men.

Resting cardiac power output showed a significant ($F(1, 67) = 22.0, P < 0.0001$) linear correlation to healthy ageing between nineteen and seventy-six years of age.

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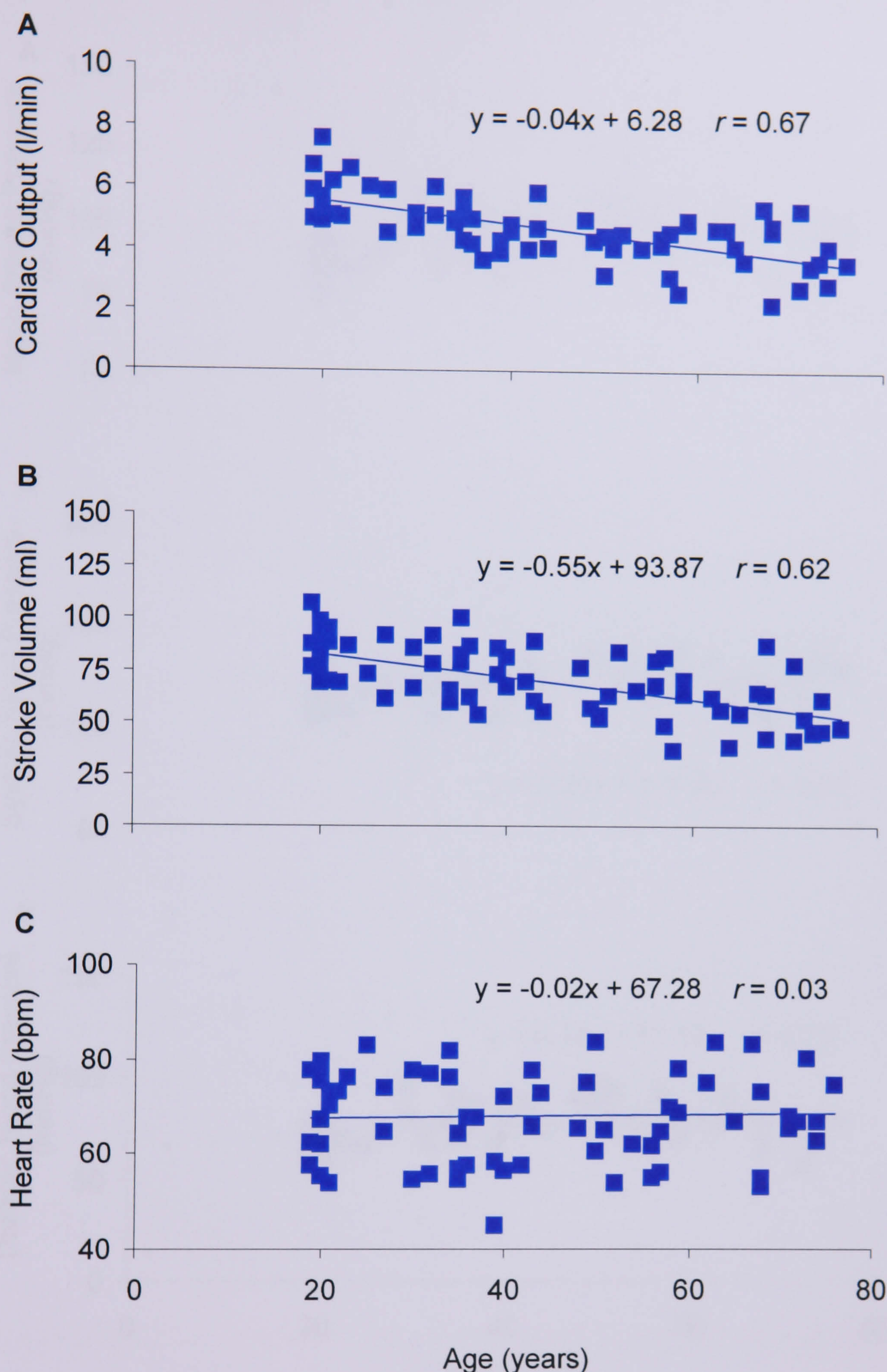


Figure 14 – The effects of healthy ageing on resting blood flow generation in men.

Resting cardiac output (A) ($F(1, 67) = 54.4, P < 0.0001$), and stroke volume (B) ($F(1, 67) = 41.9, P < 0.0001$) both decreased significantly while resting heart rate (C) ($F(1, 67) = 0.1, P > 0.7$) showed no significant change as a consequences of healthy ageing in men.

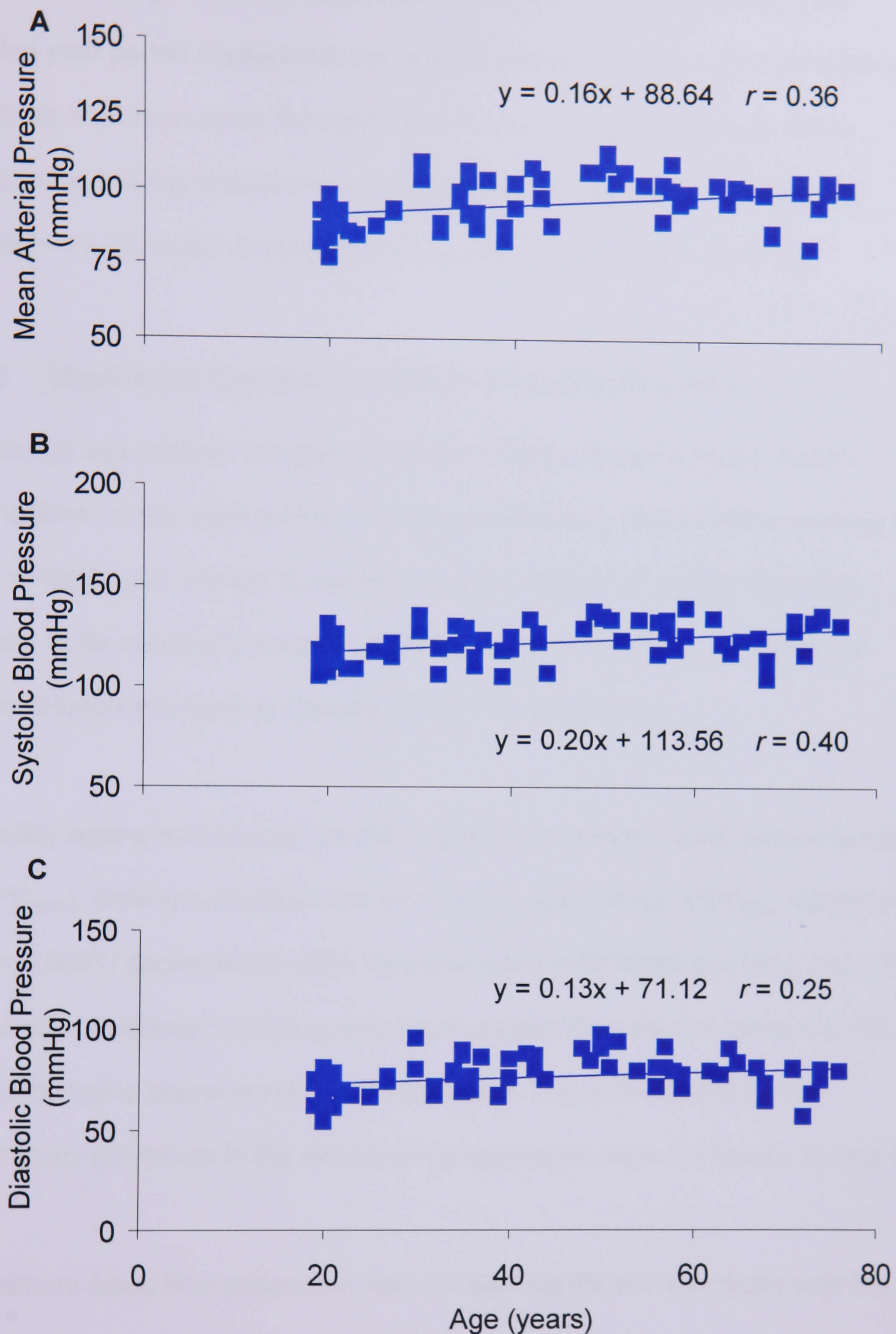


Figure 15 – The effects of healthy ageing on resting blood pressure generation in men.

Resting mean arterial (A) ($F(1, 67) = 9.8, P < 0.01$), systolic (B) ($F(1, 67) = 12.4, P < 0.001$) and diastolic (C) ($F(1, 67) = 4.6, P < 0.05$) blood pressures all increased significantly with healthy ageing.

($P < 0.0001$; Fig. 16). The magnitude of the increase (74%) over the fifty-seven year period studied was the biggest increase in any of the variables at rest. As SVR represents the resistance to blood flow within the systemic circulation this big increase as a consequence of healthy ageing helps to explain the decrease measured in SV_{rest} and the increase in MAP_{rest} .

4.3 Maximum Cardiac Function in Sedentary Men

Although age-related changes occurred in cardiac function under resting conditions, these represent small changes relative to the functional reserve of the normal heart. Hence, to establish the true affects of ageing, the heart needs to be maximally stressed, thereby enabling the impact of ageing on overall functional reserve capacity (CR) to be established.

Healthy ageing had a much greater impact on maximal overall cardiac function (CPO_{max}). Between nineteen and seventy-six years of age CPO_{max} significantly ($P < 0.0001$) decreased by 20% (approximately 0.02 Watts per year; Fig. 17). This rate of decline in CPO_{max} was much greater than the decrease in CPO_{rest} over the same period in the same individuals. This is illustrated by the significant difference in the slopes of the regression lines in Figures 13 and 17.

Maximum blood flow generation also showed significant reductions over the age range studied. Maximum \dot{Q} (Fig. 18a) decreased by 32% ($P < 0.0001$). This decrease of 0.13 l/min/year was considerably greater than the decrease of 0.04 l/min/year in \dot{Q}_{rest} (Fig. 14a), and was the result of significant ($P < 0.05$) age-related reductions in both SV_{max} (Fig. 18b) and HR_{max} .

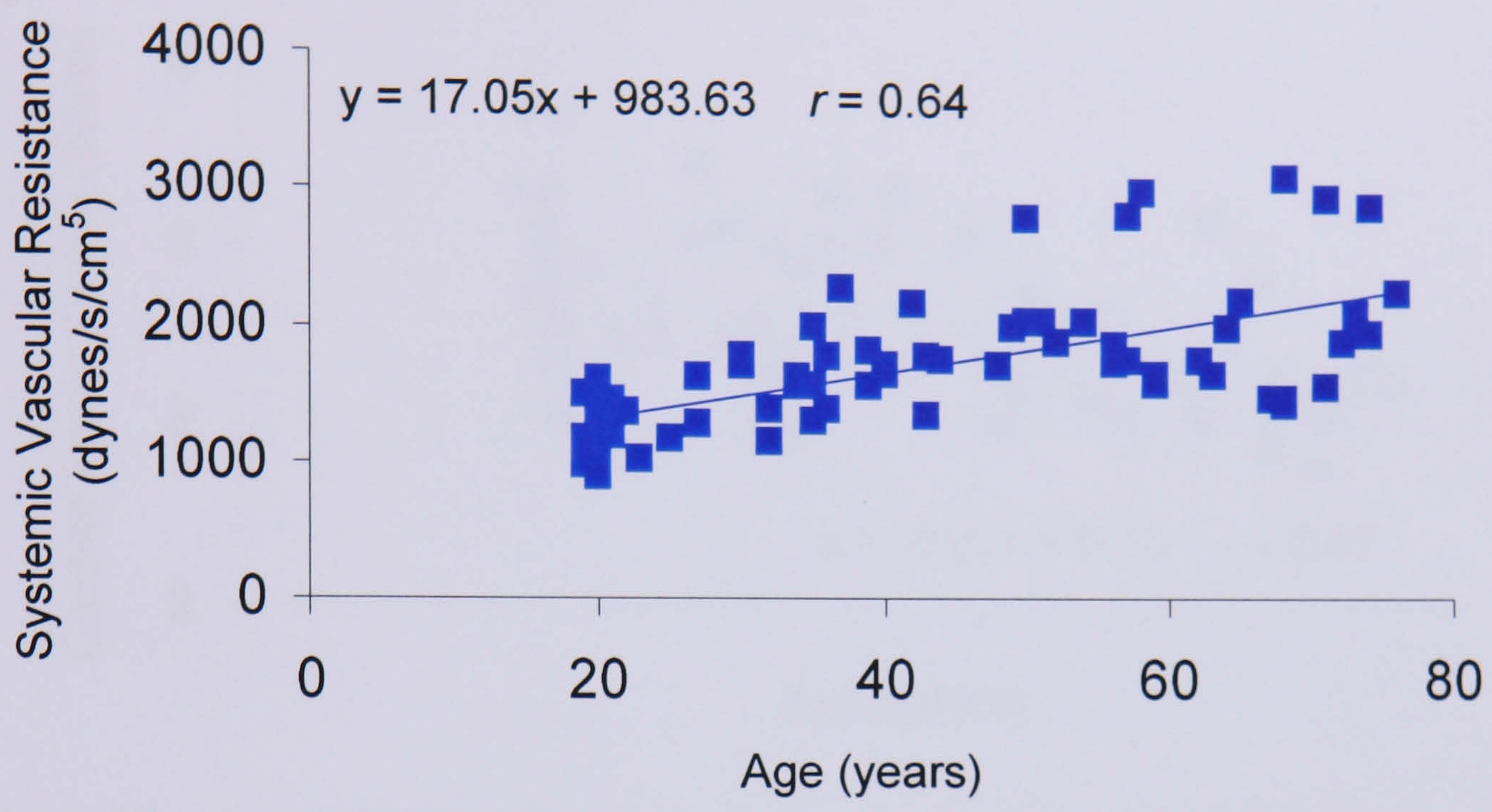


Figure 16 – The effect of ageing on systemic vascular resistance at rest.

Resting systemic vascular resistance increased significantly ($F(1, 67) = 47.1, P < 0.0001$) as a result of healthy ageing in men between nineteen and seventy-six years of age.

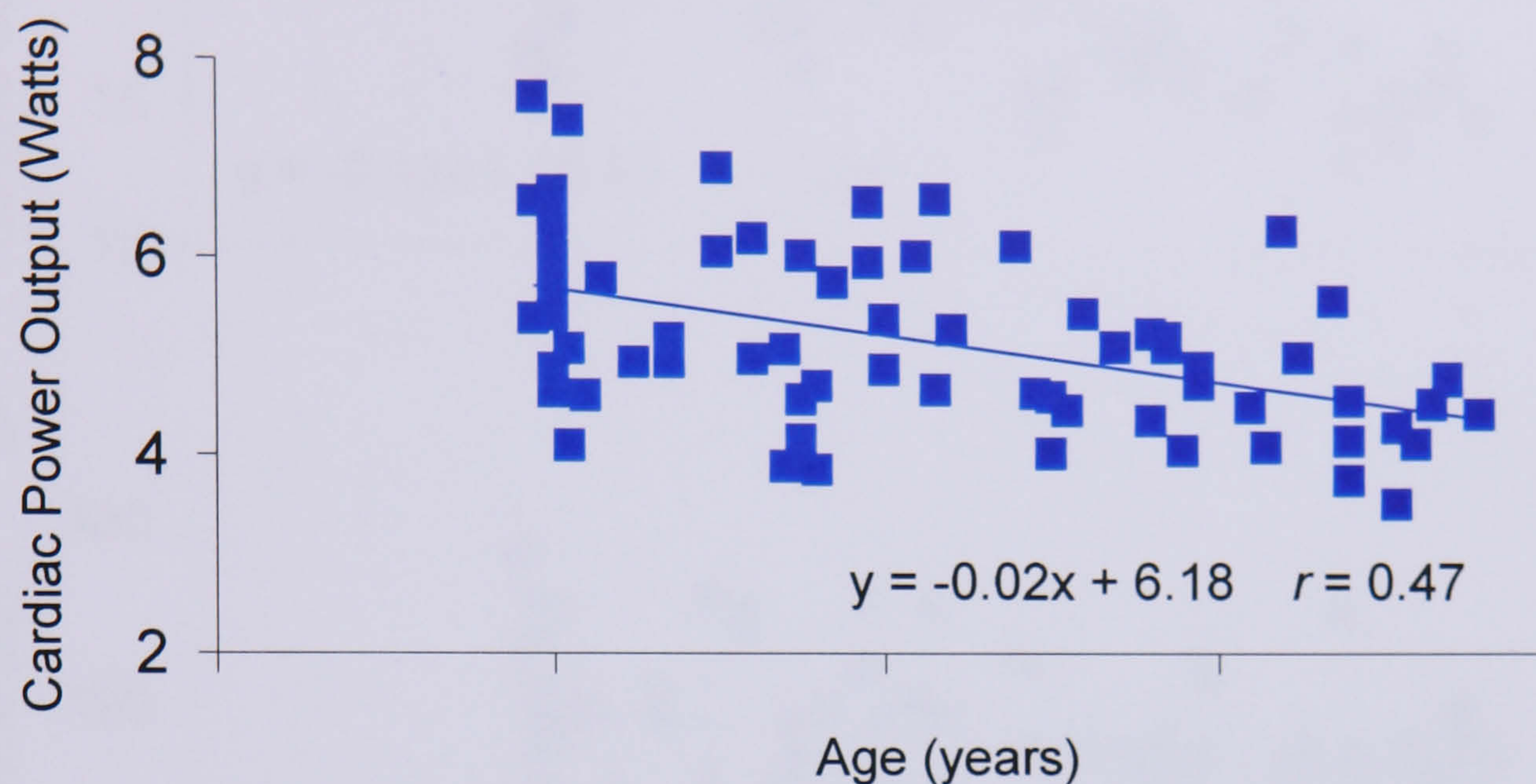


Figure 17 – Age-related changes in maximum overall cardiac function.

Maximum cardiac power output decreased significantly ($F(1, 67) = 19.2$, $P < 0.0001$) between the ages of nineteen and seventy-six years in healthy men.

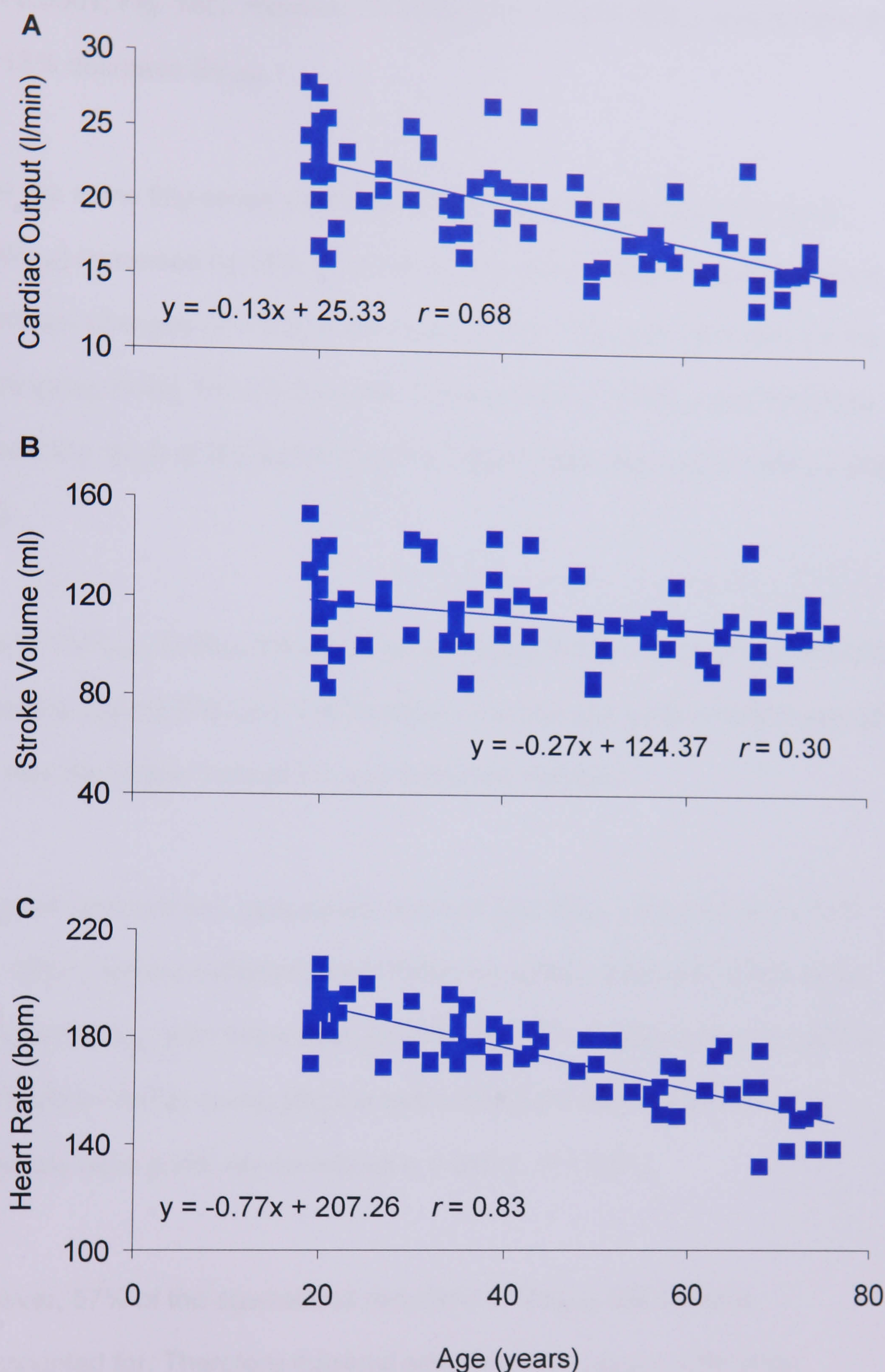


Figure 18 – Healthy ageing and its effects on maximum blood flow generation.

There were significant decreases in maximum cardiac output (A) ($F(1, 67) = 57.6$, $P < 0.0001$), stroke volume (B) ($F(1, 67) = 6.6$, $P < 0.05$) and heart rate (C) ($F(1, 67) = 153.6$, $P < 0.0001$) in healthy men.

($P < 0.0001$; Fig. 18c). However, the 23% decrease in HR_{\max} was greater than the 13% decrease SV_{\max} .

Over the same fifty-seven years maximum mean arterial blood pressure (MAP_{\max}) increased by 14% ($P < 0.0001$; Fig. 19a). There were however no significant changes ($P > 0.8$) in the SBP_{\max} (Fig. 19b), with the mean for the entire group being 196 ± 2.0 mmHg. The increase in MAP_{\max} was therefore entirely the result of the significant ($P < 0.0001$) 53% increase in DBP_{\max} (Fig. 19c).

As with SVR_{rest} , SVR_{\max} showed a very strong positive correlation ($P < 0.0001$) to healthy ageing (Fig. 20). The increase over the age range studied was 68%, and was the largest increase in any individual variable.

Between nineteen and seventy-six years of age $\dot{V}O_{2\max}$ decreased by 51% (Fig. 12) in healthy sedentary men. Over the same period, and in the same subjects CPO_{\max} also decreased by 20% (Fig. 17). Unsurprisingly, given the role that the cardiac pump plays in determining aerobic power these two measures were positively correlated ($r = 0.657$, $P < 0.01$).

However, 57% of the age-related reduction in $\dot{V}O_{2\max}$ still remains unaccounted for. Therefore maximal arteriovenous oxygen difference ($a - \bar{v} O_{2\text{diff}_{\max}}$) was calculated. This showed a significant ($P < 0.0001$) 24% reduction in peripheral extraction of oxygen over the fifty-seven years of ageing (Fig. 21).

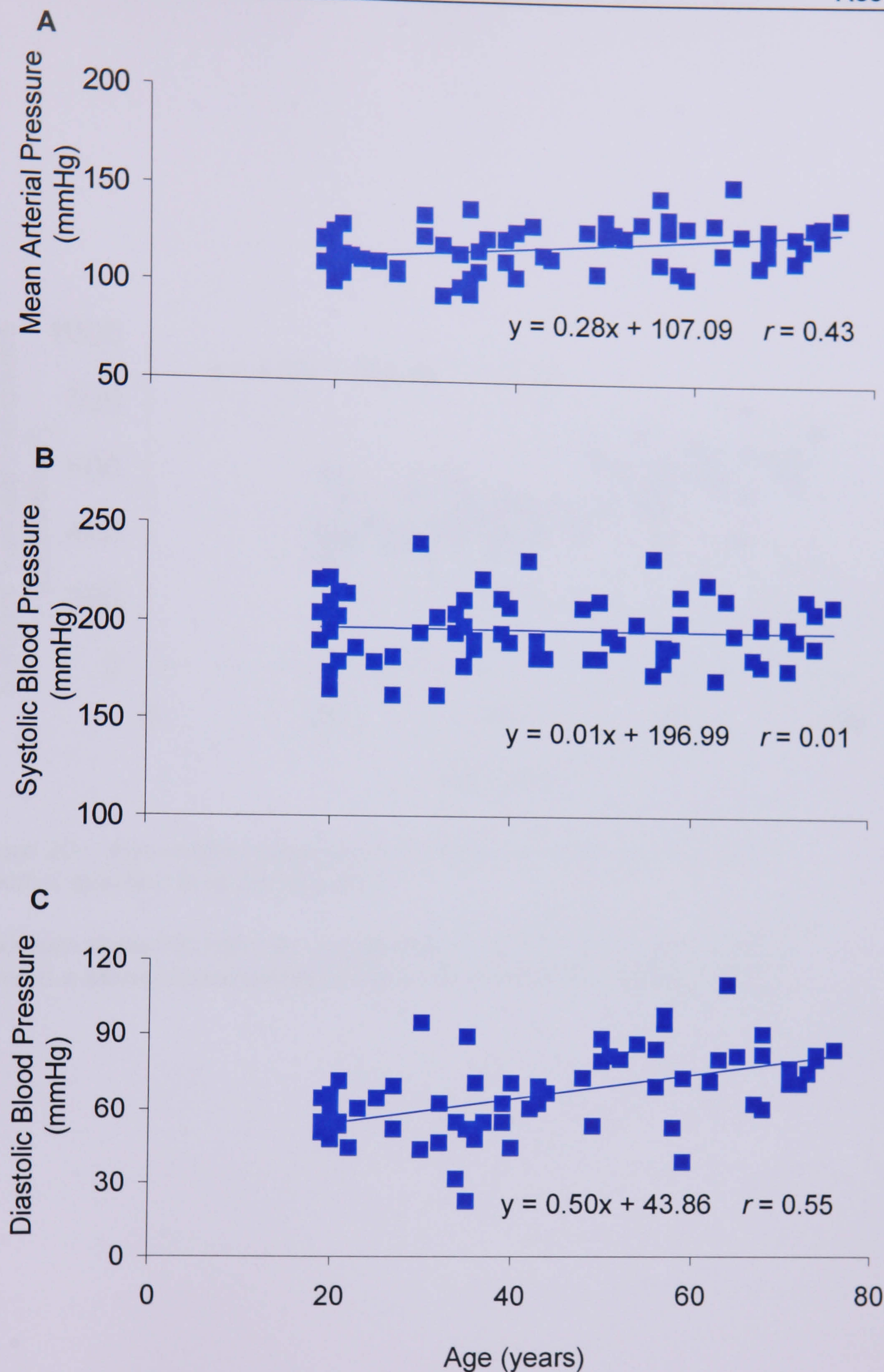


Figure 19 – The effects of healthy ageing on maximum blood pressure generation.

Maximum mean arterial (A) ($F(1, 67) = 15.6, P < 0.0001$), systolic ($F(1, 67) = 0.0, P > 0.8$) and diastolic (C) ($F(1, 67) = 28.6, P < 0.0001$) blood pressure in healthy men.

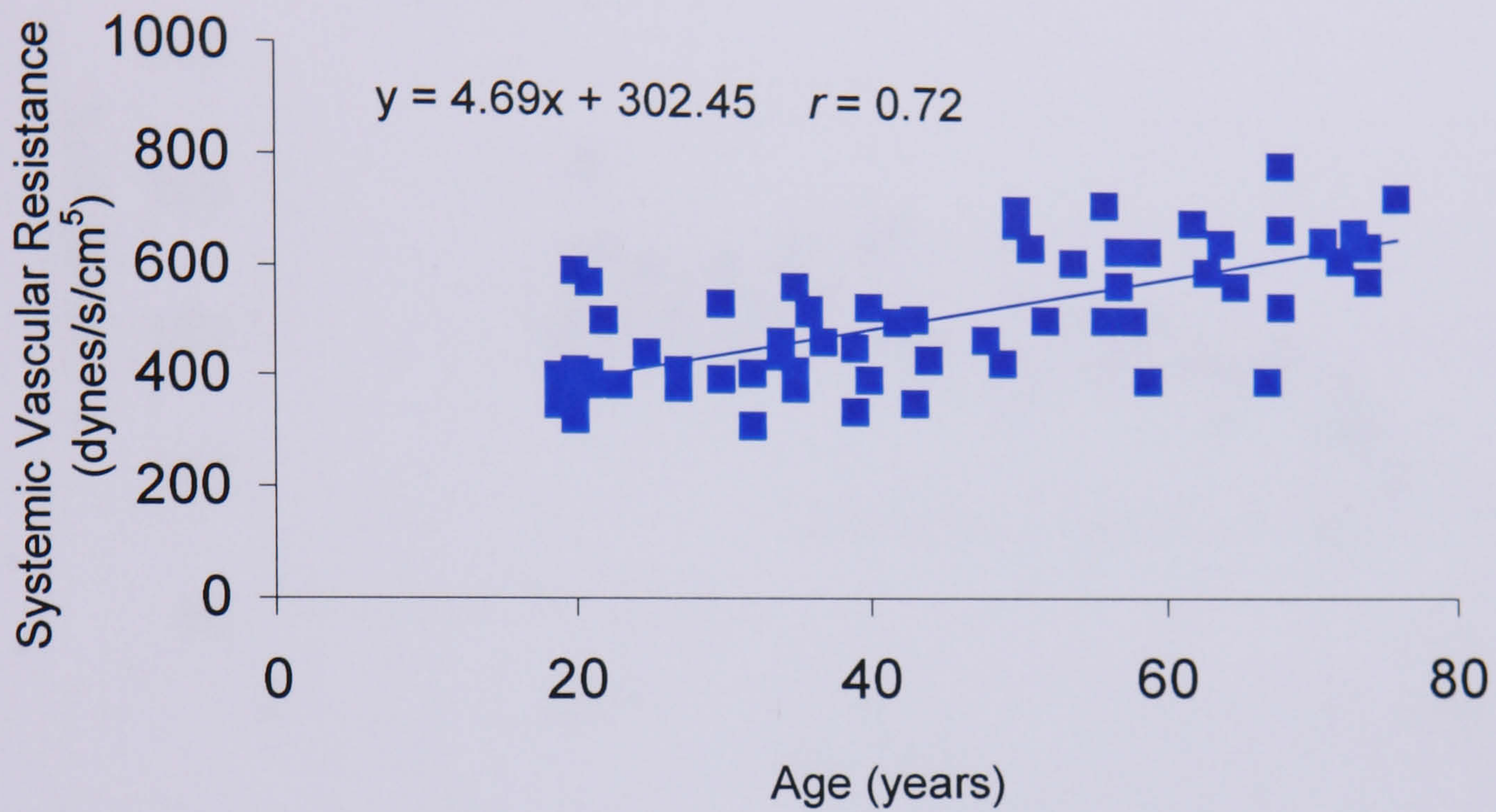


Figure 20 – Age-related changes in systemic vascular resistance at maximal exertion in sedentary men.

Maximum systemic vascular resistance ($F(1, 67) = 71.8, P < 0.0001$) showed a strong linear increase as a result of healthy ageing in men.

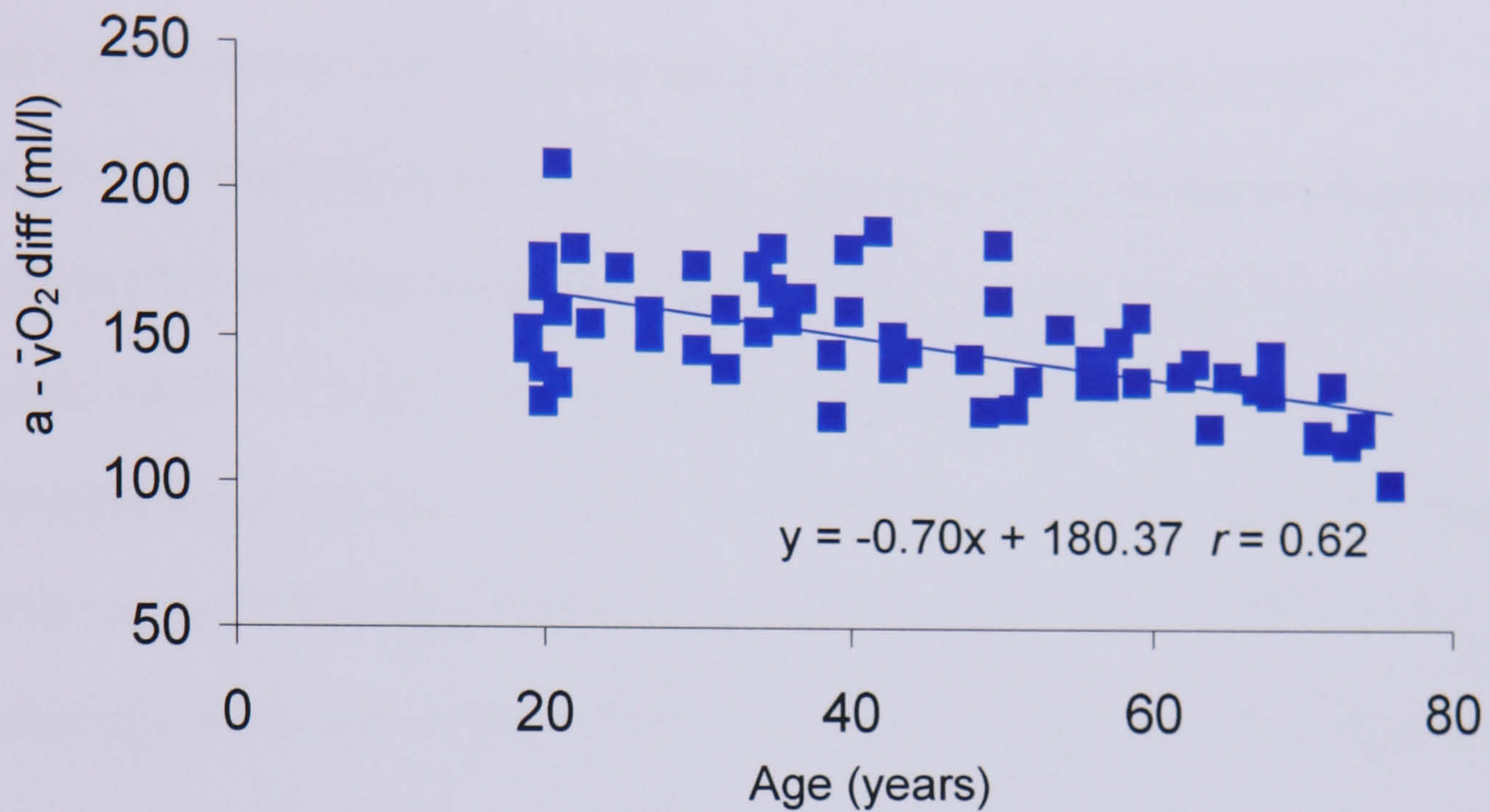


Figure 21 – The effect of ageing on maximum arteriovenous oxygen difference in healthy men.

Maximum arteriovenous oxygen difference showed a significant linear decrease ($F(1, 67) = 42.8$, $P < 0.0001$) between nineteen and seventy-six years of age.

This study shows that healthy ageing in men results in a significant reduction in maximum aerobic power. Resting overall cardiac function also declines, but importantly maximum overall cardiac function decreases to a much greater extent.

At rest and maximal exertion there were significant reductions in the generation of blood flow, but these were opposed by age-related increases in the generation of blood pressure. The net impact in these sedentary men was a significant ($P < 0.0001$) 20% decrease in the maximal pumping capacity of the healthy heart, but also a 25% ($P < 0.001$) reduction in its overall functional reserve capacity (Fig. 22). This means that at all ages studied CPO_{rest} (Fig. 13) was operating well within the reserve capacity, and furthermore that CR was well maintained between nineteen and seventy-six years of age.

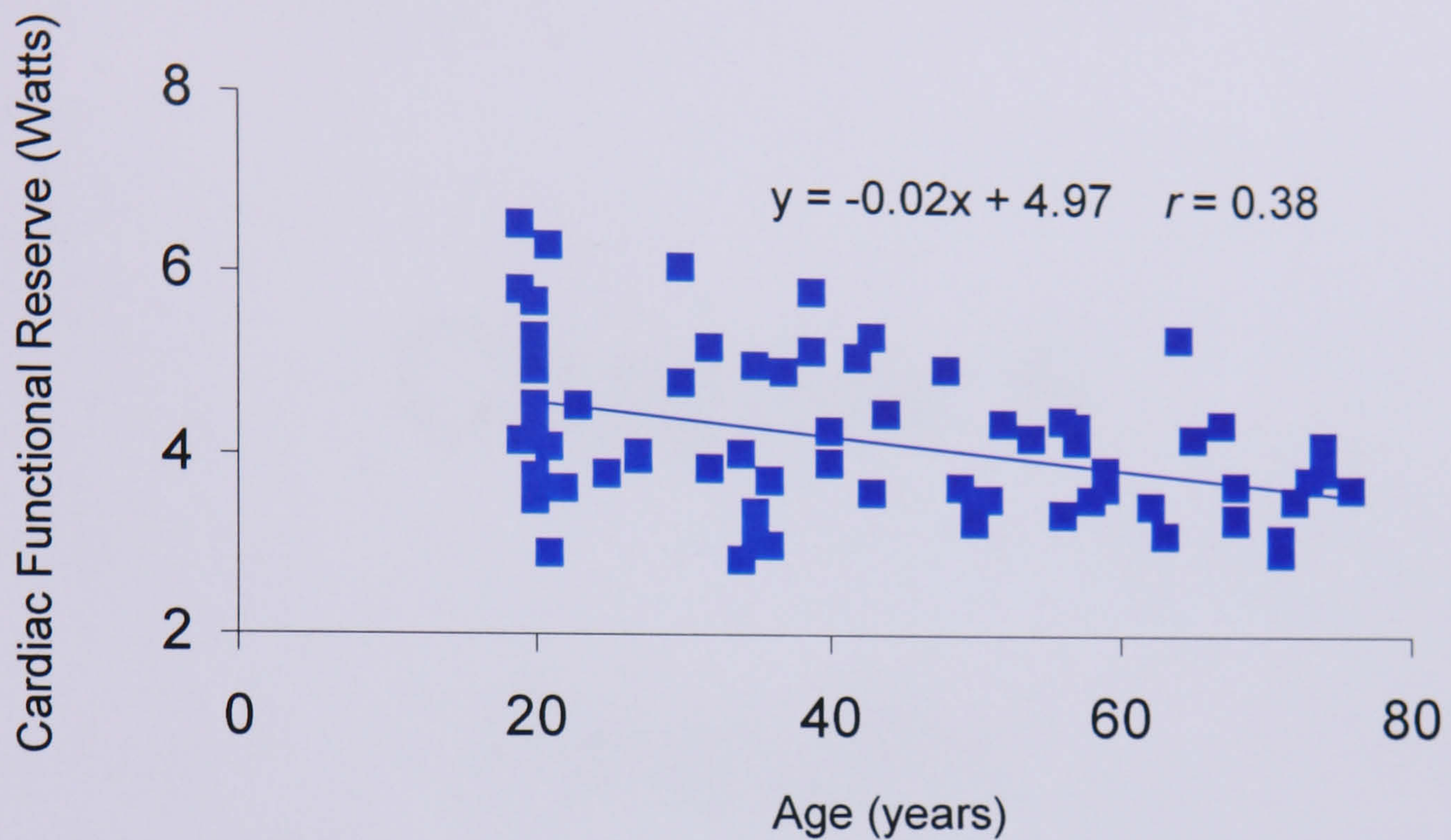


Figure 22 – Age-related changes in cardiac functional reserve in healthy men.

Cardiac functional reserve [$CR = CPO_{\max}$ (Fig.18) – CPO_{rest} (Fig. 14)] showed a significant ($F(1, 67) = 11.4$, $P < 0.001$) linear decline between nineteen and seventy-six years of age in healthy but sedentary men.

Chapter 5

Results

The Effects of Endurance Training on
Aerobic and Cardiac function in Men

5.0 Endurance Exercise Training in Men

Given the detrimental impact of healthy ageing on overall cardiac function in sedentary men (see chapter 4), male subjects who participated regularly in endurance exercise were recruited from various clubs in North-West England. The aim was to determine whether habitual participation in endurance exercise could attenuate the age-related deterioration in cardiac function.

All of the subjects conformed to the health guidelines imposed on the sedentary groups (section 2.0). Fifteen young (mean age of 19.6 ± 0.8 years) highly-trained individuals were recruited from a local rugby academy and the John Moores University student population, all participated in structured exercise training sessions at least four times per week. Twenty-eight long-term veteran athletes were also recruited. These active individuals were distinguished by their participation in four training sessions per week during which they covered on average thirty-two miles. Additionally, they had been training for at least eighteen years, and all were still competing in various distance events. Four age-matched (at approximately twenty, fifty, sixty and seventy years of age) sub-groups were extracted from the healthy sedentary male population to allow a meaningful comparison.

The anthropometric data for all groups are presented in Table 6. The main significant differences were in the amount of body fat. The absolute amount of body fat was lower in all the athletic groups, in comparison to their age-matched sedentary peers. These differences were statistically significant ($P < 0.05$) at twenty, fifty and sixty years of age. This difference was again evident when fat mass was expressed as a percentage of total body weight (BF); all of

Sedentary				
Age (Years)	20.4 ± 0.3	49.8 ± 1.0	58.6 ± 0.8	70.1 ± 1.0
n	18	8	9	13
Height (cm)	178.8 ± 2.2	174.5 ± 2.0	172.3 1.9	175.0 ±1.2
Total Body Mass (kg)	80.5 ± 2.6	82.1 ± 3.5	82.9 ± 3.3	81.4 3.5
Body Mass Index (kg/m ²)	25.1 ± 0.6	27.1 ± 1.5	27.9 ± 0.8	26.5 ± 1.0
Body Surface Area (m ²)	1.99 ± 0	1.97 ± 0	1.96 ± 0	1.97 ± 0
Fat Body Mass (kg)	16.4 ± 1.4	21.0 ± 2.4	22.4 ± 1.7 †	21.1 ± 1.5
% Body Fat	19.7 ± 1.0	25.1 ± 1.9 †	26.8 ± 1.4 †	25.3 ± 1.1 †
Lean Body Mass (kg)	62.4 ± 1.63	58.5 ± 1.4	58.0 ± 2.0	58.5 ± 1.9
Athletes				
Age (Years)	19.6 ± 0.8	49.5 ± 0.8	57.3 ± 0.7	67.8 ± 1.4
n	15	13	9	6
Height (cm)	180.8 ± 1.3	172.3 ± 2.0 †	172.9 ± 1.8 †	175.6 ± 4.5
Total Body Mass (kg)	80.1 ± 2.4	72.7 ± 3.8	72.8 ± 2.6	71.9 ± 2.8
Body Mass Index (kg/m ²)	24.5 ± 0.7	24.4 ± 1.0	24.4 ± 0.7	24.6 ± 1.3
Body Surface Area (m ²)	2.00 ± 0	1.85 ± 0.1 †	1.86 ± 0	1.83 ± 0
Fat Body Mass (kg)	11.4 ± 7.5 *	12.6 ± 1.9 *	12.6 ± 1.8 *	13.7 ± 1.3
% Body Fat	13.8 ± 0.7 *	16.5 ± 1.6 *	16.7 ± 1.8 *	19 ± 1.4 *
Lean Body Mass (kg)	66.7 ± 1.5	57.1 ± 2.2 †	58.0 ± 1.4 †	55.6 ± 2.0 †

Table 6 – Anthropometric characteristics of endurance-trained and sedentary men.

Data are presented as means ± standard error of the mean.

* Significant differences (*P* < 0.05), when comparing age-matched sedentary and athletic men.

† Significant differences (*P* < 0.05), compared to 20-year old sedentary men.

the athletic men had much lower BF in comparison to the sedentary age-matched counterparts ($P < 0.05$). The BF also increased significantly ($P < 0.05$) in the older sedentary men, compared with the younger twenty-year old sedentary group. No significant differences were found in lean body mass, and while total body mass was lower in the older active groups compared to the sedentary groups, these differences were not statistically significant. Therefore, the endurance-training regime had prevented the age-related accumulation of fat that was measured in the sedentary men.

5.1 The Effect of Habitual Endurance Exercise Training on Aerobic Power in Men

Each group of athletes had a significantly ($P < 0.0001$) higher $\dot{V}O_{2\max}$ than their age-matched sedentary counterparts (Fig. 23). In percentage terms the training-related adaptations were 25%, 45%, 52%, and 58% at twenty, fifty, sixty and seventy years of age, respectively. Furthermore, the $\dot{V}O_{2\max}$ of all the veteran athletes did not differ significantly from that of the twenty year old sedentary group. This illustrates that engaging in long-term endurance exercise can effectively attenuate the impact that fifty years of healthy ageing has on maximum aerobic power. Nonetheless, even in the highly-trained men $\dot{V}O_{2\max}$ still decline significantly ($P < 0.0001$) by 29% (16.4 ml/kg/min) between twenty and seventy years of age (Fig. 23).

The allometric scaling process was employed to minimise any effect of body size on $\dot{V}O_{2\max}$, and in an attempt to improve the precision and interpretation of the data. However, after completing the scaling process the same

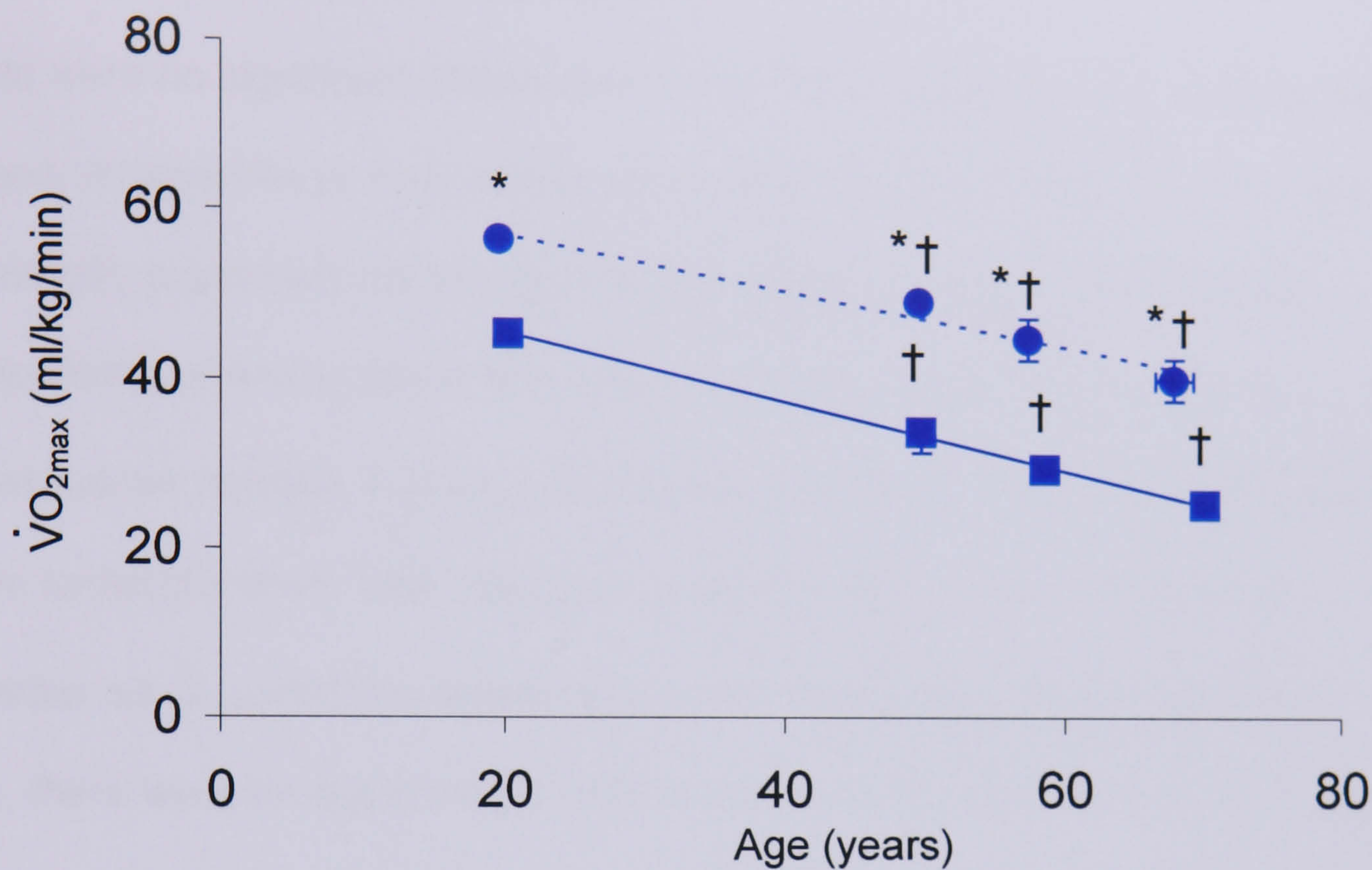


Figure 23 – Maximum aerobic power in age-matched sedentary and endurance-trained men.

Maximum aerobic power of sedentary (■), and endurance- trained men (●) of twenty, fifty, sixty and seventy years of age.

Data are presented as means \pm standard error of the mean.

- * Significant differences ($P < 0.05$) when comparing age-matched sedentary and athletic men.
- † Significant differences ($P < 0.05$) compared to either sedentary or trained twenty-year old men.

significant differences remained between the active and inactive groups, as were shown by the relative measures in Fig. 23.

5.2 The Effect of Endurance Exercise Training on Resting Cardiac Function in Men

There were no significant differences in the CPO_{rest} between any of the groups of men, irrespective of their activity status (Fig. 24). There were however some statistically significant differences between these groups in the individual components of resting blood flow and blood pressure generation (Table 7). As shown earlier (section 4.2) \dot{Q}_{rest} decreased over the course of healthy ageing in the sedentary men. This trend was unaffected by long-term endurance exercise, as \dot{Q}_{rest} also decreased with advancing years in the trained men. Also, there were no age-matched differences between any of the inactive and active groups in \dot{Q}_{rest} . While there was no age-related change in HR_{rest} , long-term endurance exercise significantly ($P < 0.05$) lowered HR_{rest} by ~23% in the fifty, sixty and seventy-year old veteran athletes, compared to their age-matched sedentary counterparts. However, these changes were balanced by higher SV_{rest} in all the groups of male athletes, although there was still an age-related decline.

Long-term endurance exercise had no significant impact on resting MAP, SBP, or DBP. Thus, the trend towards small age-related increases in resting blood pressure in men remained irrespective of activity status.

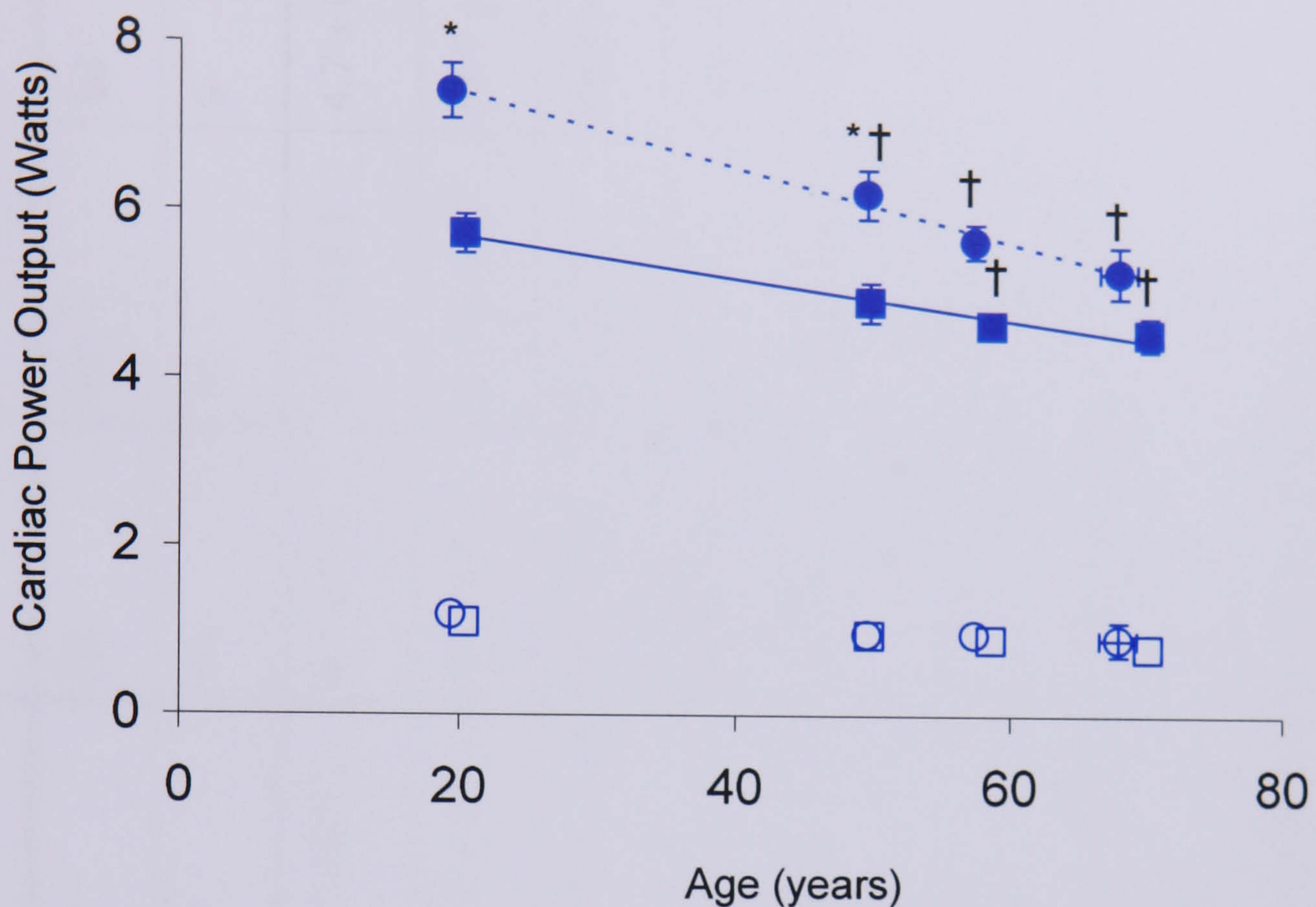


Figure 24 – The effects of healthy ageing and endurance exercise on resting and maximum cardiac power output in men.

Square symbols depict values for sedentary men and circles athletes. Open and solid symbols represent values measured at rest and maximum exercise, respectively.

Data are presented as means \pm standard error of the mean.

* Significant differences ($P < 0.05$) when comparing age-matched sedentary and athletic men.

† Significant differences ($P < 0.05$) compared to either sedentary or trained twenty year-old men.

	Sedentary					Trained				
Age (Years)	20	50	60	70		20	50	60	70	
n	18	8	9	13		15	13	9	6	
Q̇ (l/min)	5.7 ± 0.2	4.2 ± 0.2 †	4.2 ± 0.3 †	3.9 ± 0.3 †		6.1 ± 0.4	4.5 ± 0.3 †	4.7 ± 0.2	3.9 ± 0.6 †	
HR (bpm)	69.4 ± 2.2	67.2 ± 3.3	68.1 ± 3.2	71.0 ± 3.8		60.5 ± 2.3	51.3 ± 2.3 *	52.7 ± 1.8 *	54.8 ± 4.8 *	
SV (ml)	83.0 ± 2.9	63.1 ± 4.1	62.8 ± 4.8	55.5 ± 4.1 †		99.3 ± 7.0	90.1 ± 7.1 *	88.8 ± 3.0	69.0 ± 5.9 †	
MAP (mmHg)	88.9 ± 1.4	104.2 ± 2.6 †	99.1 ± 1.8	95.3 ± 2.2		88.7 ± 2.0	97.8 ± 2.1	95.2 ± 3.2	103.9 ± 6.9 †	
SBP (mmHg)	116.2 ± 1.8	129.2 ± 3.6	127.9 ± 2.7	123.7 ± 2.9		117.9 ± 2.0	123.6 ± 4.0	122.6 ± 5.7	134.6 ± 8.7	
DBP (mmHg)	69.8 ± 1.8	86.7 ± 2.7 †	79.0 ± 2.1	75.5 ± 2.6		68.3 ± 3.0	79.8 ± 1.8 †	76.1 ± 2.9	82.5 ± 6.2 †	

Table 7 – The effects of healthy ageing and endurance-exercise in men on resting measures of blood flow and blood pressure.

Data are presented as means ± standard error of the mean.

* Significant difference, (*P* < 0.05) between sedentary and age-matched endurance-trained men.

† Significant differences (*P* < 0.05) determined by comparing to either sedentary or trained twenty-year old group.

5.3 Changes in Maximum Cardiac Function as a Result of Endurance Exercise in Men

Considering the training related increase in $\dot{V}O_{2\max}$ (Fig. 23) which clearly results from engaging in long-term endurance exercise, and the role the heart plays in determining aerobic power, a similar increase in CPO_{\max} might be anticipated. Maximum CPO was higher in all the groups of athletes in comparison to their age-matched sedentary counterparts. The increase was statistically significant ($P < 0.01$) at twenty (28%) and fifty (26%) years of age. Nonetheless, the CPO_{\max} of the veteran athletes still declines with increasing age, and indeed at a steeper rate compared to that observed in the sedentary men (Fig. 24).

The individual components of CPO_{\max} i.e. maximum blood flow and blood pressure generation are shown in Table 8. As with CPO_{\max} , \dot{Q}_{\max} was higher in all the groups of trained men, in comparison to the age-matched inactive controls. This training adaptation equated to increases of between 16 and 26%, and reached statistical significance ($P < 0.05$) when the twenty and fifty year old age-matched groups were compared. Nonetheless \dot{Q}_{\max} still declined with ageing in the athletic population. But, despite this \dot{Q}_{\max} was still the same or higher in all the groups of veteran athletes when compared to the much younger twenty-year old sedentary men.

In contrast, habitually engaging in aerobic exercise had no significant effect on HR_{\max} , which still declined with increasing age irrespective of activity status. Thus the training-related increase in blood flow generation was attributable

	Sedentary					Trained				
	20	50	60	70		20	50	60	70	
Age (Years)	20					20				
n	18	8	9	13		15	13	9	6	
Q̇ (l/min)	22.6 ± 0.8	18.2 ± 1.0 †	17.2 ± 0.6 †	16.4 ± 0.7 †		28.6 ± 0.9 * †	22.8 1.0 * †	21.3 ± 0.8 †	19.1 ± 0.9 †	
HR (bpm)	191.1 ± 2.0	171.4 ± 3.1 †	161.0 ± 2.6 †	152.6 ± 4.0 †		187.0 ± 1.6	162.0 ± 2.6 †	165.6 ± 3.9 †	159.3 ± 5.3 †	
SV (ml/beat)	118.6 ± 4.6	105.9 ± 5.4	106.9 ± 3.4	107.8 ± 3.7		152.8 ± 5.0 *	141.0 ± 6.8 *	129.3 ± 5.6 †	120.0 ± 4.5 †	
MAP (mmHg)	114.4 ± 2.0	124.2 ± 3.3	124.0 ± 4.6	126.9 ± 2.9 †		115.9 ± 2.5	124.4 ± 3.0	121.4 ± 3.4	126.3 ± 3.2	
SBP (mmHg)	198.5 ± 3.9	193.5 ± 4.2	196.6 ± 7.3	195.8 ± 3.4		208.9 ± 6.2	202.4 ± 5.2	198.4 ± 4.4	202.8 ± 5.5	
DBP (mmHg)	55.2 ± 1.6	75.6 ± 4.1 †	73.1 ± 6.4 †	78.5 ± 3.6 †		53..52 ± 5.1	69.8 ± 2.4 †	67.6 ± 4.4	72.7 ± 4.4	

Table 8 – The effects of healthy ageing and endurance-exercise in men on maximum measures of blood flow and blood pressure.

Data are presented as means ± standard error of the mean.

* Significant difference, (*P* < 0.05) between sedentary and age-matched endurance-trained men.

† Significant differences (*P* < 0.05) determined by comparing to either sedentary or trained twenty-year old group.

to an increase in SV_{\max} (Table 8). Indeed, the SV_{\max} of the seventy-year old endurance trained men was still higher than that of the sedentary men fifty years their junior.

The data on the generation of maximum blood pressure is also shown in Table 8. The long-term endurance training had no significant impact on any of the measurements of maximum blood pressure.

The cumulative effect of these changes is that the endurance-trained males at all ages have a higher overall cardiac functional reserve capacity (Fig. 25). But there is an age-related decline in CR irrespective of either a sedentary or active lifestyle. Furthermore, the decline in CR is greater with the advancing years in the trained men. At twenty-years of age the exercise-induced improvement in CR is 1.7 Watts, diminishing to 0.6 Watts at seventy years of age. But the CR of the seventy-year old veteran athletes is still only 0.2 Watts below that of twenty-year old sedentary men.

In summary; when men regularly engage in long-term endurance exercise CPO_{rest} is unaffected, while the training elicits clear adaptations in both $\dot{V}O_{2\max}$ and CPO_{\max} . These adaptations translate into all the athletic men having higher functional cardiac reserves, when compared to healthy sedentary age-matched counterparts. In both cases CR decreases with age, but the rate of decrease is greater in the trained men.

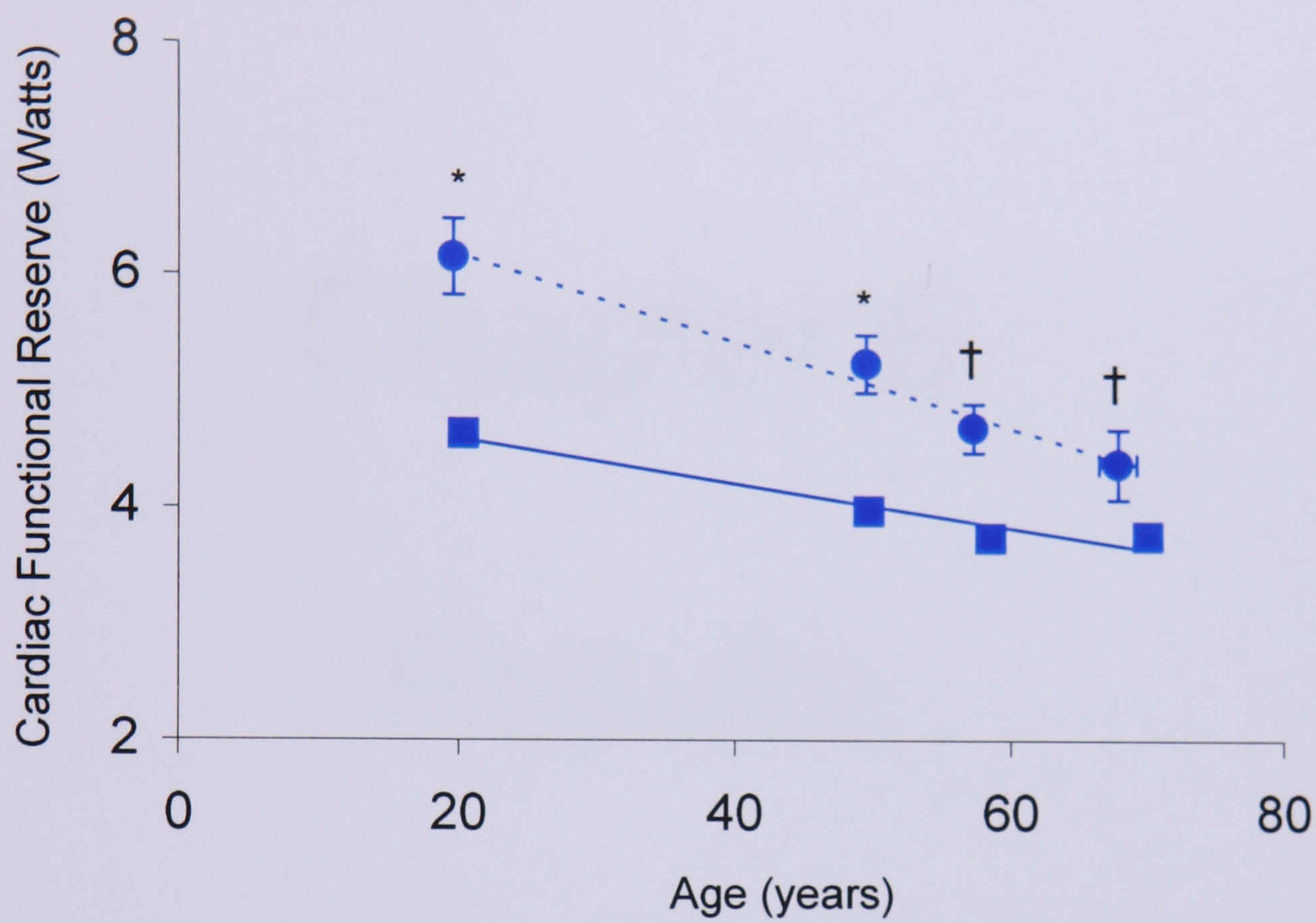


Figure 25 – Changes in overall cardiac functional reserve as a consequence of ageing and endurance exercise.

Overall cardiac function reserve of sedentary (■), and endurance- trained men (●) of twenty, fifty, sixty and seventy years of age.

Data are presented as means ± standard error of the mean

* Significant differences ($P < 0.05$) when comparing age-matched sedentary and athletic men.

† Significant differences ($P < 0.05$) compared to either sedentary or trained twenty-year old men.

Chapter 6

Results

The Effects of Heart Failure in Men

6.0 The Impact of a Failing Heart on Overall Function

Studying the effects of heart failure provides an extreme contrast to the hearts of endurance trained athletes, which have been conditioned through endurance exercise over many years, i.e. physiological versus the patho-physiological changes. Indeed, this is one of the strengths of using CPO and CR, i.e. it allows you to determine whether the heart is operating well or poorly as a hydraulic pump.

The decision was taken to measure CPO in heart failure patients as it would provide an ideal opportunity to determine the minimum baseline of human *in vivo* physiological function. Secondly, testing these patients would also add further validity to the use of CPO by testing the techniques sensitivity.

Twenty-one male patients (NYHA class III and IV) were recruited and completed the full testing protocol. Within one week of completing the tests all the patients underwent surgery to have bio-ventricular pacemakers implanted in an attempt to improve the performance of their hearts, and hence their quality of life.

As detailed in section 2.0 each patient was undergoing individualised treatment with various drugs in an attempt to prevent any further deterioration in their condition prior to surgery. The most commonly used drugs were various beta-blockers, diuretics, spiro-lactones, ACE-inhibitors and aspirin.

The mean age of the heart failure patients was 68.1 ± 1.8 years, but their ages ranged from forty-six to eighty years. To allow the effects of the patho-

physiological disease to be accurately quantified, an age-matched (mean age of 67.9 ± 1.3) group of seventeen sedentary healthy males was extracted from the earlier collected data and used as a control group. The age range of this group was the same as that of the heart failure patients. The anthropometric characteristics of both groups are shown in Table 9.

6.1 Changes in Aerobic Function as a Result of Heart Failure in Men

When compared to the control group, the $\dot{V}O_{2\text{rest}}$ of the heart failure group was significantly ($P < 0.05$) higher (14%), but without being outside the normal range (Fig. 26a). When maximally stimulated the $\dot{V}O_{2\text{max}}$ of the heart failure group was significantly ($P < 0.0001$) lower. Indeed, it was 45% below that of the healthy control group (Fig. 26b). These significant differences remained whether the measures were reported in absolute terms, or relative to total body mass. Therefore, it is apparent the process of heart failure had significantly compromised the aerobic power of the patients.

6.2 The Impact of Heart Failure on Resting Cardiac Function

At 0.6 ± 0.0 Watts the CPO_{rest} of the heart failure patients was significantly ($P < 0.05$) below (30%) that of the control group (Fig. 27a). In terms of blood flow generation \dot{Q}_{rest} was 11% ($P < 0.05$) below the mean of the healthy male group. This was entirely attributed to a lower SV_{rest} (17%), although this failed to reach the level of statistical significance because there was no difference in HR_{rest} between the groups (Table 10).

	Healthy Control Group	Heart Failure Patients
n	17	21
Age (years)	67.9 ± 1.3	68.1 ± 1.8
Height (cm)	174.4 ± 1.2	170.7 ± 1.6
Total Body Mass (kg)	82.3 ± 3.1	84.4 ± 3.2
Body Mass Index (kg/m ²)	27.0 ± 0.8	28.9 ± 0.9
Body Surface Area (m ²)	2.0 ± 0.0	2.0 ± 0.0

Table 9 – Anthropometric characteristics of male healthy control group heart failure patients.

Data are presented as means ± standard error of the mean.

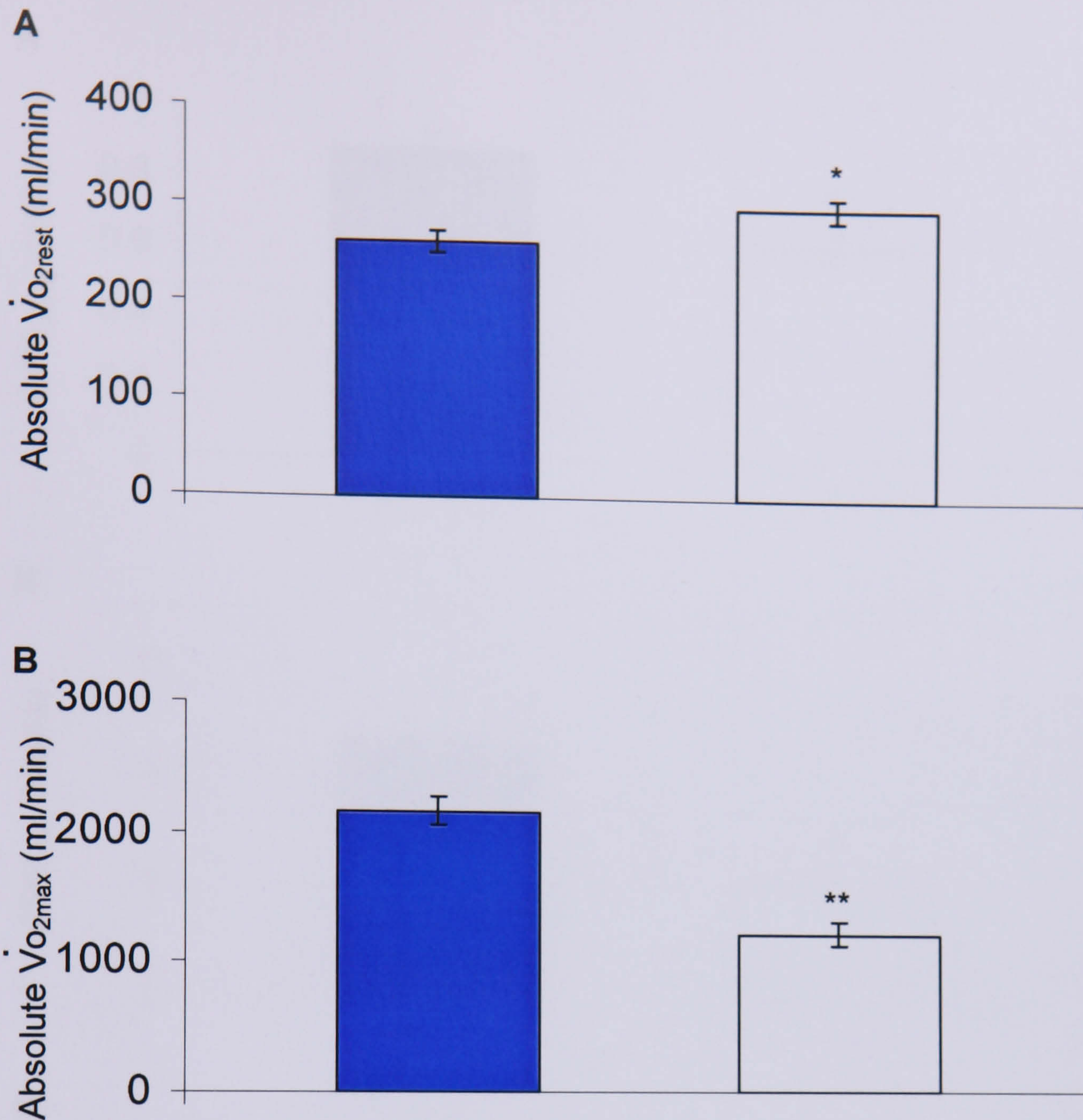


Figure 26 – Changes in aerobic function as a consequence of heart failure.

Resting (A) and maximum $\dot{V}O_2$ (B) values are expressed in absolute terms for both the healthy sedentary male control group (■), and heart-failure patients (□).

Data are presented as means \pm standard error of the mean.

Significant differences (* $P < 0.05$; ** $P < 0.0001$) between the control and heart failure groups.

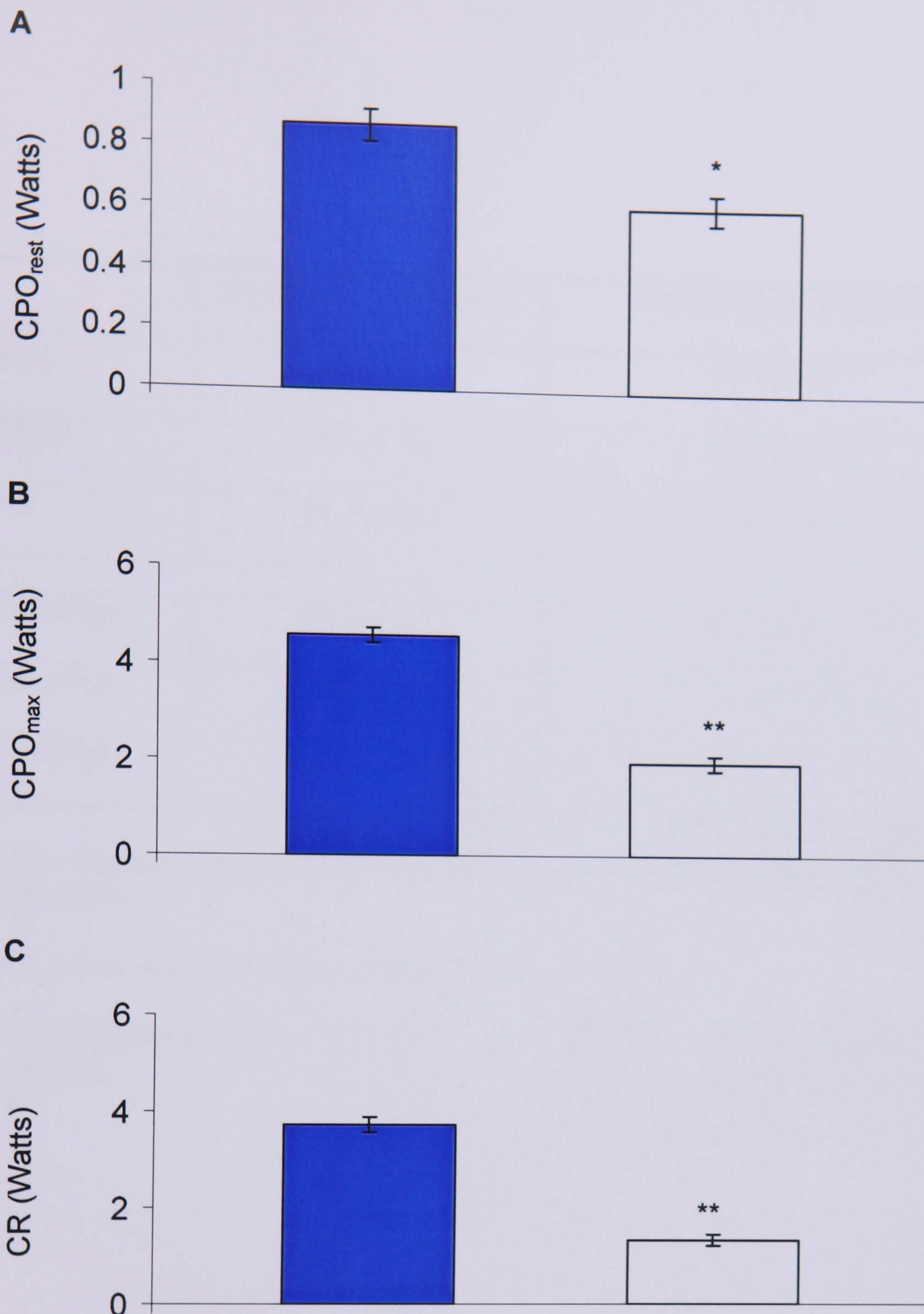


Figure 27 – Changes in overall cardiac function in men as a consequence of heart failure.

Resting CPO (A), maximum CPO (B) and overall function reserve (C) values for the healthy sedentary control group (■), and the group of male heart-failure patients (□).

Data are presented as means \pm standard error of the mean.

Significant differences (* $P < 0.001$; ** $P < 0.0001$) between the control and heart failure groups.

	Healthy Control Group	Heart Failure Patients
Q̇ (l/min)	4.1 ± 0.2	3.2 ± 0.2 *
HR (BPM)	72.2 ± 3.0	70.1 ± 2.9
SV (ml)	57.2 ± 3.3	47.6 ± 4.6
MAP (mmHg)	96.1 ± 1.7	86.6 ± 2.1 **
SBP (mmHg)	125.3 ± 2.5	116.9 ± 3.0
DBP (mmHg)	75.7 ± 2.0	65.3 ± 2.0 **

Table 10 – Resting blood flow and blood pressure in healthy males and heart failure patients.

Data are presented as means ± standard error of the mean.

Significant differences (* $P < 0.05$; ** $P < 0.01$) between the control and heart failure groups.

Resting mean arterial blood pressure was 10% ($P < 0.01$) lower in the heart failure group (Table 10), as a consequence of a 14% depression of DBP_{rest} ($P < 0.01$).

6.3 The Impact of Heart Failure on Maximum Cardiac Function in Men

As with aerobic power, the effects of heart failure on overall cardiac function become even starker when examined at maximal stimulation. The CPO_{max} of the heart failure group was 57% below that of the healthy sedentary men ($P < 0.0001$; Fig. 27b).

The generation of maximum blood flow was significantly impaired by the disease process. Maximum cardiac output was 47% ($P < 0.0001$) below that of the healthy sedentary men (Table 11). This large suppression in \dot{Q}_{max} in the heart failure patients was the result of significant ($P < 0.01$) decreases in both HR_{max} (23%) and SV_{max} (28%).

The ability of the heart failure patients to generate blood pressure was also severely impaired. Over the entire cardiac cycle MAP_{max} was 20% ($P < 0.0001$) below that of the healthy controls (Table 11). This was mainly due to the significant ($P < 0.0001$) 26% decrease in SBP_{max} . While DBP_{max} did show a trend to be lower in the heart failure patients, this was not statistically significant ($P > 0.05$).

Hence, both resting and maximum overall cardiac function decreased significantly as a consequence of heart failure. The impact of the disease was

	Healthy Control Group	Heart Failure Patients
Q̇ (l/min)	16.6 ± 0.6	8.8 ± 0.7 **
HR (BPM)	155.1 ± 3.4	119.3 ± 5.6 **
SV (ml)	107.2 ± 3.2	77.7 ± 8.1 *
MAP (mmHg)	125.6 ± 2.6	100.4 ± 2.4 **
SBP (mmHg)	197.2 ± 3.5	145.1 ± 4.2 **
DBP (mmHg)	75.4 ± 3.6	69.1 ± 2.1

Table 11 – Maximum blood flow and blood pressure in healthy males and heart failure patients.

Data are presented as means ± standard error of the mean.

Significant differences (* $P < 0.001$; ** $P < 0.0001$) between the control and heart failure groups.

greater on CPO_{max} than CPO_{rest} . The result was that the overall cardiac functional reserve of these heart failure patients was only 1.3 ± 0.1 Watts (Fig. 27c). This is significantly ($P < 0.0001$) below (64%) the CR of a healthy sedentary male. Furthermore, these patients only have 30% of the reserve capacity that was measured in the healthy seventy year old endurance-trained males (section 5.3). With a CR of only 1.3 Watts it is apparent the impact of the disease has hugely compromised the hearts ability to operate as a hydraulic pump, and sustain a good quality of life.

By comparing a range of men from the very active endurance trained, to those suffering from heart failure, it has been possible to examine the different impacts physiological and pathophysiological processes have on the overall reserve capacity of the male human heart. The effectiveness of an individual's heart in pumping blood around the body has a huge impact on their ability to cope with the demands of daily life. Focus will now move to determine what impact ageing has on overall cardiac function in healthy women, and the effects of endurance-exercise.

Chapter 7

Results

Changes in Aerobic Power and Overall
Cardiac function in Sedentary Women

7.0 The Effects of Healthy Ageing in Sedentary Women

One hundred and thirteen healthy sedentary women, between nineteen and seventy-six years of age were recruited, and consequently used to assess the effects of healthy ageing on overall cardiac function. Forty-seven of these women between nineteen and forty-nine years of age were pre-menopausal, five between forty-three and forty-nine years of age were peri-menopausal, and the remaining sixty-one between forty-five and seventy-six years of age were post-menopausal. Within the pre-menopausal group twenty-one (45%) were taking oral contraceptives, and twelve of the post-menopausal women (20%) were on hormone replacement therapy.

7.1 Changes in Body Mass and Aerobic Function in Sedentary Women

Total body mass (TBM) and body surface area (BSA) did not change significantly ($P > 0.05$) as a result of fifty-seven years of healthy ageing in this large group of women. The mean values were 68.0 ± 1.0 kg and 1.7 ± 0.0 m² respectively. In contrast, body mass index (BMI) did increase significantly ($P < 0.01$) by 14%, ranging from 17.9 to 34.5 kg/m².

Resting oxygen consumption ($\dot{V}O_{2\text{rest}}$) in both absolute terms (Fig. 28a) and relative to total body mass (Fig. 28b) did not change significantly between nineteen and seventy-six years of age. In contrast, $\dot{V}O_{2\text{max}}$ declined significantly ($P < 0.0001$) in both absolute terms (Fig 28a) and relative to total body mass (Fig. 28b). The reduction in $\dot{V}O_{2\text{max}}$ was 40%, both in absolute and relative terms, and equated to a total decrease of 878 ml/min over the

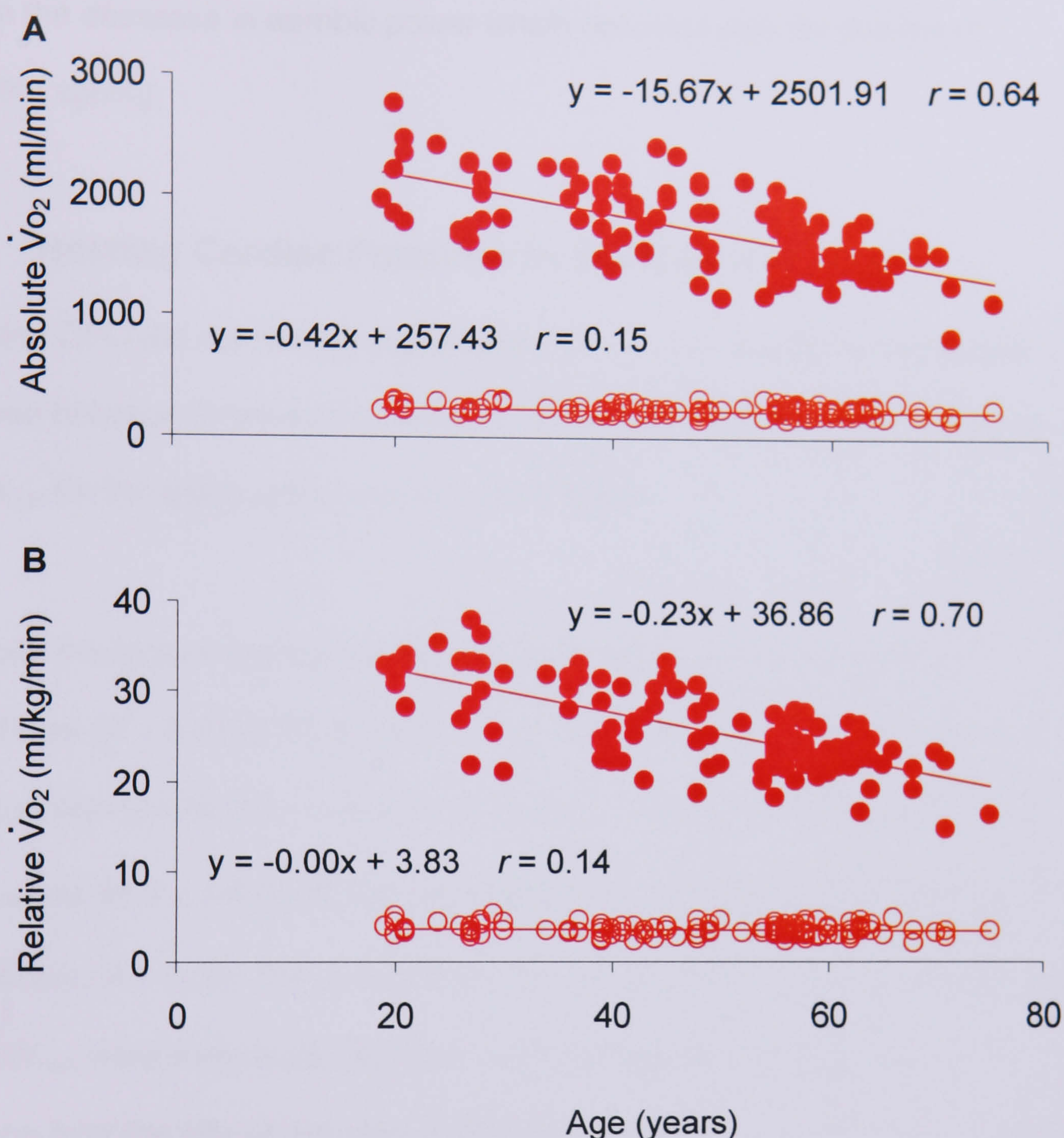


Figure 28 – Changes in aerobic function in women as a consequence of healthy ageing.

Resting $\dot{V}O_2$ (○) expressed in (A) absolute terms ($F(1,111) = 2.6$, $P > 0.1$), and (B) relative to total body mass ($F(1,111) = 2.2$, $P > 0.1$) did not change significantly over fifty-six years ageing.

In contrast both $\dot{V}O_{2\max}$ (●) expressed in (A) absolute terms ($F(1,111) = 78.6$, $P < 0.0001$), and (B) relative to total body mass ($F(1,111) = 106.8$, $P < 0.0001$) declined significantly over the same period in the same subjects.

fifty-seven year period studied.

A similar reduction in cardiac function might be anticipated in these women given the decrease in aerobic power which occurred over the course of healthy ageing.

7.2 Resting Cardiac Function in Sedentary Women

Resting CPO did not change significantly ($P > 0.1$) in healthy but sedentary women between nineteen and seventy-six years of age (Fig. 29). The mean CPO_{rest} for the entire group was 0.8 ± 0.0 Watts.

Despite the lack of any significant change in CPO_{rest} , \dot{Q}_{rest} did show a significant ($P < 0.01$) 23% decrease (Fig. 30a). As HR_{rest} (Fig. 30c) did not change significantly ($P > 0.2$) over the same period in these subjects (mean HR_{rest} was 69.5 ± 0.9 bpm), the reduction in \dot{Q}_{rest} was ascribed entirely to the significant ($P < 0.05$) 19% reduction in SV_{rest} (Fig. 30b). The decreases in \dot{Q}_{rest} and SV_{rest} were statistically significant, but the absolute magnitude of the change over the fifty-seven year period was very small, 1.0 l/min and 11.5 ml \dot{Q}_{rest} and SV_{rest} , respectively.

In these sedentary women, all of the components of resting blood pressure increased significantly as a consequence of ageing. Over the entire cardiac cycle MAP_{rest} increased ($P < 0.0001$) by 16% between nineteen and seventy-six years of age (Fig. 31a). Over the same period SBP_{rest} also increased significantly ($P < 0.0001$) by 25% (Fig. 31b). Although the increase in DBP_{rest} was less (9.1%), it was still significant ($P < 0.01$) over the same period

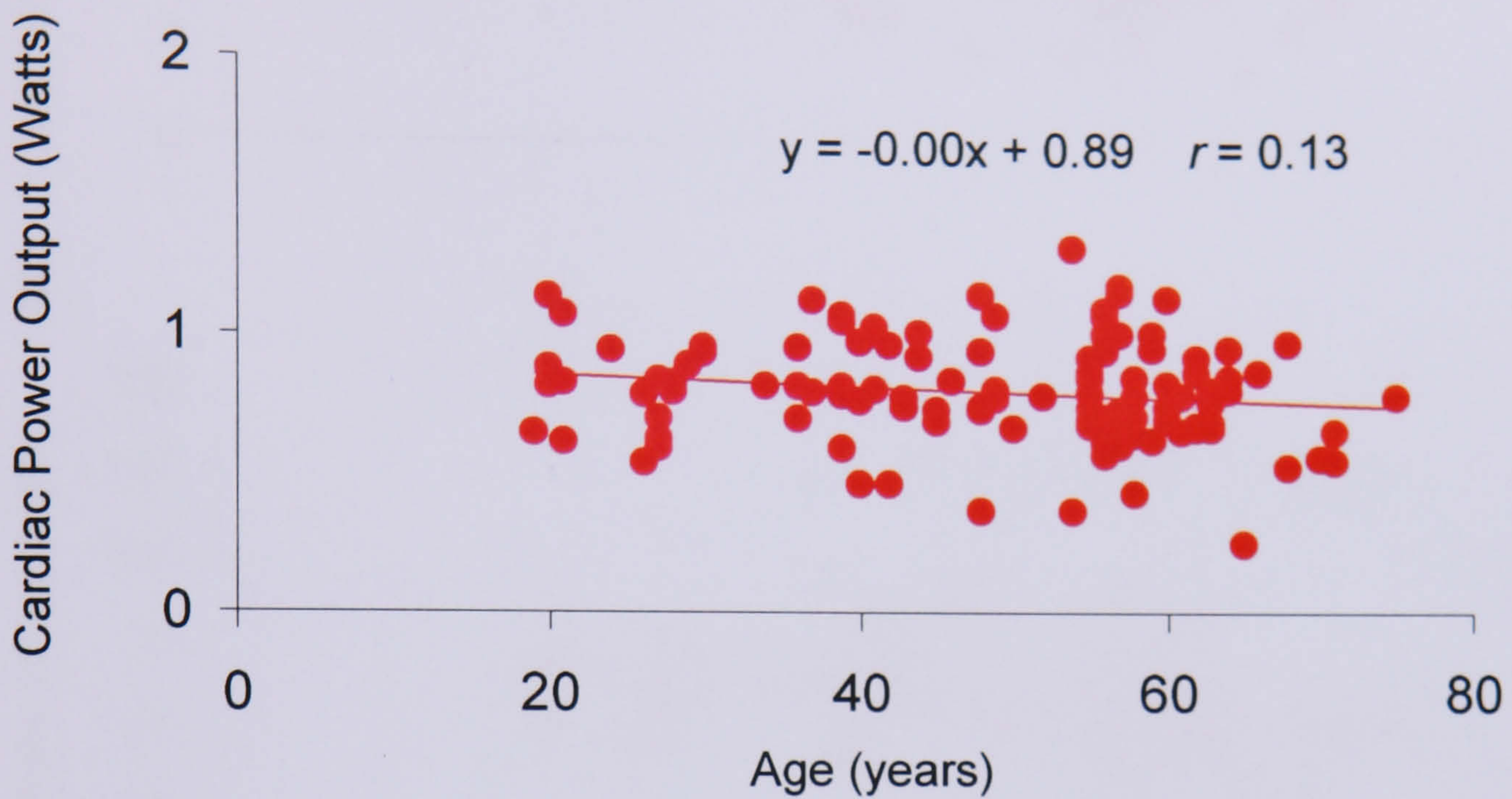


Figure 29 – The effects of fifty-six years of healthy ageing on resting overall cardiac function in women.

Resting CPO ($F(1,111) = 1.9$, $P > 0.1$) showed no correlation to healthy ageing in these sedentary women, between nineteen and seventy-six years of age.

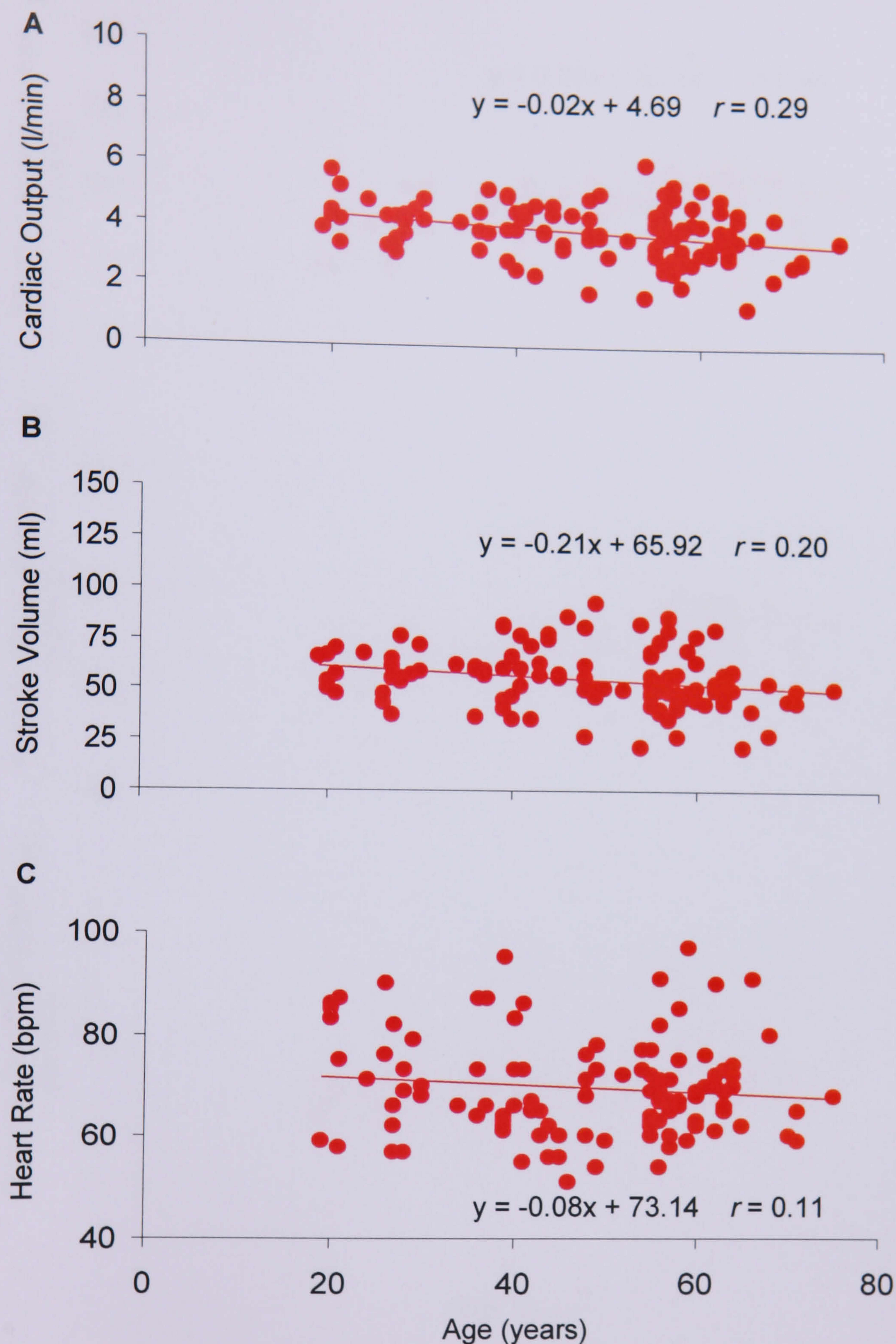


Figure 30 – The effects of healthy ageing on resting blood flow in women.

Resting cardiac output (A) ($F(1,111) = 10.3$, $P < 0.01$), and stroke volume (B) ($F(1,111) = 4.6$, $P < 0.05$) decreased significantly while resting heart rate (C) ($F(1,111) = 1.3$, $P > 0.2$) showed no significant change between nineteen and seventy-six years of age.

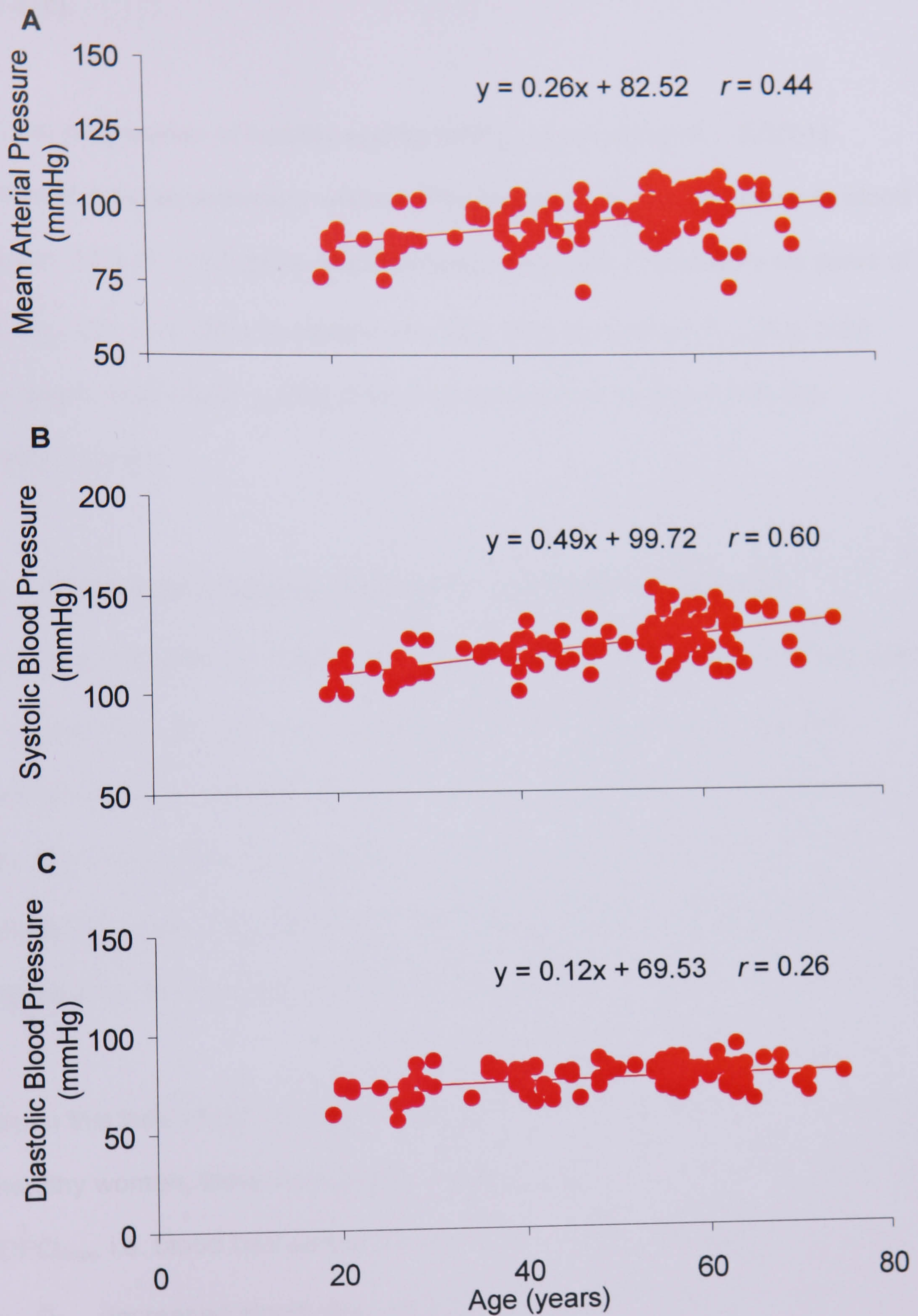


Figure 31 – Ageing and its effects on resting blood pressure in women.

Resting MAP (A) ($F(1,111) = 27.3, P < 0.0001$), SBP (B) ($F(1,111) = 61.1, P < 0.0001$) and DBP (C) ($F(1,111) = 8.2, P < 0.01$) all increased significantly as a consequences of healthy ageing.

(Fig. 31c).

With the progression of healthy ageing SVR_{rest} significantly ($P < 0.0001$) increased in these sedentary women. The escalation in the resistance to blood flow was 64% or $1013 \text{ dynes/s/cm}^5$ between nineteen and seventy-six years of age (Fig. 32), and helps to explain why \dot{Q}_{rest} (Fig. 30a) and SV_{rest} (Fig. 30b) decreased, whilst MAP_{rest} (Fig. 31a) increased in these women with the advancing years.

7.3 Maximum Cardiac Function in Sedentary Women

The lack of a significant change in CPO_{rest} in healthy women is interesting, but not surprising given the lack of an age-related change in $\dot{V}O_{2rest}$ (Fig. 28). However, the lack of a significant change ($P > 0.3$) in CPO_{max} over the same age-range (Fig. 33) is very important, and was unexpected given the 40% reduction in $\dot{V}O_{2max}$ (Fig. 28). The mean CPO_{max} for the entire group of sedentary healthy women was 4.07 ± 0.07 Watts.

Despite this lack of any change in overall cardiac function as a result of ageing in healthy women, there were significant changes in the two component parts of CPO_{max} , i.e. blood flow and blood pressure. In terms of maximum blood flow, \dot{Q}_{max} decreased significantly ($P < 0.0001$) by 26% (Fig. 34a). The SV_{max} of these women did not change significantly ($P > 0.1$), the mean SV_{max} for the group was $87.6 \pm 1.2 \text{ ml}$ (Fig. 34b). Therefore, the significant ($P < 0.0001$) 19% decrease in HR_{max} (Fig. 34c), which equates to a reduction of 0.6 beats per year was the main reason for the decline of \dot{Q}_{max} .

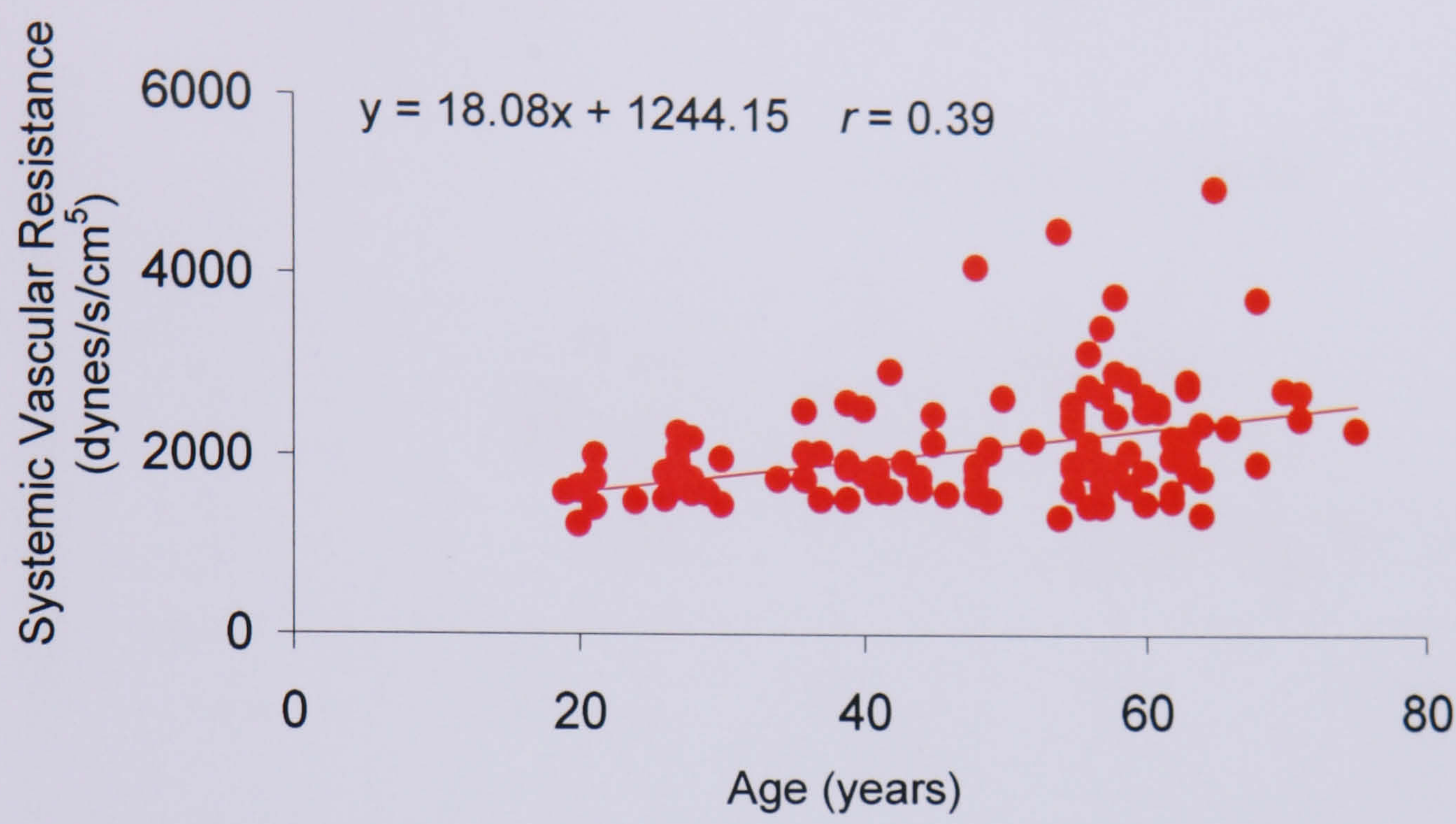


Figure 32 – Resting systemic vascular resistance and the age-related change in sedentary women.

Resting systemic vascular resistance ($F(1,111) = 19.7, P < 0.0001$) showed a strong linear increase as a result of healthy ageing in women.

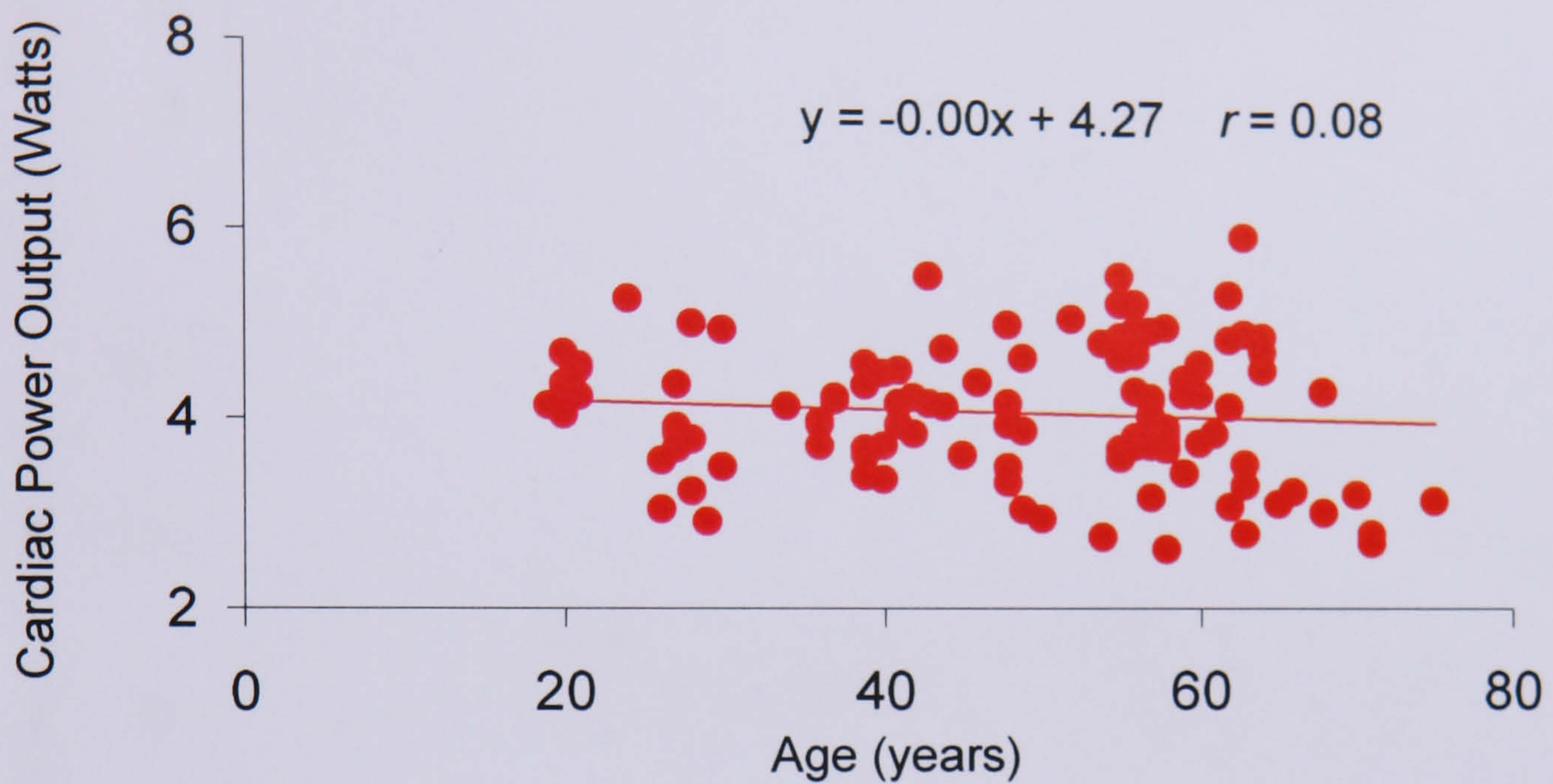


Figure 33 – Maximum overall cardiac function in sedentary women between nineteen and seventy-six years of age.

Maximum cardiac power output did not change significantly ($F(1,111) = 0.8$, $P > 0.3$) as a result of healthy ageing in women.

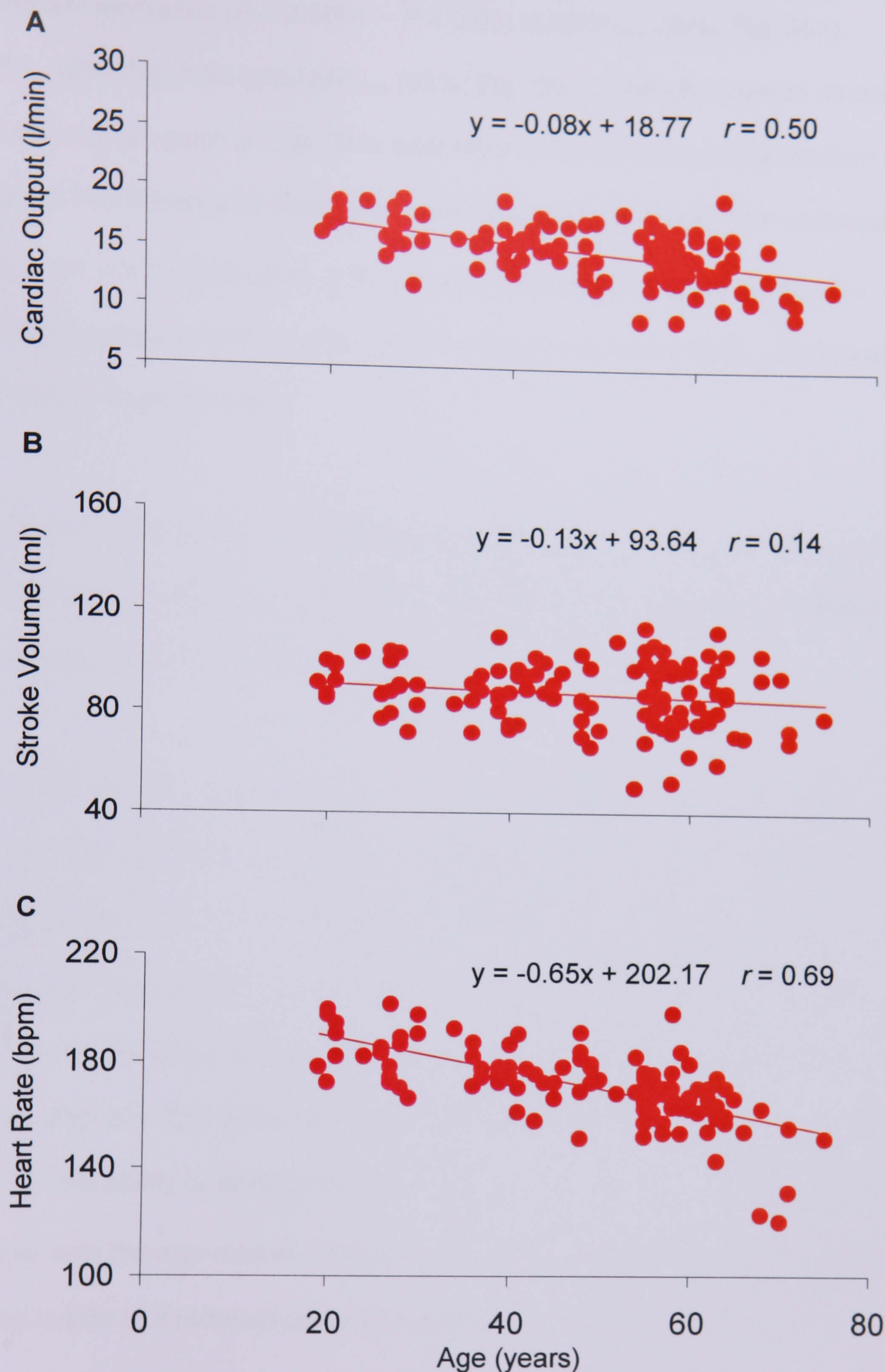


Figure 34 – The effects of ageing on maximum blood flow generation in women.

Maximum cardiac output (A) ($F(1,111) = 37.5$, $P < 0.0001$), stroke volume (B) ($F(1,111) = 2.2$, $P > 0.1$), and heart rate (C) ($F(1,111) = 84.9$, $P < 0.0001$) were measured between nineteen and seventy-six years of age in healthy women.

Significant increases ($P < 0.0001 - P < 0.05$) in MAP_{\max} (26%; Fig. 36a), SBP_{\max} (9%; Fig. 36b) and DBP_{\max} (63%; Fig. 36c) occurred between nineteen and seventy-six years of age. This adaptation in blood pressure generation opposes the decrease in blood flow over the same age-range. The decrease in \dot{Q}_{\max} as with the decrease in \dot{Q}_{rest} is partly the result of a significant ($P < 0.0001$) increase in SVR_{\max} (Fig. 36). The magnitude of the SVR_{\max} increase was 75% in these women.

Hence, by directing more of its pumping energy into pressure generation, as opposed to flow generation, the CPO_{\max} of the healthy female heart remains unchanged over most of its adult life span.

Given the 40% decrease in $\dot{V}O_{2\max}$ (Fig. 28), but the lack of any change in CPO_{\max} (Fig. 33), there is an unexplained discrepancy between the central (cardiac) pumps maintained function, and a reduced ability to consume oxygen with advancing age in healthy women. When the $a - \bar{v} O_{2\text{diff}\max}$ was calculated it showed a significant ($P < 0.0001$) 17% decline in these healthy women (Fig. 37). This illustrates that healthy ageing in women has an adverse effect on the ability of skeletal muscles to extract and consume oxygen. And together with the age-related decline in \dot{Q}_{\max} (Fig. 34a) explains why healthy ageing results in a reduced exercise capacity.

So, between nineteen and seventy-six years of age no significant changes occur in either resting aerobic function (Fig. 28), or resting overall cardiac function (Fig. 29) in healthy women. Maximal aerobic power does however decrease dramatically (Fig. 28) over the same age range. But, while \dot{Q}_{\max}

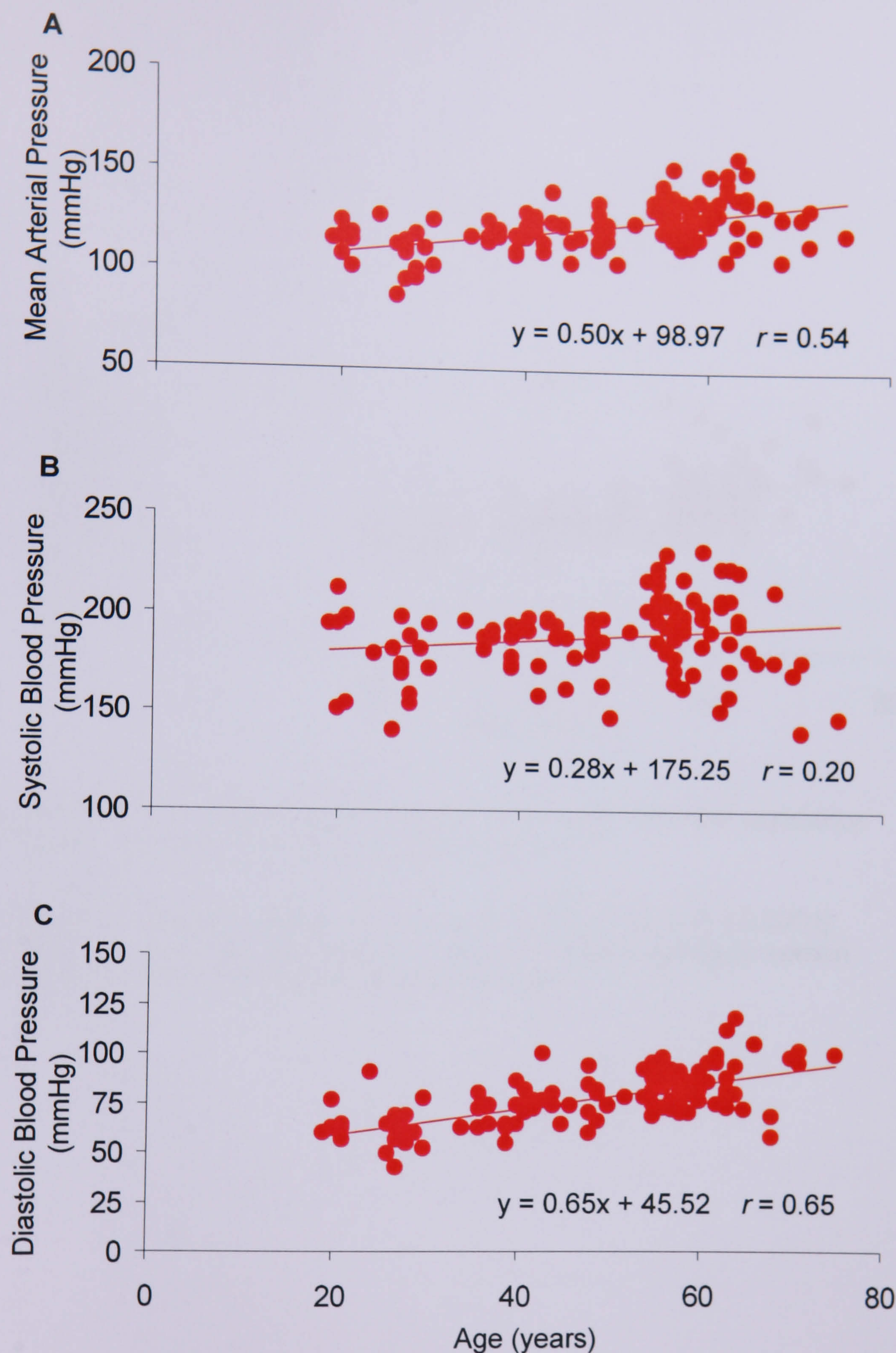


Figure 35 – Age-related values of maximum blood pressure in sedentary women.

Maximum mean arterial (A) ($F(1,111) = 44.7, P < 0.0001$), systolic (B) ($F(1,111) = 4.7, P < 0.05$) and diastolic (C) ($F(1,111) = 83.1, P < 0.0001$) blood pressures all increased significantly as a consequence of healthy ageing in women.

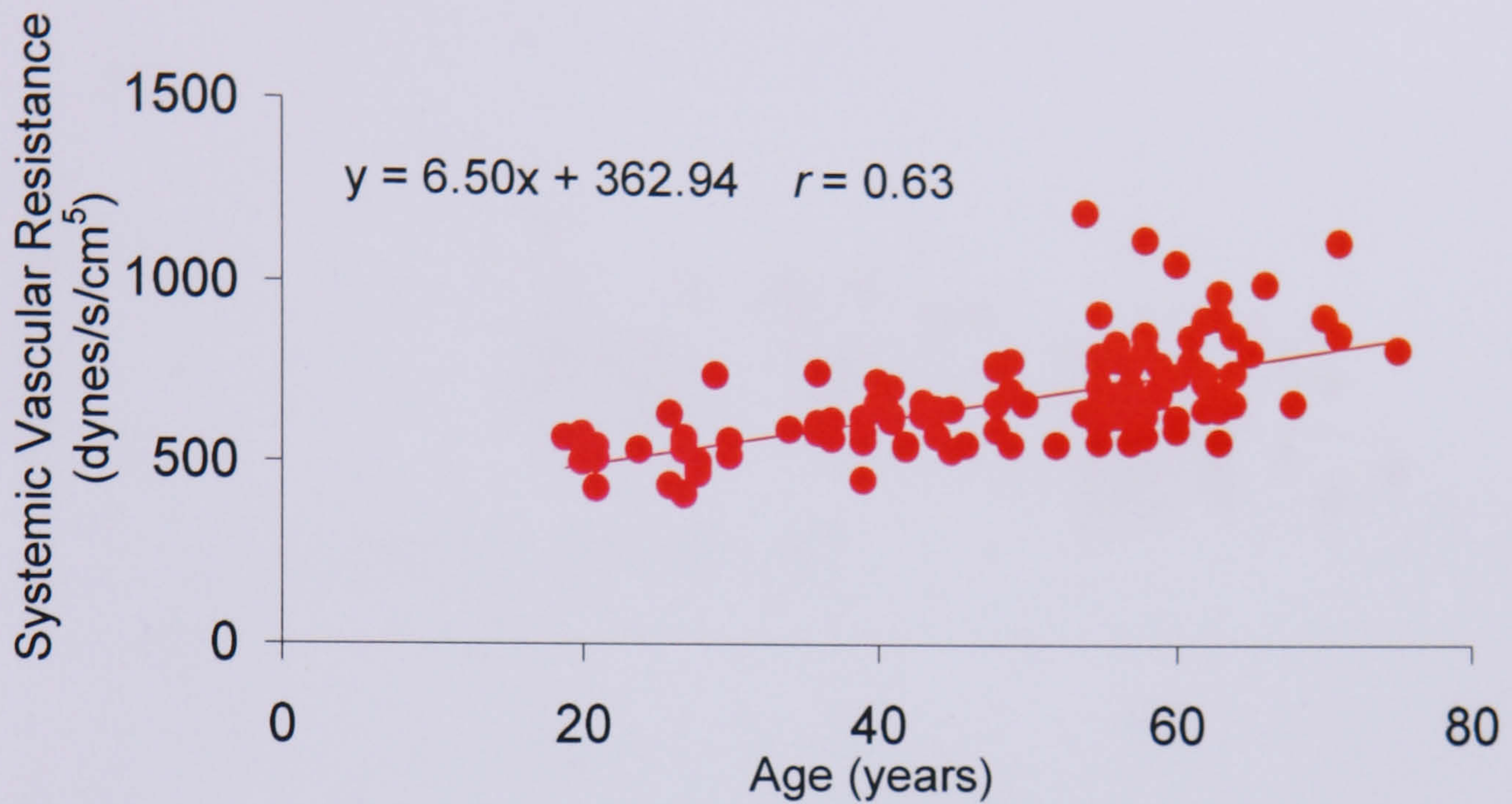


Figure 36 – The effect of healthy ageing on systemic vascular resistance at maximum aerobic power in sedentary women.

Systemic vascular resistance at $\dot{V}O_{2\max}$ ($F(1,111) = 72.6$, $P < 0.0001$) showed a strong linear increase as a result of healthy ageing in women between nineteen and seventy-six years of age.

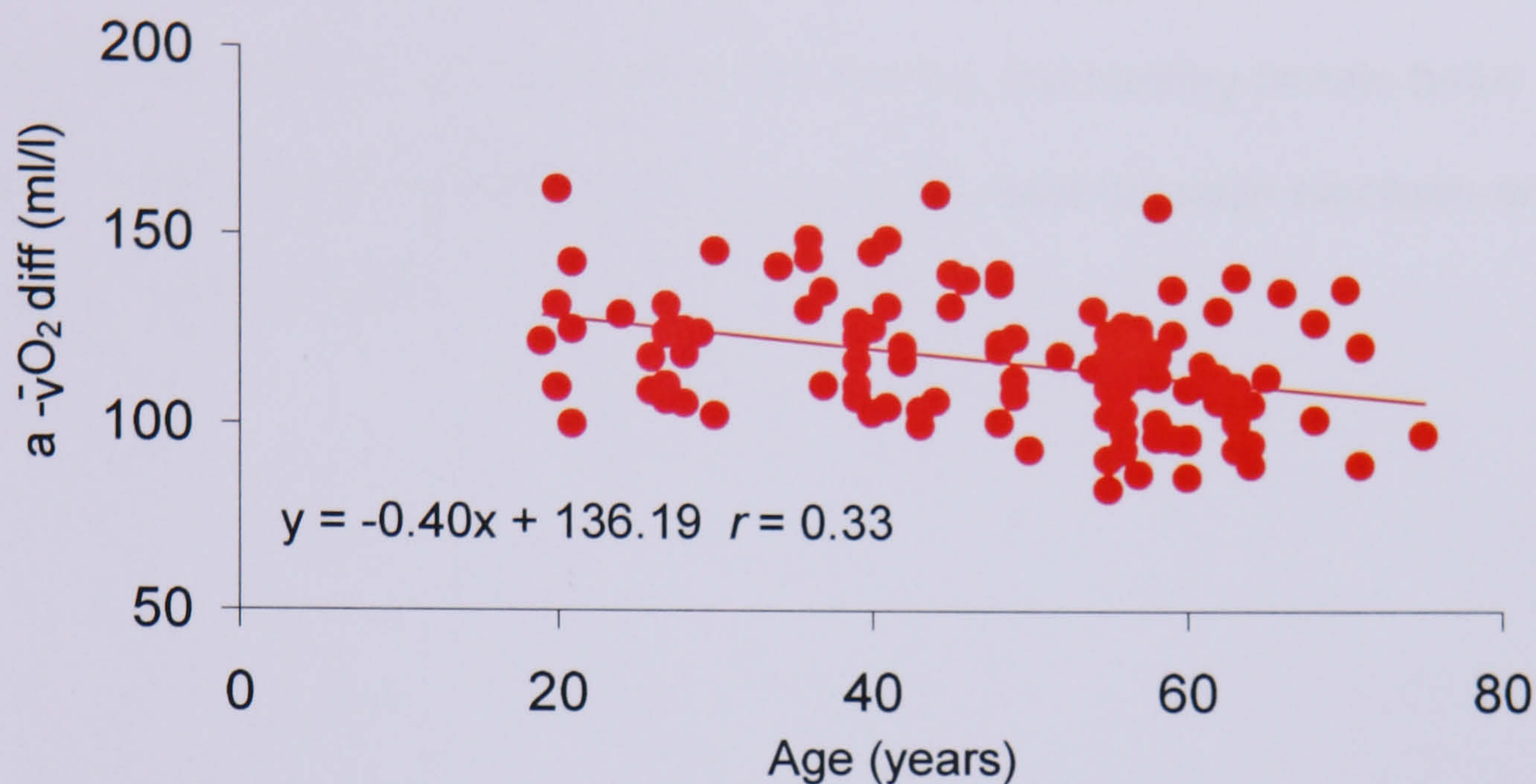


Figure 37 – The effect of ageing on maximum arteriovenous oxygen difference in healthy women.

Maximum arteriovenous oxygen difference $a - \bar{v}O_2$ diff declined significantly ($F(1,111) = 13.21$, $P < 0.0001$) in healthy women between nineteen and seventy-six years of age.

This value was calculated from the measurement of $\dot{V}O_2$ and \dot{Q} .

(Fig. 34a) also declines, there is a concomitant increases in MAP_{max} (Fig. 35a) which helps to effectively maintain maximal overall cardiac function (Fig. 33).

With both CPO_{rest} and CPO_{max} being effectively maintained in women, there was no significant deterioration ($P > 0.5$) in the overall functional reserve capacity (CR) of the female heart (Fig. 38). Hence, the healthy female heart appears to be resistant to the effects of ageing, at least between nineteen and seventy-six years of age.

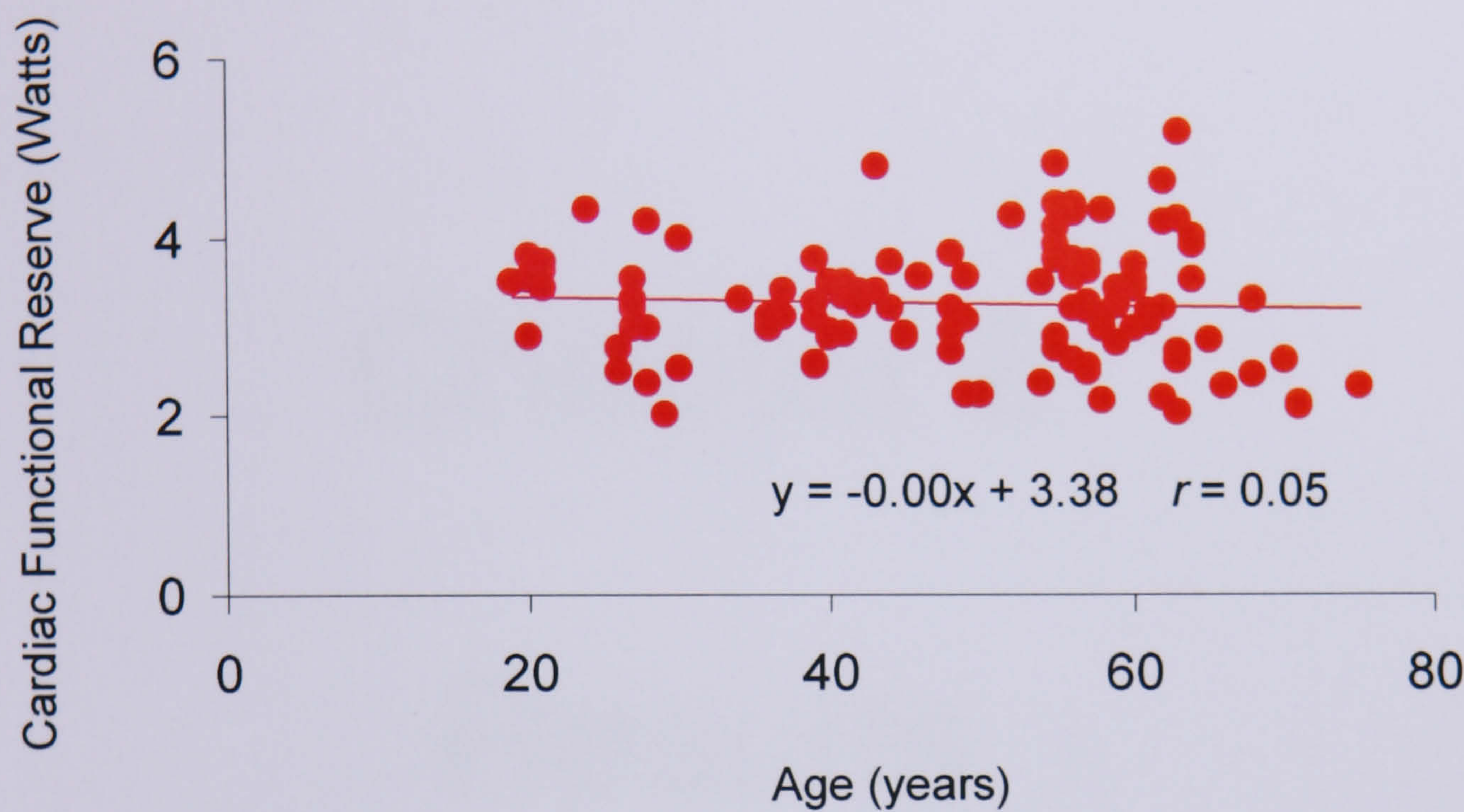


Figure 38 – Cardiac functional reserve in women between nineteen and seventy-six years of age.

Cardiac function reserve determined as $CPO_{\max} - CPO_{\text{rest}}$ (see Figs. 34 and 30) showed no significant ($F(1,111) = 0.3, P > 0.5$) change in healthy women.

Chapter 8

Results

The Effects of Endurance-Training in Women

8.0 Long-Term Endurance Exercise Training in Women

The healthy female heart appears to be remarkably resilient, maintaining its overall function in the face of ageing (see chapter 7). However, the question of what impact long-term endurance training has on overall cardiac function in women has not been previously studied.

Three groups of female athletes were recruited; they were approximately twenty-five, fifty and sixty years of age and were compared to healthy but sedentary age-matched women. Only active females who trained and competed on a regular basis were chosen. Unfortunately, the total number of recruits that met our stringent selection criteria was less, this being due to the fact that there are less active females than males, especially in the older age ranges.

All of the athletes who were recruited were still competitive in various distance events. In the twenty-five year old age group some individuals were of national or international competition standard. All of these younger athletes covered forty-one miles per week, and had been training for, on average, thirteen years. All the women in the two older age groups (fifty and sixty years of age) were recruited from athletics clubs across Merseyside. The fifty year old age group covered thirty-six miles per week, and had been training for an average of twenty years. The sixty year old age group still covered twenty-nine miles per week, and had been training for, on average, fourteen years. These volumes of exercise were in marked contrast to the sedentary women who engaged in less than ninety minutes of exercise (both structured and recreational) per week. Also, by only recruiting women who completed these

high volumes of endurance training, it also ensured a meaningful comparison could be made to the male athletes, i.e. the training stimulus was as comparable as possible.

The anthropometric data for the groups is presented in Table 12. The percentage of total body weight which was fat was significantly ($P < 0.0001$) lower in all the athletic groups in comparison to their age-matched sedentary counterparts. Furthermore, the sixty year old veteran athletes had a lower body fat percentage than the twenty-five year old sedentary group. In all the other anthropometric respects the sedentary and trained women were comparable.

8.1 Long-Term Endurance Exercise Training and Aerobic Power in Women

As expected, engaging in long-term endurance training had a significant impact on $\dot{V}O_{2\max}$ (Fig. 39). Each of the three groups of endurance-trained women had significantly ($P < 0.0001$) greater aerobic power than the sedentary age-matched groups. The adaptations were 81%, 60% and 64% at twenty-five, fifty and sixty years of age, respectively. Furthermore, the fifty and sixty year old athletic female groups had a significantly ($P < 0.05$) greater $\dot{V}O_{2\max}$ than the sedentary twenty-five year old group. These changes illustrates that engaging in long-term endurance exercise has a positive effect on $\dot{V}O_{2\max}$, despite the confounding influence of healthy ageing. These significant differences between active and sedentary women remained whether aerobic power was reported in absolute terms, per kilogram of total body mass, or scaled to lean body mass. But, healthy ageing still resulted in a

Sedentary			
Age (Years)	25.7 ± 0.7	48.1 ± 0.5	60.8 ± 0.5
N	18	13	37
Height (cm)	167.1 ± 1.5	164.0 ± 1.9	159.1 ± 0.9 †
Total Body Mass (Kg)	63.4 ± 1.6	68.7 ± 3.2	67.3 ± 1.3
Body Mass Index (Kg/m ²)	22.8 ± 0.6	25.5 ± 1.1	26.5 ± 0.5 †
Body Surface Area (m ²)	1.7 ± 0.0	1.7 ± 0.0	1.7 ± 0.0
Fat Body Mass (Kg)	18.4 ± 0.8	23.0 ± 2.2	24.4 ± 0.8 †
% Body Fat	28.9 ± 0.8	32.8 ± 1.8	36.0 ± 0.6 †
Lean Body Mass (Kg)	42.6 ± 1.0	43.4 ± 1.5	40.9 ± 0.7 †
Athletes			
Age (Years)	26.8 ± 1.1	50 ± 1.0	60.8 ± 2.5
N	6	8	4
Height (cm)	164.9 ± 1.4	162.2 ± 2.8	163.2 ± 3.1
Total Body Mass (Kg)	56.0 ± 2.6	61.2 ± 2.6	63.4 ± 4.4
Body Mass Index (Kg/m ²)	20.6 ± 0.8	23.3 ± 0.9	24.0 ± 2.3
Body Surface Area (m ²)	1.6 ± 0.0	1.7 ± 0.0	1.7 ± 0.0
Fat Body Mass (Kg)	9.5 ± 1.4 *	16.4 ± 1.8 †	16.5 ± 2.6
% Body Fat	16.7 ± 1.7 *	26.4 ± 2.0 *†	25.7 ± 2.4 *†
Lean Body Mass (Kg)	44.2 ± 1.8	42.6 ± 1.4	44.6 ± 2.2 *

Table 12 – Anthropometric characteristics of endurance-trained and sedentary women.

Data are presented as means ± standard error of the mean.

* Significant differences (*P* < 0.05) when comparing age-matched sedentary and athletic women.

† Significant differences (*P* < 0.05) compared to either sedentary or trained twenty-five year old women.

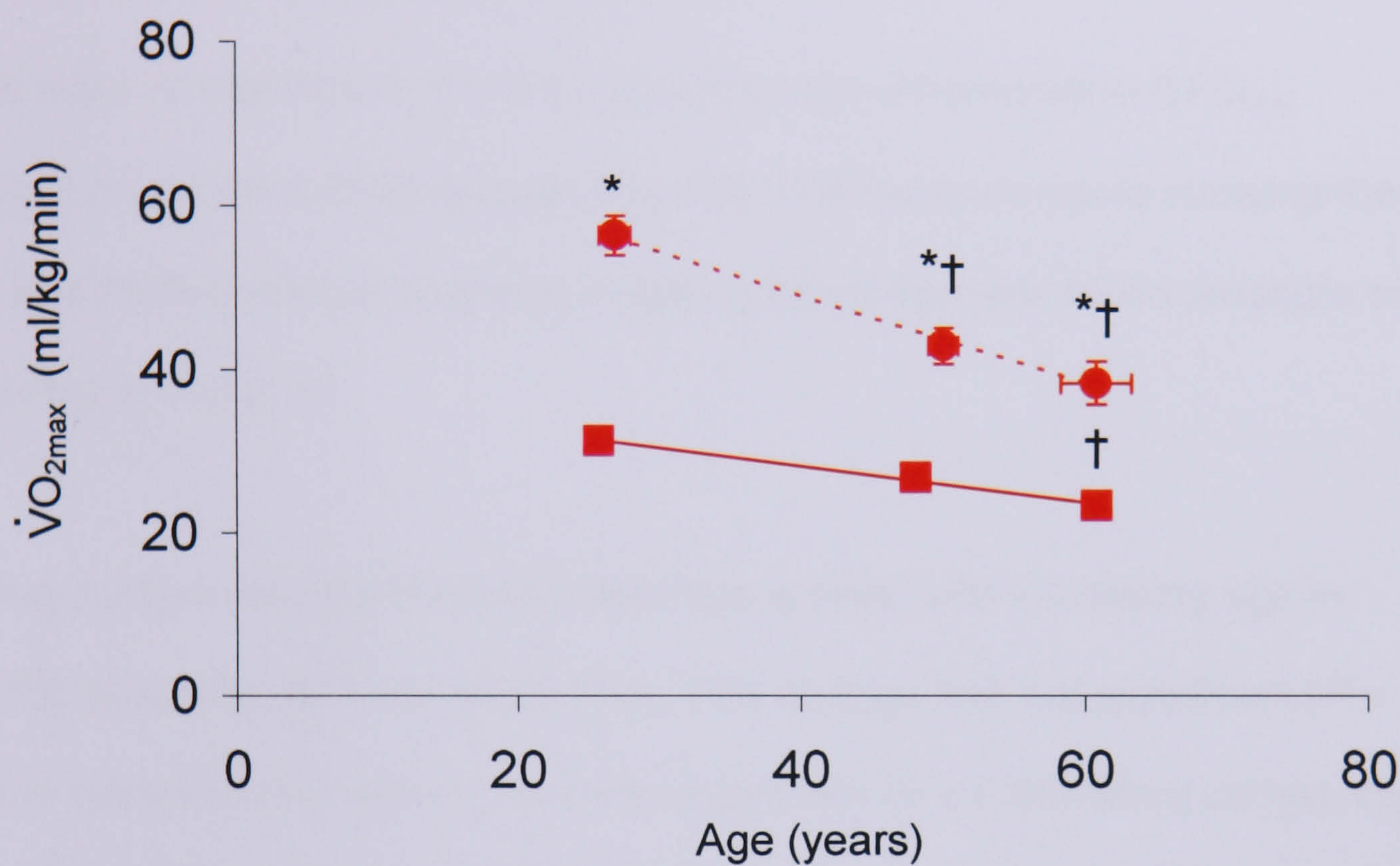


Figure 39 – Maximum aerobic power in age-matched sedentary women and female athletes.

The maximum aerobic power sedentary (■) and long-term endurance-trained women (●) of twenty-five, fifty and sixty years of age.

* Significant differences ($P < 0.05$) when comparing age-matched sedentary and athletic women.

† Significant differences ($P < 0.05$) compared to either sedentary or trained twenty-five year old women.

significant ($P < 0.0001$) 32% reduction in the $\dot{V}O_{2\max}$ of the athletic women, between twenty-five and sixty years of age (Fig. 39).

8.2 Long-Term Endurance Exercise Training and Resting Cardiac Function in Women

There were no significant ($P > 0.6$) discriminatory differences in CPO_{rest} between any of the female groups (Fig. 40). The measurements showing the age- and training-related changes in resting blood flow and blood pressure are presented in Table 13.

Resting cardiac output exhibited a decreasing trend with increasing age in both the sedentary and trained women. This change was not significant ($P > 0.05$) in the sedentary women, but was significant ($P < 0.05$) when comparing the youngest and oldest endurance trained groups. All of the trained groups had a lower HR_{rest} than their age-matched sedentary counterparts. However, the differences only reached statistical significant ($P < 0.05$) at twenty-five and sixty years of age. In the twenty-five year old athletes SV_{rest} was significantly ($P < 0.05$) increased by 44%, thus compensating for the decline in HR_{rest} and maintaining \dot{Q}_{rest} . In contrast, there were no significant ($P > 0.9$) age-matched differences in SV_{rest} at either fifty or sixty years, and an age-related decrease in SV_{rest} was evident in both the sedentary and trained women.

Training induced no meaningful changes in resting blood pressure generation (Table 13). In the athletic populations MAP_{rest} , SBP_{rest} and DBP_{rest} all showed similar increasing trends with age, as was evident in the sedentary women.

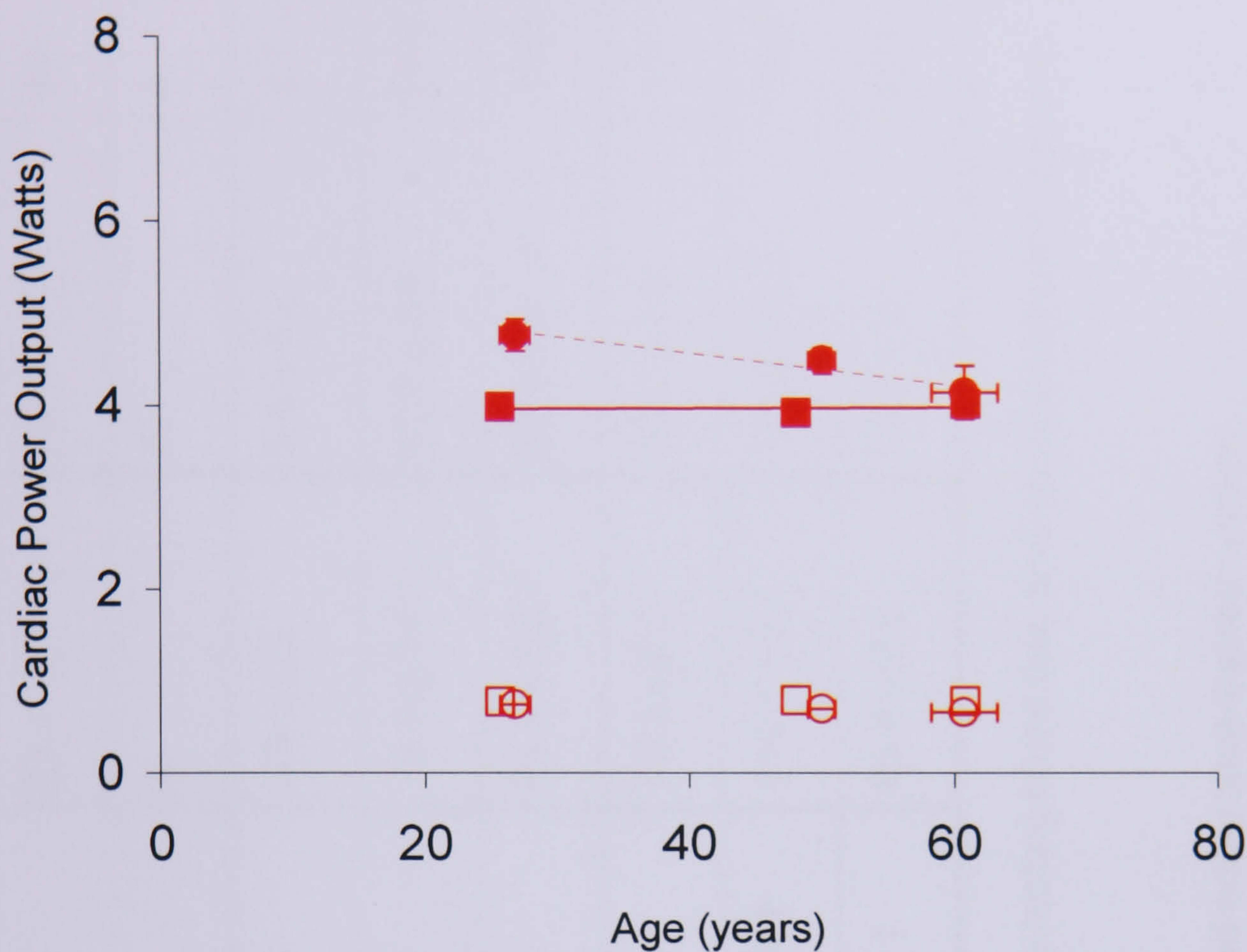


Figure 40 – The effects of healthy ageing and long-term endurance exercise on cardiac power output in women.

Square symbols depict values for sedentary women and circles athletes. Open and solid symbols represent values measured at rest and maximum exercise, respectively.

Data are presented as means ± standard error of the mean.

There were no statistically significant ($P > 0.05$) differences between any of the measurements of CPO, when comparing any of the sedentary or trained groups at rest, or at maximal exertion.

	Sedentary				Trained			
Age (Years)	25	50	60		25	50	60	
n	18	13	37		6	8	4	
Q̇ (l/min)	4.0 ± 0.2	3.7 ± 0.2	3.6 ± 0.2		3.9 ± 0.2	3.4 ± 0.2	2.7 ± 0.3 †	
HR (bpm)	71.6 ± 2.9	64.5 ± 2.5	70.2 ± 1.5		49.3 ± 2.9 *	57.6 ± 3.5	54.6 ± 2.2 *	
SV (ml)	56.9 ± 2.9	59.4 ± 5.1	52.7 ± 2.5		81.8 ± 8.2 *	59.3 ± 3.1 †	49.6 ± 7.0 †	
MAP (mmHg)	87.2 ± 1.6	94.2 ± 2.5	97.8 ± 1.4 †		86.2 ± 2.7	93.7 ± 3.6	111.1 ± 4.0 * †	
SBP (mmHg)	111.1 ± 1.9	122.1 ± 2.1	129.3 ± 1.8 †		110.1 ± 3.1	122.3 ± 4.5	149.0 ± 6.4 * †	
DBP (mmHg)	70.1 ± 1.8	77.4 ± 1.5 †	76.2 ± 1.0 †		69.6 ± 2.8	73.7 ± 3.1	84.6 ± 2.6 †	

Table 13 – The effects of ageing and long-term endurance exercise on resting blood flow and blood pressure in women.

Data are presented as means ± standard error of the mean.

* Significant difference, (*P* < 0.05) between sedentary and age-matched endurance-trained women.

† Significant differences (*P* < 0.05) compared to either sedentary or trained twenty-five year-old women.

As mentioned previously CPO_{rest} represents only a small proportion of the overall cardiac reserve. Hence, changes at rest might be expected to be small and not discriminate between very different populations.

8.3 Long-Term Endurance Exercise Training and Maximum Cardiac Function in Women

Unexpectedly and very interesting there were no significant ($P > 0.05$) changes in the CPO_{max} of long-term endurance trained women, compared with the sedentary controls (Fig. 40). This lack of any adaptation to the training stimulus is perhaps surprising given the marked adaptation in $\dot{V}O_{2max}$ in the same subjects (Fig. 39). Also, the lack of a training induced adaptation in CPO_{max} in the very active women is in stark contrast to the changes seen in the equivalent male populations (Fig. 24), despite the fact that both sexes were engaging in comparable exercise protocols, and therefore receiving a similar training stimulus. While there did appear to be a small increase (17 %) in CPO_{max} in the twenty-five year old female athletes, this difference was not statistically significant ($P > 0.05$) when compared to the age-matched sedentary women.

In terms of maximum blood flow generation, \dot{Q}_{max} was higher in all the trained groups of women, when compared to the age-matched sedentary groups. However, these differences only reached statistical significance ($P < 0.05$) at twenty-five years of age (Table 14). There was also a significant ($P < 0.05$) age-related decline in \dot{Q}_{max} in both the trained and sedentary women. The higher \dot{Q}_{max} values measured in the athletic groups were the result of positive

	Sedentary			Trained			
Age (Years)	25	50	60		25	50	60
n	18	13	37		6	8	4
Q̇ (l/min)	16.6 ± 0.6	14.9 ± 0.6	14.1 ± 0.3 †		19.7 ± 1.1 *	16.5 ± 0.4 †	14.7 ± 1.1 †
HR (bpm)	182.3 ± 2.6	174.0 ± 2.7	164.4 ± 2.0 †		175.4 ± 3.2	166.6 ± 2.1	161.3 ± 5.3 †
SV (ml)	91.3 ± 2.8	86.0 ± 3.5	86.1 ± 2.3		112.9 ± 7.1 *	98.8 ± 2.5	91.9 ± 9.7
MAP (mmHg)	107.9 ± 2.9	118.4 ± 2.4	129.0 ± 2.1 †		109.8 ± 2.9	123.7 ± 3.4 †	128.2 ± 3.3 †
SBP (mmHg)	174.6 ± 4.8	182.0 ± 4.3	193.5 ± 3.2 †		185.0 ± 6.9	200.0 ± 6.7	204.5 ± 5.9
DBP (mmHg)	61.0 ± 2.9	73.8 ± 2.7 †	83.8 ± 2.1 †		57.2 ± 1.9	70.4 ± 3.5 †	74.8 ± 2.7 †

Table 14 – The effects of ageing and endurance-training on maximum measures of blood flow and blood pressure in women.

Data are presented as means ± standard error of the mean.

* Significant difference, (*P* < 0.05) between sedentary and age-matched endurance-trained women.

† Significant differences (*P* < 0.05) compared to either sedentary or trained twenty-five year-old women.

adaptations in SV_{\max} in response to the training stimulus (Table 14). Maximum stroke volume was higher in all the trained groups, but again the difference was only statistically significant when comparing the youngest age-matched groups. There were no age-matched differences in HR_{\max} , which decreased with increasing age in both the active and sedentary women (Table 14).

As with the resting measures of blood pressure (Table 13), training had no effect on any of the measures of blood pressure at maximum exercise (Table 14). Hence, MAP_{\max} still increased with age in both populations, regardless of their activity lifestyles.

The impact of these changes (both significant and non-significant) was that all the athletic groups had higher cardiac functional reserves than their age-matched sedentary counterparts (Fig. 41). These increases though were not statistically significant ($P > 0.05$), and equated to only 25%, 21% and 8% at twenty-five, fifty and sixty years of age, respectively in women.

To explain how the endurance trained women could increase their $\dot{V}O_{2\max}$ by up to 81% in comparison to their age-matched sedentary counterparts, despite there being very little significant adaptations in \dot{Q}_{\max} and CPO_{\max} , maximum arteriovenous oxygen differences ($a - \bar{v} O_{2\text{diff}_{\max}}$) were calculated. In response to the long-term endurance training stimulus the $a - \bar{v} O_{2\text{diff}_{\max}}$ increased significantly ($P < 0.0001$) in all three of the trained groups of women, compared to the age-matched sedentary groups (Fig. 42). The magnitude of the increase was 33%, 29%, and 48% at twenty-five, fifty and sixty years of age, respectively. Furthermore, engaging in long-term endurance exercise

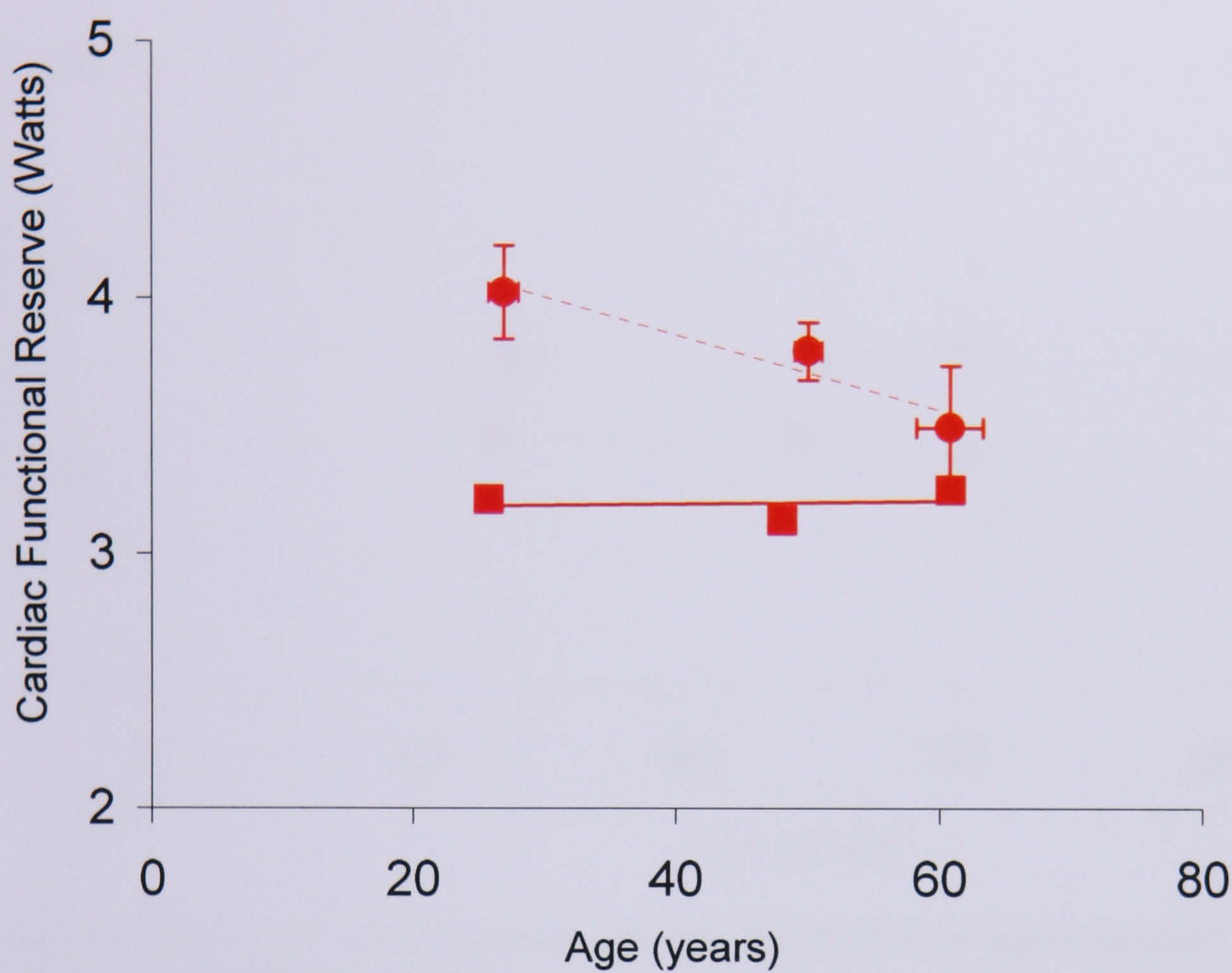


Figure 41 – Overall cardiac functional reserve in sedentary and endurance-trained women.

Overall cardiac functional reserve of sedentary (■) and long-term endurance-trained women (●) of twenty-five, fifty and sixty years of age.

Data are presented as means ± standard error of the mean.

There were no statistically significant ($P > 0.05$) differences between any of the measurements of CR when comparing any of the sedentary or trained groups.

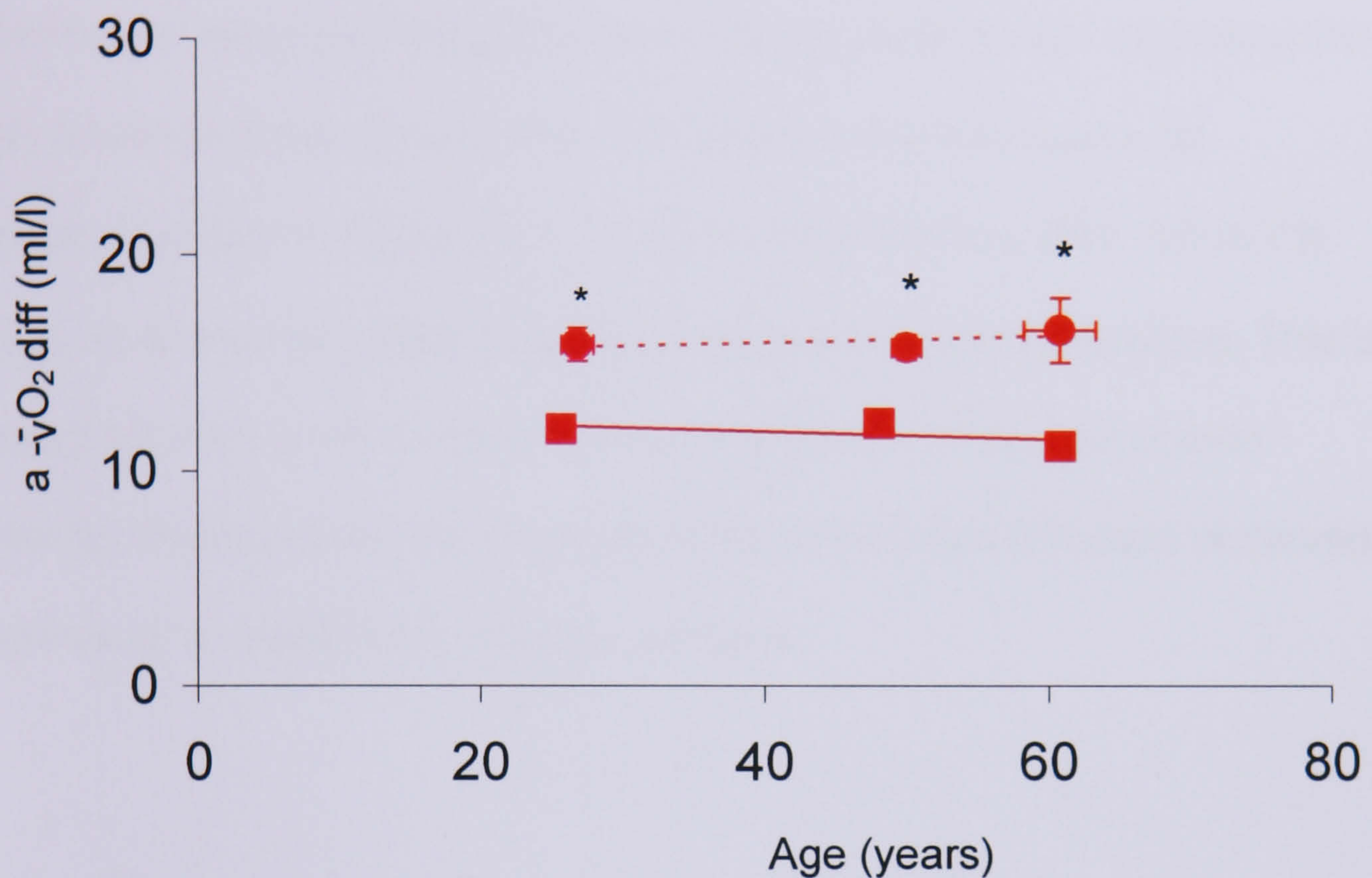


Figure 42 – Maximum arteriovenous oxygen difference in age-matched sedentary and athletic females.

The $a - \bar{v} O_2 \text{diff}_{\text{max}}$ of age-matched sedentary (■) and long-term endurance trained women (●).

This value was calculated from the measurement of $\dot{V}O_2$ and \dot{Q} .

* Significant differences ($P < 0.05$) when comparing age-matched sedentary and athletic women.

† Significant differences ($P < 0.05$) compared to either sedentary or trained twenty-five year-old women.

prevented any age-related decrease in a $\bar{V}O_2 \text{ diff}_{\text{max}}$, illustrated by the fact that the fifty and sixty year old athletes had significantly ($P < 0.0001$) higher a $\bar{V}O_2 \text{ diff}_{\text{max}}$ values than the younger sedentary (twenty-five year old) women.

Participating in long-term endurance exercise was effective in increasing the aerobic power of these women (Fig. 39). Despite this there were no statistically significant changes ($P > 0.05$) in either CPO_{max} (Fig. 40) or CR (Fig. 41), as a result of healthy ageing or endurance-exercise training. This is in marked contrast to the training induced adaptation measured in men (chapter 5), where substantial changes in the overall function were observed in response to a comparable exercise stimulus.

Chapter 9

Results

Sex-Related Differences in Body
Composition and Overall Cardiac
Function in Response to Ageing.

9.0 The Impact of Body Composition

The effect of healthy ageing on overall cardiac function therefore seems to differ between the two sexes. Healthy women maintain cardiac function, while in stark contrast over the same period the overall capacity of the male heart decreases significantly. Hence, it seemed appropriate to study these sex-related differences in more detail.

Clearly there are distinct differences in body size and composition between men and women, these dissimilarities need to be taken into account when comparing potential sex-related differences in cardiac function. Sex specific changes also occur in body mass and composition (Starling, 2001) as a consequence of ageing. Therefore, some of the reported changes in the dynamic functions e.g. $\dot{V}O_{2\max}$ and CPO could be the result of changes in body composition rather than ageing *per se*.

Of the original cohort one-hundred and sixty-eight individuals (fifty-seven men, and one-hundred and eleven women, between nineteen and seventy-six years of age) had their body composition measured using DEXA, and were therefore included in this analysis for sex-related difference in relation to ageing.

9.1 Changes in Body Composition as a Result of Healthy Ageing

In the males total body mass (TBM), body mass index (BMI) and body surface area (BSA) did not change significantly ($P > 0.1$) between nineteen and seventy-six years of age. The mean values for these measures were 83.0 ± 1.3 kg, 26.7 ± 0.4 kg/m² and 2.0 ± 0.0 m² respectively. Most importantly there

were significant changes in body composition (Fig. 43). Between nineteen and seventy-six years lean body mass (LBM) decreased by 9% in healthy men, but this did not reach the level of statistical significance ($P > 0.05$) (Fig. 43a), while total body fat (FM) significantly ($P < 0.05$) increased by 29% (Fig. 43b).

Similarly, in the women there were no significant changes in TBM or BSA; the mean values were 68.2 ± 1.0 kg and 1.7 ± 0.0 m² respectively. However, BMI in the sedentary females did increase significantly ($P < 0.01$) by 16% over the age-range studied. The age-related changes in the body composition of the sedentary women were very similar to those seen in the sedentary men (Fig. 43). Between nineteen and seventy-six years of age LBM significantly ($P < 0.05$) decreased by 11% (Fig. 43a), and FM increased ($P < 0.05$) by 31% (Fig. 43b). The rate of the age-related changes in body composition was comparable in both the sedentary men and women. This is represented by the slopes of the trendlines in Figure 43.

Finally, at all points of the age continuum the men had greater amounts of LBM (Fig. 43a), and smaller amounts of FM (Fig. 43b) in comparison to the age-matched women.

9.2 Allometric Scaling of Aerobic Power

For many years differences in body mass between men and women have been recognised and normalised accordingly. However, allometric scaling allows changes in dynamic physiological functions to be investigated independently of changes in both body size and crucially composition. By

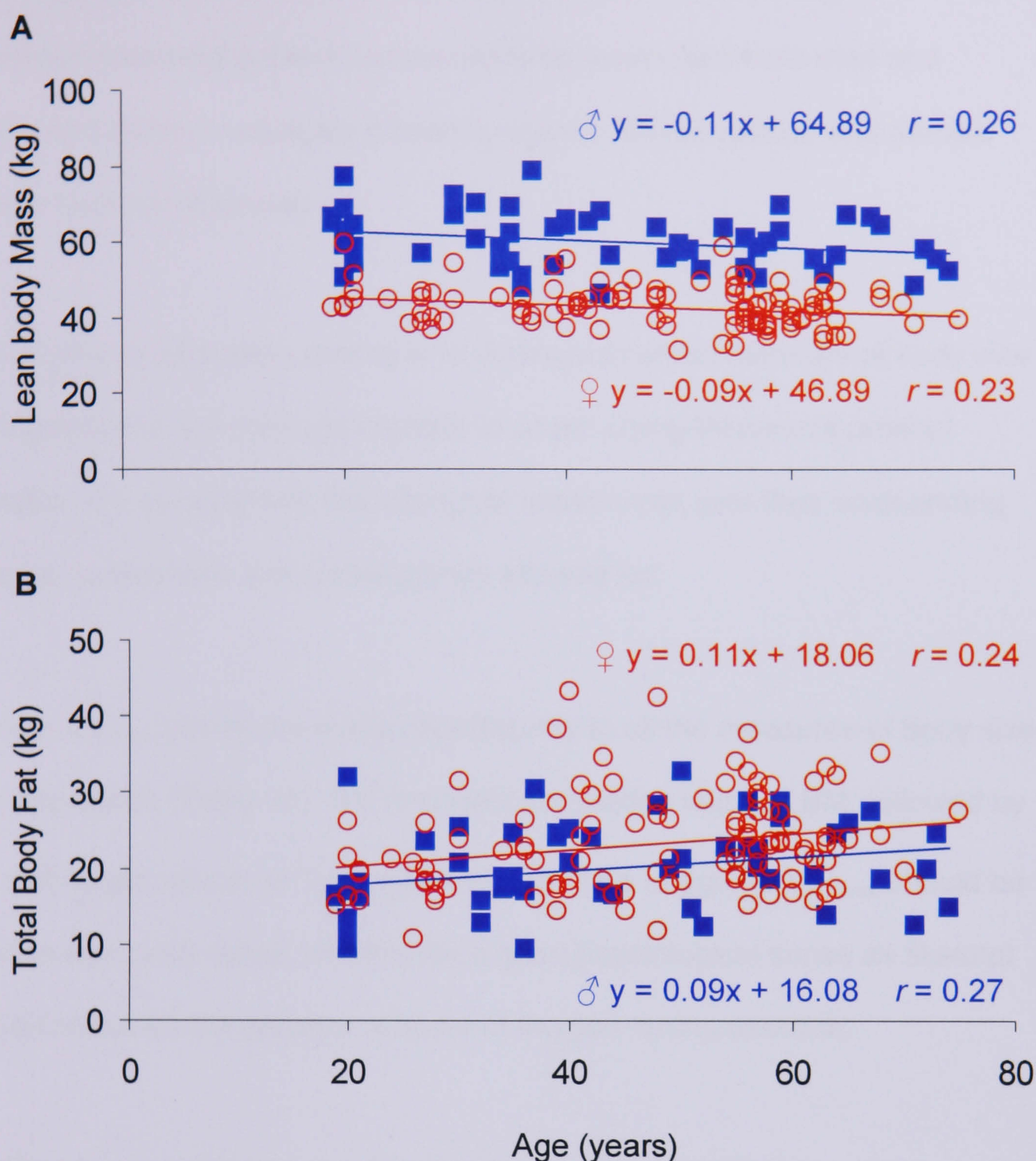


Figure 43 – Changes in body composition as a consequence of healthy ageing.

Lean body mass (A) showed a no significant change with ageing in men (■) ($F(1, 55) = 3.8$, $P > 0.05$), but did show a significant negative correlation to age in women (○) ($F(1, 109) = 6.1$, $P < 0.05$).

Total body fat (B) increased significantly with healthy ageing in both men (■) ($F(1, 55) = 4.4$, $P < 0.05$), and women (○) ($F(1, 109) = 6.7$, $P < 0.05$).

controlling the impact of body composition as well as mass, it is possible to make more meaningful direct comparisons between data from men and women, and hence investigate if healthy ageing affects cardiac and aerobic exercise function differently.

The first step in allometric scaling is to distinguish which measure of body size or composition is the most appropriate to scale. Using Pearson's product correlation the variable with the strongest relationship, and thus confounding influence, is identified and subsequently allowed for.

Absolute $\dot{V}O_{2\max}$ (l/min) correlated significantly to all the measures of body size and composition (Table 15); the strongest correlation was to LBM, followed by BSA and height, ahead of TBM, FM and BMI. This suggests $\dot{V}O_{2\max}$ should be scaled to lean body mass, which makes good physiological sense as skeletal muscle consumes the greatest amount of oxygen during exercise.

The allometric equation ($y = a x^b \varepsilon$) was then applied to derive the most appropriate b exponent ($b = 1.38$). This was then used to control the confounding influence that changes in LBM have on $\dot{V}O_{2\max}$ in healthy men and women.

Maximum aerobic power declines significantly ($P < 0.0001$) in both men and women as reported earlier (chapters 4.1 and 7.1). However, by plotting the absolute measurements of $\dot{V}O_{2\max}$ for both men and women on a single graph, the sex-specific changes that occur over the course of healthy ageing can be investigated. Doing this revealed a significant difference in the rate at which

	Correlation to $\dot{V}O_{2\max}$ (l/min)
Height (cm)	0.754**
Total Body Mass (kg)	0.643**
Body Mass Index (kg/m ²)	0.174*
Body Surface Area (m ²)	0.755**
Fat Mass (kg)	-0.179*
Lean Mass (kg)	0.861**

Table 15 – Correlation of maximal aerobic power to body size and composition.

Pearson’s product r values are shown for the correlation of absolute $\dot{V}O_{2\max}$ and the various measures of body size and composition.

* Correlation significant at $P < 0.05$
** Correlation significant at $P < 0.01$

$\dot{V}O_{2\max}$ decreased between nineteen and seventy-six years of age. The aerobic power of healthy men declines at a greater rate than that of healthy women (Fig. 44a). By simply dividing $\dot{V}O_{2\max}$ by total body mass (Fig. 44b) the interpretation of the data does not change. Both sexes both still experience an age-related decline in aerobic power, and the decline is still greater in men.

But, by allometrically scaling the data to the most appropriate measure of body composition (in this case LBM) the difference in $\dot{V}O_{2\max}$ between the sexes is effectively removed (Fig. 44c). Furthermore, although $\dot{V}O_{2\max}$ still significantly ($P < 0.0001$) declines in both sexes as a consequence of healthy ageing, the rate of the decline is the same in both men and women, equating to a 37% reduction in men, and a 30% reduction in women between nineteen and seventy-six years of age.

9.3 Allometric Scaling of Resting Overall Cardiac Function

In a similar manner resting overall cardiac function was correlated to the same measures of body size and composition (Table 16).

Resting CPO showed the strongest correlation to LBM (Table 16). Significant correlations in order of strength also existed between CPO_{rest} and BSA, TBM and height. Resting CPO showed no significant correlation to FM. This therefore confirmed that CPO_{rest} should be scaled to LBM. This allowed the effects of healthy ageing on CPO_{rest} to be accurately interpreted independently of any influence of body size, and a meaningful direct comparison to be made between healthy men and women.

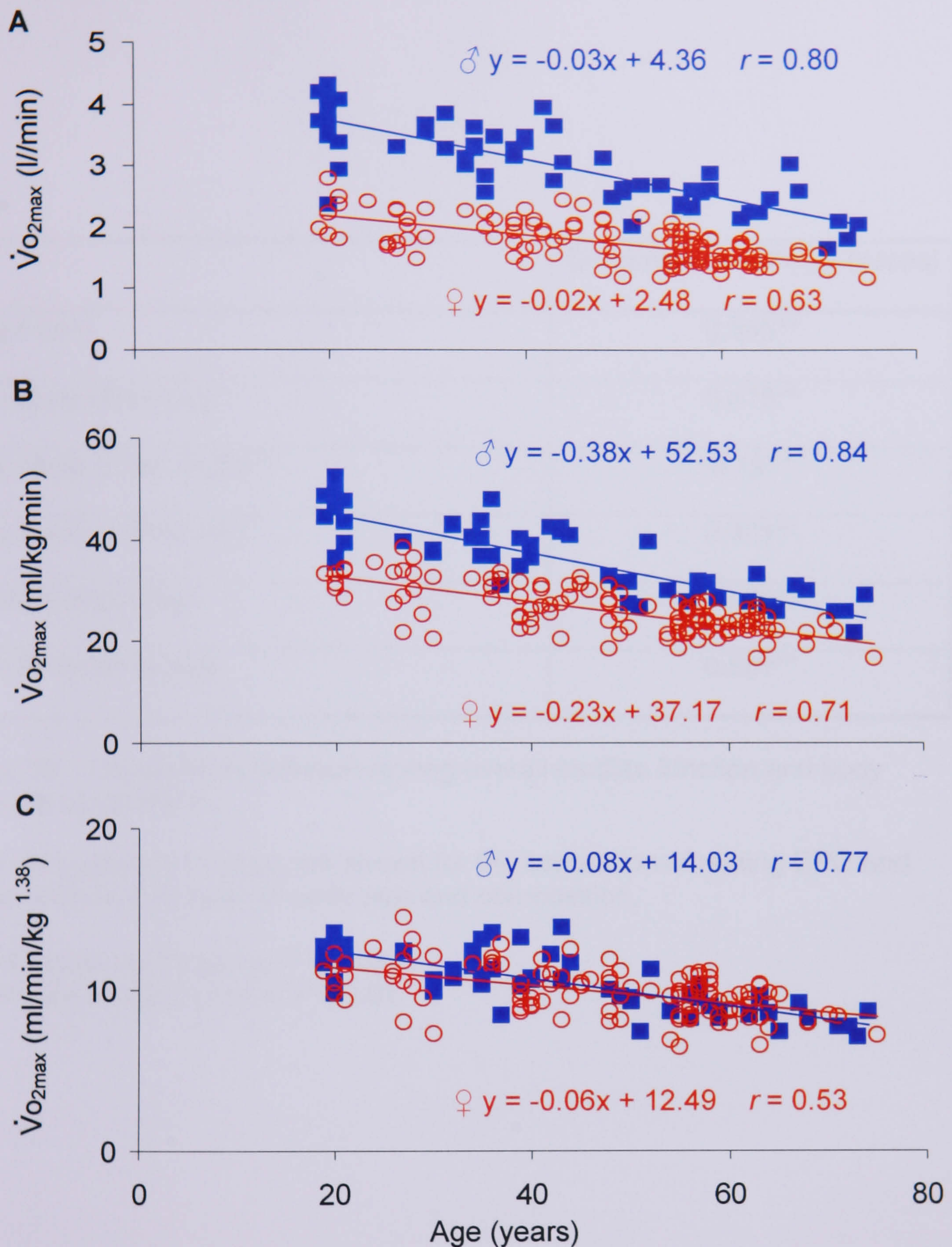


Figure 44 – The effect of appropriate scaling on the maximum aerobic power of healthy men and women.

The maximum aerobic power of healthy men (■) and women (○).

A. Absolute measure (l/min)

Men ($F(1, 55) = 100.07$, $P < 0.0001$)

Women ($F(1, 109) = 71.65$, $P < 0.001$)

B. Normalised to total body mass (ml/kg/min)

Men ($F(1, 55) = 132.54$, $P < 0.0001$)

Women ($F(1, 109) = 111.34$, $P < 0.001$)

C. Allometrically scaled for the influence of lean body mass

Men ($F(1, 55) = 80.23$, $P < 0.0001$)

Women ($F(1, 109) = 42.79$, $P < 0.001$)

	Correlation to CPO _{rest} (Watts)
Height (cm)	0.396**
Total Body Mass (kg)	0.415**
Body Mass Index (kg/m ²)	0.197*
Body Surface Area (m ²)	0.451**
Fat Body Mass (kg)	-0.016
Lean Body Mass (kg)	0.507**

Table 16 – Correlations between resting overall cardiac function and body size and composition.

Pearson’s product *r* values are shown for the correlation of resting CPO and to the various measures of body size and composition.

* Correlation significant at *P* < 0.05
** Correlation significant at *P* < 0.01

In terms of the CPO_{rest} , the derived b exponent was $b = 0.64$. Nevertheless, the scaling of CPO_{rest} does not change the overall conclusions drawn from the non-scaled data. In men CPO_{rest} still significantly ($P < 0.05$) declined by 17% between nineteen and seventy-six years of age (Fig. 45). While in women, CPO_{rest} still remained unchanged ($P > 0.6$) over the course of healthy ageing (Fig. 45).

9.4 Allometric Scaling of Maximum Overall Cardiac Function

Finally, the allometric process was applied to the measures of maximum overall cardiac function and overall cardiac reserve. These two measures were again correlated to the same measures of body size and composition to distinguish which was the most appropriate measure to scale (Table 17).

Both CPO_{max} and CR were also most strongly correlated to LBM (Table 17).

As with CPO_{rest} , CPO_{max} and CR showed weaker correlations to BSA, TBM and height, in rank order. Both CPO_{max} and CR showed no significant correlation to FM. As a result, the measures of maximum overall cardiac function and overall reserve capacity should also be scaled to LBM.

The b exponent derived from the allometric process to normalised the changes that occur in CPO_{max} for the changes in LBM was $b = 0.73$.

By calculating a body size-independent measure of CPO_{max} the difference between the sexes in early adulthood is significantly reduced (Fig. 46).

However, there is still a significant sex-based difference in the age-associated preservation of CPO_{max} . In men a significant ($P < 0.01$) 22% decline in CPO_{max}

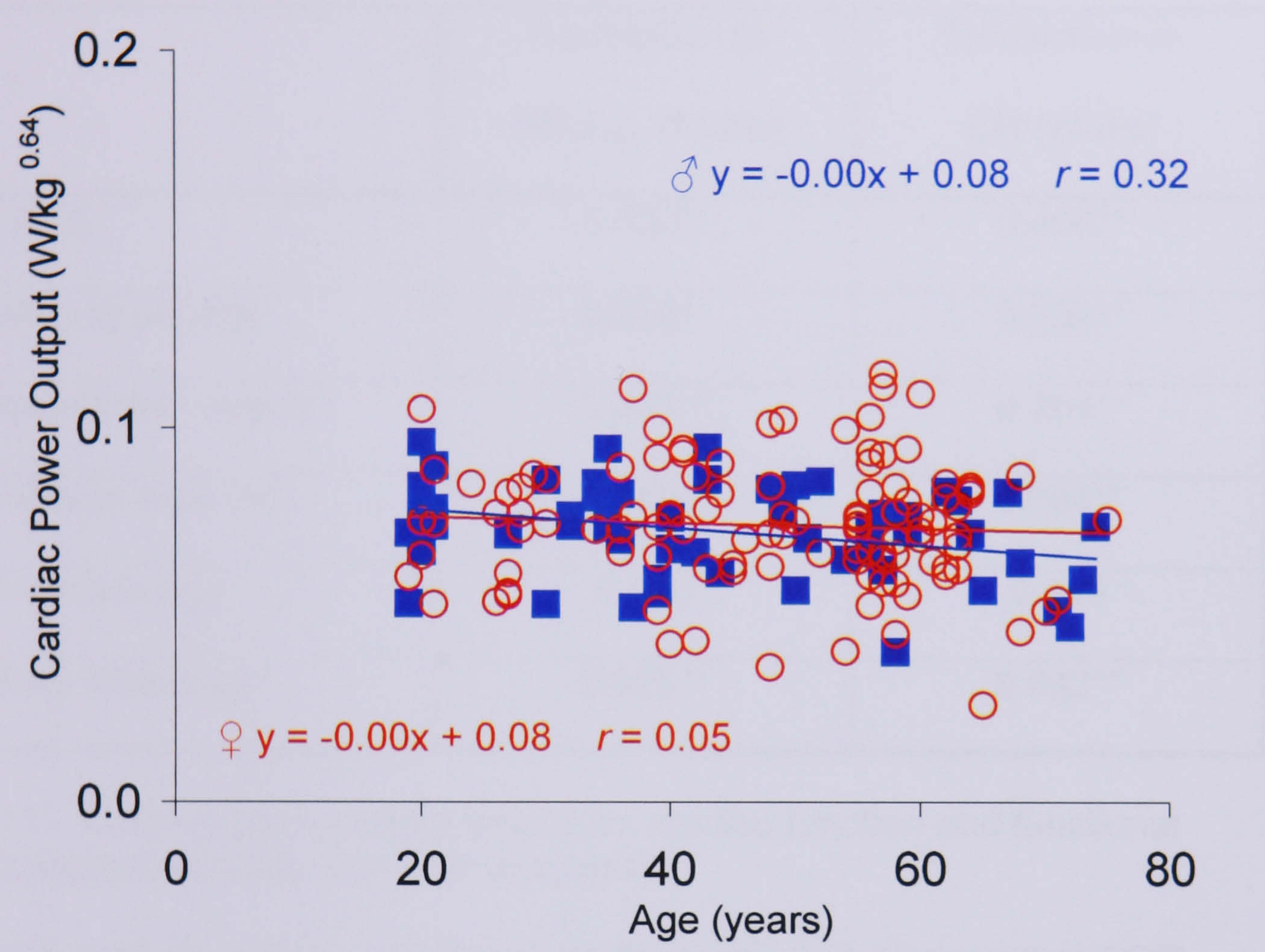


Figure 45 – Resting overall cardiac function allometrically scaled for changes in lean body mass in healthy men and women.

The CPO_{rest} of men (■) and women (○) was allometrically scaled to normalise the changes which occur as a result the age-related decline in lean body mass.

The derived exponent was ^b = 0.64.

As a result CPO_{rest} still decreased significantly ($F(1, 55) = 6.1, P < 0.05$) in men, in contrast there was no significant ($F(1, 109) = 0.3, P > 0.6$) change in healthy women between nineteen and seventy-six years of age.

	Correlation to CPO _{max} (Watts)	Correlation to CR (Watts)
Height (cm)	0.538**	0.496**
Total Body Mass (kg)	0.600**	0.559**
Body Mass Index (kg/m ²)	0.311**	0.294**
Body Surface Area (m ²)	0.640**	0.594**
Fat Body Mass (kg)	0.023	0.029
Lean Body Mass (kg)	0.695**	0.642**

Table 17 – Correlations between maximum cardiac function and functional reserve capacity to body size and composition.

Pearson’s product *r* values are shown for the correlation of maximum CPO and CR to the various measures of body size and composition.

* Correlation significant at *P* < 0.05

** Correlation significant at *P* < 0.01

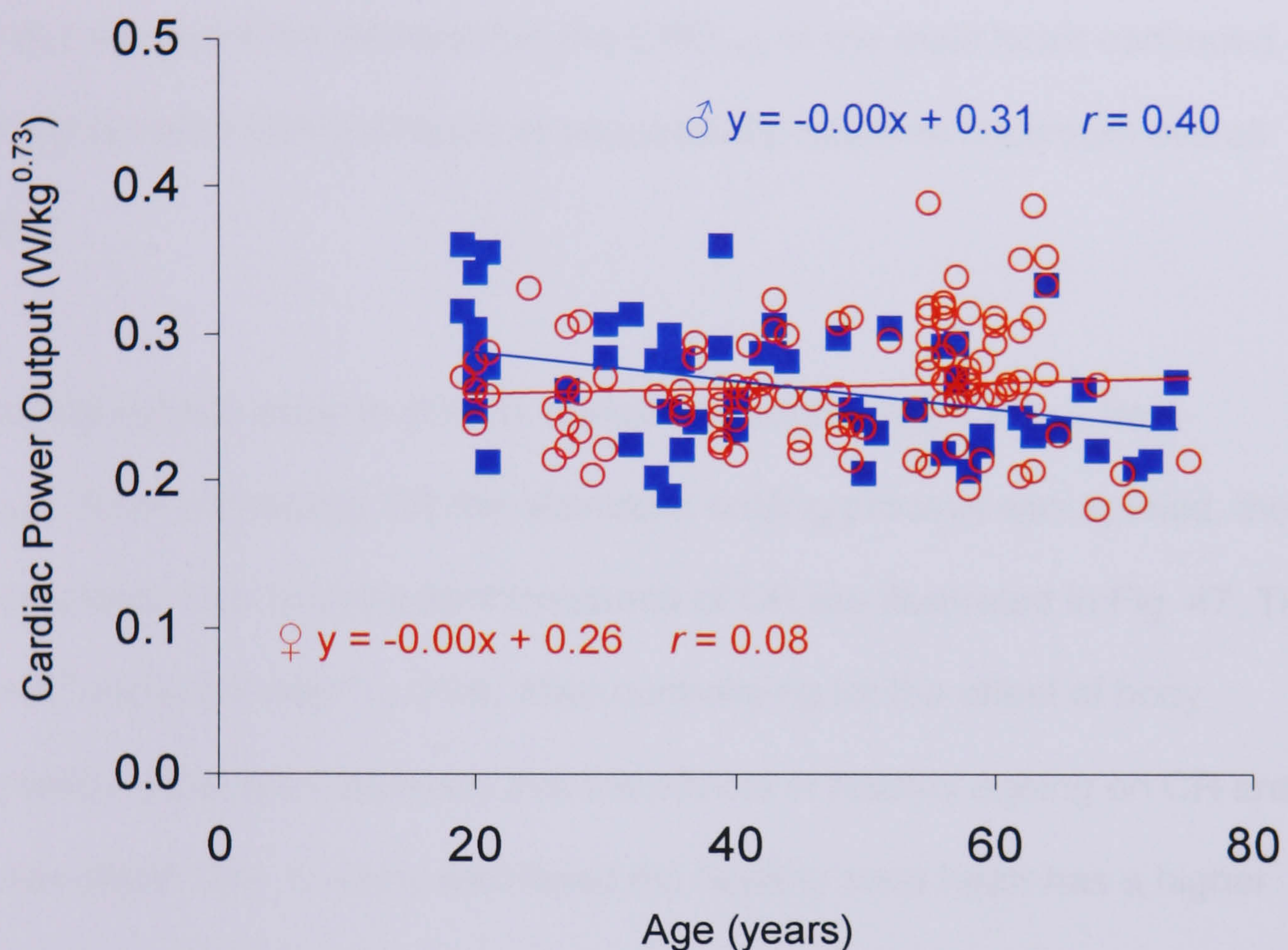


Figure 46 – Maximum overall cardiac function allometrically scaled for changes in lean body mass in healthy men and women.

The CPO_{max} of men (■) and women (○) was allometrically scaled to isolate the changes that occur directly as a result of healthy ageing, independent of the concomitant declines in lean body mass.

The derived exponent was $b = 0.73$.

As a result CPO_{max} still decreased significantly ($F(1, 55) = 10.24$, $P < 0.01$) in men. In contrast there was no significant ($F(1, 109) = 0.7$, $P > 0.4$) change in healthy women between nineteen and seventy-six years of age.

still occurs between nineteen and seventy-six years of age (Fig. 46). In contrast there was no significant ($P > 0.4$) age-related change in healthy women (Fig. 46). At forty-four years of age the maximum overall capacity of the male and female hearts (now unaffected by the influence of changes in body composition) converged, and they became indistinguishable (Fig. 46). After this age point the decrease in the CPO_{max} of the male heart continued, while the female heart continued to successfully retain its maximum overall function.

Functional cardiac reserve (CR) is derived by subtracting CPO_{rest} from CPO_{max} . After calculating CR the allometric scaling process was applied, the resulting body size-independent measures of CR are illustrated in Fig. 47. The derived b exponent was $b = 0.76$. After normalising for the effect of body composition it became apparent that the effects of healthy ageing on CR are also sex-dependant. In early adulthood the healthy male heart has a higher CR than the healthy female heart. But, with advancing years the size-independent CR of the male heart declined significantly ($P < 0.05$) by 19% (Fig. 47). In contrast, the female heart showed no such decline ($P > 0.3$) between the ages of nineteen and seventy-six. As a result the hearts of healthy men and women became functionally indistinguishable at forty-five years of age. Furthermore, the size-independent reserve capacity of the heart of a healthy seventy-six year old female is the same as that of a healthy nineteen year old.

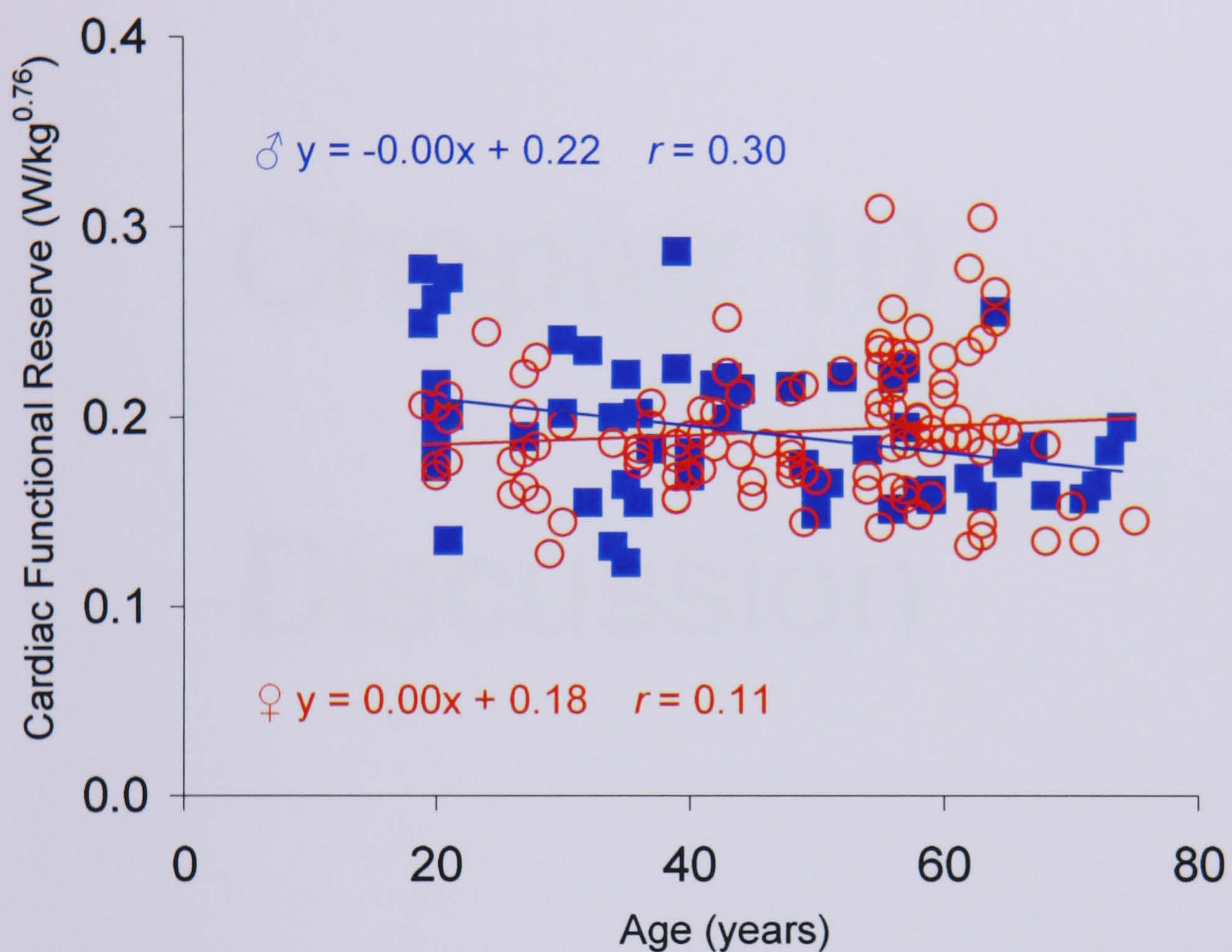


Figure 47 – Sex and age-related changes in cardiac functional reserve.

The overall cardiac functional reserve capacity (CR) of healthy men and women were allometrically scaled to normalise the effects of any body composition differences.

The derived exponent was $b = 0.76$.

The CR of men (■) ($F(1, 55) = 5.5$, $P < 0.05$) declined significantly as a consequence of healthy ageing. In contrast the CR of the female group (○) did not change significantly ($F(1, 109) = 1.2$, $P > 0.2$) between nineteen and seventy-six years of age.

Chapter 10

Discussion

10.0 Key Findings

The major novel findings of this thesis were that:

1. Healthy ageing has a sex-specific impact on overall cardiac function.

The CPO_{max} and CR of the healthy male heart declined by 20% and 25%, respectively, between nineteen and seventy-six years of age.

In contrast there were no changes in the healthy female heart over the same period.

2. The effects of habitual long-term endurance-training are also different between men and women. Athletic males exhibit a 25% to 58% adaptation in $\dot{V}O_{2max}$, a 16% to 28% increase in CPO_{max} and a 17% to 33% improvement in CR when compared to age-matched sedentary men. Endurance-trained women of similar ages despite showing greater adaptations in $\dot{V}O_2$ (60% to 81%) do not significantly improve either their CPO_{max} or CR.
3. The above age- and sex-related changes are independent of the concomitant changes in body size and composition, particularly when scaled allometrically to LBM.

This work represents the first time that cardiac power output (CPO) which measures both blood flow and blood pressure simultaneously, has been employed to measure overall cardiac function in healthy populations of this size. Previous work has refined and developed the concept of CPO, but this work represents a major progression in its application, especially outside the clinical domain.

The experimental protocols and the procedures were carefully designed, and rigorously tested before the recruitment of any subjects to ensure the accuracy and reliability of the collected data. The protocol for measuring CPO was refined to ensure true resting and maximal states were obtained on repeated occasions (coefficients of variability were 2.2% to 4.5%), and a novel but reliable technique was developed to allow blood pressure to be measured at maximum aerobic exertion.

All of the healthy subjects underwent a rigorous screening process to ensure their previous and current medical status was not affected by any overt or covert disease processes, and to quantify all previous and current levels of activity. This process of screening involved both qualitative and quantitative techniques, specifically an initial questionnaire, which was followed by telephone and face-to-face interviews, and finally an ECG stress test. For this reason approximately only one in every three applicants to the study was eventually included in the final data analysis. This process represents an improvement on most previous studies into ageing where less robust screening may have admitted subjects with cardiovascular problems, or contravening medications.

The male heart failure patients were also screened thoroughly. All were long-term patients of Broadgreen Cardiothoracic Centre, and they all possessed numerous symptoms of chronic heart failure which was confirmed via ECG, echocardiography and blood screening. After completing the testing protocol all underwent exacting surgery to implant bio-ventricular pacemakers in an

attempt to synchronise the activity of their ventricles, improve their long-term prognosis and their quality of life.

The thorough screening process ensured that the conclusions based on the data collected from the healthy subjects were valid, accurate, and less likely to be misinterpreted as a result of any superimposed disease processes, e.g. CHD and CVD. It also allowed distinct populations to be dissected from each other, and the results for these subpopulations to be meaningfully compared.

10.1 Limitations

Despite all of the attempts to ensure the accuracy and applicability of the data there are a number of limitations which must be recognised when interpreting the results of this study.

Firstly and most crucially the cross-sectional nature of the study design must be recognised. This was unavoidable given the logistical constraints, but the ideal when studying the effects of ageing would be to employ a longitudinal design, which examined and re-examined the same subjects over a long time frame. As a result of using a cross-sectional design Masoro (2001) highlights the two major confounding influences. Firstly, the physiology of the different generations within the cohort may have been affected differently by psychosocial changes which have evolved with time in society. And secondly, as a result of selective mortality it is possible that our older individuals do not represent a true cross-section of society, but rather specifically a hardy subsection (via their genetic disposition or lifestyle) who have aged well.

With advancing age it becomes increasingly difficult to delineate healthy ageing from disease, as disease processes are inevitably linked with ageing, but this study employed what Masoro (2001) terms a reductionist approach. Furthermore, all of our healthy subjects were community dwellers, and were not recruited from long-term care facilities as has been the case in previously studies (Masoro, 2001). As a result, all of the subjects in this study were still fully exposed to modern society, and to any psychosocial or physiological changes that may occur as a result.

With regard to the pre-stress test screening, we found that some subjects falsified details when they knew the nature of study that they were applying to join. Generally though via the interviews, interacting with the volunteers and the quantitative measurements (i.e. the ECG and $\dot{V}O_{2max}$) individuals who had not truthfully or satisfactorily completed the entire pre-test questionnaire were detected. There was often a considerable mismatch between an individual's concept of their activity levels, and their measured $\dot{V}O_{2max}$.

The equipment used throughout the study was extensively tested and validated before starting the collection of data. Macfarlane (2001) recognised that there are no universal guidelines stipulating the accuracy which automated gas analysis systems must achieve. Validation studies encompass both the day to day variability within the machine and its operator, and the physiological variability inherent in human subjects. It is concluded that we have the utmost confidence in the accuracy of our measurements of respiratory gases, with low coefficients of variance of 2.2% to 4.5%. These are

much better than most other studies which have reported coefficients ~10% (Gore *et al.*, 2003; Matthews *et al.*, 1987; Miles *et al.*, 1994).

To measure cardiac output at rest and at maximal exertion the Collier (1956) and Defares (1958) methods using carbon dioxide rebreathing were employed. These techniques were chosen as they are clearly much less restricting on the subject, particularly when exercising. The accuracy of carbon dioxide rebreathing has been validated by previous studies (Beekman *et al.*, 1984; Cade *et al.*, 2004; Cooke *et al.*, 1998; Gabrielsen *et al.*, 2002; Russell *et al.*, 1990) against invasive thermodilution techniques, and compared to acetylene rebreathing (Laszlo, 2004; Tordi *et al.*, 2004; Warburton *et al.*, 1999). Also, the accuracy of infra-red analysers when measuring carbon dioxide has been validated (Barazanji *et al.*, 1996). From a purely scientific prospective it would be preferable to be able to directly measure the resting and maximal cardiac output of the healthy human heart invasively, but this was not ethically or technically possible in this study. The chosen non-invasive techniques were validated by testing their reliability and reproducibility before the collection of data for physiological interpretation began. Furthermore, previous work has validated the use of CPO using invasive measurements of both blood flow and blood pressure (Tan, 1986).

As recommended by Sun *et al.* (2000) before performing a measure of cardiac output, either at rest or maximal exertion, numerous physiological variables were observed e.g. $\dot{V}O_2$, $\dot{V}CO_2$, \dot{V}_E , P_{ETCO_2} and heart rate. This ensured that at rest the subject was fully relaxed, that any carbon dioxide inhaled during a previous measure had been fully washed out, and that the subject was not

suffering from any stress-induced physiological changes. When exercising, before measuring cardiac output all subjects had to attain maximal values for all the physiological variables. This ensured that each subject was fully exerting themselves, and not suffering unduly or performing in a way that would invalidate the measurement, e.g. hyperventilating. The rebreathing period was adjusted appropriately to avoid the impact of recirculation (Sowton *et al.*, 1968), and a suitable recovery period was allowed between bouts of maximal exercise to avoid an exercise induced suppression of \dot{V}_{CO_2} (Burnley *et al.*, 2000).

The use of stethoscopes and sphygmomanometers to measure blood pressure has been previously validated against invasive measurements of blood pressure (Henschel *et al.*, 1954; Hossack *et al.*, 1982; Nagle *et al.*, 1966). Invasive measurements with indwelling arterial lines were not a viable alternative in this study. When using an ergometer there are inherent difficulties in the measurement of blood pressure using an auscultation method. These are the result of ergometer noise and the movement of the subject (Robinson *et al.*, 1988). After much practise and the development and refinement of a technique where the arm of the subject was elevated, supported, and arm motion minimized we effectively overcame these obstacles. This technique allowed systolic and diastolic blood pressures to be measured accurately and with confidence both at rest and at maximal exertion.

In total over two-hundred and forty different individuals completed the full testing protocol and were included in the final data analysis. This is a

substantial number on which to base our conclusions, but as with all studies a higher number of subjects would have been ideal. This is particularly true when looking at the female cohort. Some studies have found that hormonal changes as the result of menstrual cycle phase, the menopause, oral contraceptives or hormonal replacement therapy (HRT) can significantly affect aerobic function (Casazza *et al.* 2002; Lynch *et al.*, 2002; Redman *et al.*, 2003; Xanne and de Jonge, 2003) and various individual indices of cardiac (Hayward *et al.*, 2000; Moran *et al.*, 2000; Lim *et al.*, 1999; Pines *et al.*, 1993;) and vascular (Majmudar *et al.*, 2000; Scuteri and Ferrucci, 2002) function. These conclusions are not universally accepted (Burrows and Bird, 2005; Lebrun *et al.*, 1995; Littler *et al.*, 1974), and none of the previous studies have examined if there is any effect of female hormones on cardiac power output. Even when the women were sub-divided based on their hormonal status this did not change any of the data and conclusions drawn. But the number of healthy women within each hormonal group was small and generally insufficient to draw any meaningful conclusions relating to the possible effects of hormones on cardiac power output.

It would also have been beneficial if we had managed to recruit more particularly active endurance-trained women. However, the decision was taken not to relax the selection criteria in an attempt to increase the total number of subjects, as doing this would have diluted the scientific power of the study. After approaching many athletics clubs in North-West England it became apparent that there are relatively few habitually active females compared with males. This was the major reason for the smaller numbers of female subjects within this sub-population.

Also with regard to the habitually active populations, attempts were made to ascertain their past and present exercise stimulus with as much detail as possible. Inevitably although duration and volume could be accurately established, it is much more difficult to determine exercise intensity. This is due to the fact that many active individuals base their training on qualitative factors such as how they feel physically, and seldom use any quantitative measure of training intensity, e.g. heart rate monitors. Therefore, an age-related decline in exercise intensity cannot be totally discounted, even though every possible attempt was made to recruit the most highly trained athletes, with as much attention as possible paid to their training volume, duration and competitive performance records.

Despite this study being designed in the most scientific and efficient manner possible, there are a number of possible confounding influences. These have been recognised and discussed above, as have the ways which the investigators have attempted to control and eradicated their impact. Whatever the shortcoming or systematic errors, these were the same in all of the experiments and were therefore consistent in each and every study undertaken.

The focus of the remainder of the discussion will be on the physiological conclusions that can be drawn from the data. Specifically the changes that occurred in $\dot{V}O_{2\max}$, CPO_{\max} and CR as a consequence of healthy ageing, long-term endurance-exercise and heart failure. This is because these are the factors which have the most significant impact on an individual's exercise capacity, quality of life and their ability to meet everyday environmental

demands. The magnitudes of the adaptive changes measured in CPO_{rest} were very small in comparison to the changes in CPO_{max} . Furthermore any significant changes in CPO_{rest} are reflected in CR. For the entire healthy male group (active and sedentary) CPO_{rest} ranged from 0.43 to 1.92 Watts, in the male heart failure patients it ranged from 0.31 to 1.21 Watts, and in healthy female population the range of CPO_{rest} was from 0.25 to 1.32 Watts. The lack of difference and the considerable overlap between male and female data, sedentary and active, healthy and diseased populations shows that CPO_{rest} is well maintained in all extreme physiological conditions. But the ability of the technique to detect these small changes illustrates its sensitivity.

10.2 Changes in Maximum Aerobic and Overall Cardiac Function in Men

Three groups of men were recruited, each was subjected to distinctly different activity patterns which could significantly affect their overall cardiac function.

The three groups were:

1. Healthy sedentary men.
2. Long-term endurance-trained male athletes.
3. NYHA class III and IV heart failure patients.

All of the male subjects were between nineteen and seventy-six years of age.

10.2.1 The Effects of Healthy Ageing in Men

Fifty-seven years of healthy ageing in men who had a sedentary lifestyle resulted in a 49% decrease in $\dot{V}O_{2max}$ (Fig. 12). This decrease is comparable to previous research which has found age-related decreases in $\dot{V}O_{2max}$ of

between 4% and 12% per decade (Hawkins and Wiswell, 2003). Importantly though, all the individuals included in this analysis reported as undertaking less than ninety minutes of exercise per week. Therefore the age-related decrease in $\dot{V}O_{2\max}$ is more likely to be attributable to the impact of healthy ageing rather than a dramatic change in activity patterns. This is in contrast to the conclusion of Jackson *et al.* (1995) who attributed 50% of the age-related decrease in aerobic power to a self-reported decrease in activity levels.

In this same population CPO_{\max} decreased by 23% or 1.1 Watts (Fig. 17). This decrease was the result of a 33% reduction in maximum cardiac output (Fig. 18). Age-related decreases \dot{Q}_{\max} have been observed in previous studies (Ehsani *et al.*, 1991; Fleg *et al.*, 1995; Ogawa *et al.*, 1992). Furthermore in agreement with these studies SV_{\max} also decreased by 13% (Fig. 18). Ogawa *et al.* (1992) reported that the age-related decrease in \dot{Q}_{\max} was equally attributable to decreases in SV_{\max} and HR_{\max} . In contrast this study found that while SV_{\max} decrease by 13%, HR_{\max} fell by 23% in the same subjects. As such these results are in closer agreement with the findings reported by Julius *et al.* (1967) who reported that over a four decade period HR_{\max} decreased by 18%, whilst SV_{\max} declined by only 9%.

What this and all the previous studies do agree on is that HR_{\max} decreases with advancing age. Both the contraction and relaxation phases in the cardiac cycle are prolonged (Pugh and Wei, 2001) as a result of age-related changes in myocardial composition and structure, the loss of pacemaker cells (Lev, 1954) and a reduced responsiveness to circulating catecholamines (Fleg *et al.*, 1985; Kitzman and Edwards, 1990). There is some disagreement though

regarding the rate of the decline in HR_{max} . In this study HR_{max} decreased by 0.77 beats per year, this finding is in close agreement with the work of Tanaka *et al.* (2001). They proposed that the traditional equation ($HR_{max} = 220 \text{ bpm} - \text{age}$) that is widely used to predict maximum heart rate should be amended. They found that $HR_{max} = 208 - 0.7 \times \text{age}$ was a more accurate equation for the prediction of HR_{max} . The data collected in this study supports this finding.

With advancing age in sedentary males, this study also measured a concomitant 15% increase in maximum mean arterial blood pressure. Mean arterial pressure is important when assessing overall cardiac function as it represents blood pressure over the duration of the entire cardiac cycle. This finding is in agreement with the previous work of Stratton *et al.* (1994) and Ogawa *et al.* (1992). The increase in the generation of blood pressure illustrates the changing characteristic of the male human heart from a flow, to a pressure generator. That is, a greater proportion of the energy injected into the blood by the contracting heart is diverted from flow generation to pressure generation to overcome the age-related increase in systemic vascular resistance (Fig. 20).

However, the increase in the generation of blood pressure was insufficient to effectively maintain CR in healthy sedentary men. Hence, overall the functional reserve of the male heart decreased by 22% between nineteen and seventy-six years of age (Fig. 22). In absolute terms this means that a seventy-six year old healthy male possesses a CR of 3.5 Watts. Although this figure is significantly lower than that of a younger male, it still represents a healthy functional reserve capacity, over the 1 Watt of CPO_{rest} that is needed

for basal existence. It is entirely possible that this reduction in the overall capacity of the male heart reflects the huge loss (35%) of cardiomyocytes which occurs as a consequence of ageing (Olivetti *et al.*, 1995; Fig. 1), despite the potential for some compensatory hypertrophy of the existing myocytes.

It is concluded that healthy age has a detrimental effect on overall cardiac function in sedentary men. This change is however over estimated if only blood flow is measured as the index of cardiac function. However, in the absence of any disease processes a sufficient functional reserve can be effectively maintained up to seventy-six years of age to prolong a good quality of life.

10.2.2 The Effect of Habitual Long-term Endurance Exercise in Healthy Men

Individuals habitually engage in endurance exercise for many reasons. The benefits in terms of offsetting the age-related accumulation of body fat (Pollock *et al.*, 1987) and reduction in $\dot{V}O_{2\max}$ (Strømme *et al.*, 1977) are widely recognised. This study confirms these effects. Each group of habitually active males had a significantly higher $\dot{V}O_{2\max}$ than their age-matched sedentary counterparts (Fig. 23). The adaptation to the training stimulus was such that a seventy year old endurance trained male had the same $\dot{V}O_{2\max}$ as sedentary male fifty years their junior. Despite this there was still an age-related decline in the aerobic power of the endurance trained men, which paralleled the decline observed in the sedentary population. Therefore, it appears that there is an upper ceiling to how much $\dot{V}O_{2\max}$ can be increased, and that this ceiling is reduced with increasing age. Tanaka and Seals (2003) found that the

$\dot{V}O_{2\max}$ decreased more steeply in endurance-trained men than in sedentary men. They attributed this difference to a greater decline in the habitual activity volumes undertaken. This was not the case in this study, and supports the use of rigorous inclusion criteria.

Maximum overall cardiac function was also higher in all the athletic male populations, compared to their sedentary age-matched counterparts, even though these differences were only statistically significant in the two younger, i.e. twenty and fifty year-old, age groups (Fig. 24). Over the range of healthy ageing studied the CPO_{\max} of habitually active men still declined, and at a greater rate than that of the sedentary subjects. However, the CPO_{\max} of the sixty and seventy year old athletic populations was not significantly different from that of the twenty year old sedentary group. This shows that the exercise stimulus is effective at attenuating the negative effect the ageing process has on overall cardiac function. Furthermore, the greater CR possessed by the older athletic men in comparison to their sedentary age-matched counterparts means they would be better able to withstand a myocardial infarction of the same size, and recover to restore a good quality of life.

In both the sedentary and active men the decline in cardiac function could be due to the age-related attrition of cardiomyocytes (Olivetti *et al.*, 1995). If so, exercise training does not appear to be protective against the net loss of cardiomyocytes, as CPO_{\max} declines with age in both lifestyles. For obvious ethical reasons, no cellular study of the endurance-trained human heart has been possible to either confirm or deny this superstition. Work in the hearts of rats that has looked at both exercise (Kemi *et al.*, 2005) and haemodynamic-

induced cardiac overload resulting from either infarction (Anversa *et al.*, 1986) or aortic stenosis and hypertension (Lorell and Carabello, 2000) has confirmed cardiac remodelling. These studies suggest that the increases in cardiac mass are the result of cellular hypertrophy of the existing myocytes, as opposed to hyperplasia and new myocyte production.

In terms of the individual components of maximum cardiac function and the effects of habitual endurance exercise, the \dot{Q}_{\max} values for each trained group were greater than their sedentary age-matched counterparts (Table 8). This occurs in response to an enhanced demand for oxygen, and contributes towards the greater $\dot{V}O_{2\max}$ of the athletes. This increase in the generation of maximum blood flow was predominately due to training-induced adaptation in SV_{\max} , HR_{\max} did not change significantly and continued to decline with increasing age in the trained population. Such an increase in stroke volume is supported by other studies which have also found a similar reliance on stroke volume (Boutcher *et al.*, 2003; Goodman *et al.*, 2005; Hopkins *et al.*, 1996). As with CPO_{\max} , the magnitude of exercise-induced adaptation in blood flow generation diminished with advancing age. It is postulated that this could be the result of age (Henry *et al.*, 1980; Kitzman and Edwards, 1990) and exercise-induced (Spataro *et al.*, 1985) changes in cardiac structure. The consequence of these changes is a less compliant myocardium, which results in a reduced ability of the Frank-Starling mechanism to respond to the exercise stimulus.

There was no significant change in MAP_{\max} in any of the endurance-trained groups when compared to their age-matched sedentary counterparts (Table

8). Hence, the age-related increase in MAP_{max} was of equal magnitude in both the trained and sedentary populations. There have not been many studies conducted where blood pressure has been measured at maximum aerobic exertion, but the results of this study are in agreement with those of (Ehsani, 1987).

Overall the long-term exercise training stimulus resulted in an increase in CR in all the endurance trained male groups in comparison to their sedentary counterparts. Indeed, if anything the decline over the age range studied was greater in the trained groups, and the difference between the trained and sedentary population was only statistically significant at twenty and fifty years of age. But, as the CR of the endurance-trained seventy year old group was not significantly different from that sedentary twenty year old group (i.e. fifty years younger), it can be concluded that engaging in long-term endurance exercise is effective at attenuating the age-related decline in overall cardiac function. This is the first time this has been reported, and adds significant weight to the argument that men need to maintain active lifestyles if they wish to promote a higher quality of life with advancing age. The age-related changes here are similar to those reported by Pearson *et al.* (2002) for skeletal muscle reserve, when comparing competitive and novice weightlifters. While force and power generation decreased with age in both populations, the resistance exercise had endowed the competitive lifters with a considerably greater reserve capacity.

10.2.3 The Effect of Heart Failure in Men

The chronic heart failure patients and the impacts of the disease represented the other extreme to the veteran athletes. Neither $\dot{V}O_{2\max}$ nor CPO_{\max} changed significantly within this group, despite the fact that the age range covered a thirty-four year period. This illustrates that the disease process had a deteriorative effect on both the aerobic power and cardiac functional reserve that was greater than any normal age-related impact. This of itself is important as currently cardiologists are unable to distinguish the effects of heart disease from the effects of the ageing process.

The mean $\dot{V}O_{2\max}$ for these patients was 14.6 ml/kg/min, which is 45% lower than that of healthy age-matched males (Fig. 26b). This figure is in agreement with previous studies that have examined patients with a similar severity of heart failure (Osada *et al.*, 1998; Wilson *et al.*, 1984). Indeed $\dot{V}O_{2\max}$ has been reported to be as low as 10 ml/kg/min in the most severe cases (Remme and Swedberg, 2001).

Previous research by Tavazzi *et al.* (2001) has concluded that to fully determine and quantify the impacts of heart failure, patients must be assessed when the heart is maximally stressed, because under resting conditions cardiac function is well maintained. In terms of blood flow generation, the mean \dot{Q}_{\max} measured in the patients in this study was 8.8 l/min (Table 11), this is 47% below that of a sedentary but healthy age-matched male.

Few studies have measured maximum blood pressure generation in heart failure patients, and have therefore failed to report changes in overall cardiac

function. The MAP_{max} in our patients was 100.4 mmHg (Table 11), this is also significantly below (20%) the figure measured in sedentary but healthy age-matched males. In the study by Cooke *et al.* (1998) MAP_{max} was 102.3 mmHg in a group of similarly classified heart failure patients. Hence, heart failure patients have a significantly impaired ability to generate both blood flow and blood pressure.

This impaired ability to generate both blood flow and blood pressure (the result of a dyssynchronous cardiac function in all of these patients) resulted in a group mean CPO_{max} of only 1.96 Watts (Fig. 27b). Furthermore, CR was only 1.3 Watts (Fig. 27c), which is 64% lower than the reserve capacity of an age-matched healthy sedentary male, and 71% below that of a seventy year old male veteran athlete. This difference represents a huge reduction in overall cardiac functional reserve. And whilst the patients were able to exist under basal conditions, the disease severely affected their exercise capacity and hence quality of life.

These data on the effects of heart failure are in close agreement with the findings of Bain *et al.* (1990) and Cooke *et al.* (1998). In the study by Tan (1986) twenty out of twenty-three patients who had a CPO_{max} below the normal resting value of 1 Watt died within one year (Fig. 3). The subjects tested in this study were getting very close to this value and clearly had a poor prognosis. Fortunately for them a surgical intervention was available which was going to be used in an attempt to improve their long-term prognosis.

It is evident that all three situations; healthy but sedentary ageing, engaging in long-term endurance exercise and chronic heart failure have significant impacts on overall cardiac function in men. This is the first time that cardiac power output has been used to study such a range and size of different populations. These quantitative values of CR clearly illustrate the life/death and exercise capacity limitations of men in the general population.

10.3 Changes in Maximum Aerobic and Overall Cardiac Function in Women

Given the sex-specific differences that have been reported in a few previous studies on individual indices of cardiac structure and function, it was logical to employ cardiac power output for the first time to measure overall cardiac function in women.

Two groups of healthy women were recruited in which aerobic power, and overall cardiac function was measured. They were:

1. Healthy sedentary women between nineteen and seventy-six years of age, and
2. Long-term endurance-trained athletes who were in three groups with mean ages of twenty-six, forty-eight and sixty-one years.

10.3.1 The Effects of Healthy Ageing in Women

All the women included in this analysis were thoroughly screened and reported to doing less than ninety minutes of activity per week. As with the men the $\dot{V}O_{2\max}$ values of this group of healthy women showed a significant negative correlation to age. In total $\dot{V}O_{2\max}$ decreased by 40% between nineteen and

seventy-six years of age, this equated to a decrease of approximately 7% per decade (Fig. 28). The latter is precisely the same as that reported by Stathokostas *et al.* (2004). Other cross-sectional studies have reported the aerobic power in women to decline by 9-10% per decade, but their subjects were not as rigorously screened, and included moderately-active individuals (Drinkwater *et al.*, 1975; Hossack and Bruce, 1982; Toth *et al.*, 1994; Jackson *et al.*, 1996; Tanaka *et al.*, 1997). Longitudinal studies have tended to report slightly higher rates of decline in $\dot{V}O_{2\max}$ e.g. 11% per decade (Åstrand *et al.*, 1973; Plowman *et al.*, 1979). It appears the data collected in this study are in close agreement with previous work, and confirmed the self-reported information that the cohort was healthy and sedentary in nature.

Given this decline in aerobic power a similar age-related decline in cardiac function might be anticipated. This was not the case. The CPO_{\max} and CR of healthy women did not change between nineteen and seventy-six years of age (Figs. 33 and 38). On a cellular level the paper by Olivetti *et al.* (1995) indicated that ageing in women did not result in much if any myocyte cell loss or reactive hypertrophy (Fig. 1), hence one might predict that the female heart has a greater potential to withstand the ageing process, compared with the male heart. This is the first time maximal overall cardiac function has been reported in healthy women, and leads to a different interpretation, as compared to only measuring blood flow. The data illustrates the remarkable resistance of the female heart to the effects of ageing.

There were significant age-related changes in the ability of the female heart to generate blood flow and blood pressure. Maximal blood flow decreased by

26% (less than the 32% decline in healthy men), and was the result of an age-related decrease in HR_{\max} , SV_{\max} did not change significantly (Fig. 34). The lack of any age-related change in maximum stroke volume illustrates that the female heart retains its distensibility with advancing age. This adds further weight to the conclusion that there is an absence of reactive myocyte hypertrophy in the female heart. This is not the first time this lack of change in stroke volume has been observed in women. Spina *et al.* (2000) reported a similar finding in a longitudinal study. Furthermore, they confirmed a lack of any cardiac hypertrophy via echocardiography. However in contrast, the cross-sectional study by McCole *et al.* (1999) reported decreases in stroke volume in healthy women. The data in this study were collected using a design more akin to the work of McCole *et al.* (1999). Nonetheless the findings are in agreement with those of Spina *et al.* (2000).

The 26% decrease in \dot{Q}_{\max} which occurred in these healthy women over fifty-seven years of healthy ageing was offset by a 26% increase in MAP_{\max} (Fig. 35). Significantly less work has been conducted examining the age-related changes in maximum blood pressure generation during dynamic exercise, but the data from this study are in agreement with the age-related increases in MAP_{\max} reported by Ogawa *et al.* (1992).

The female heart over the age-range studied appears to be effective in resisting age-related detrimental changes in its overall function, with CR unchanged (Fig. 38). It would seem that more of the energy injected into the blood is diverted towards pressure generation, and less towards blood flow

generation, with increasing age. However the overall power output, as opposed to its proportioning, remains unchanged.

This change in the characteristics of the female heart could be attributed to age-related changes in oestrogen levels. But this study cannot provide convincing evidence relating to the effect of oestrogen, due to the insufficient number of subjects around the menopause, who were taking or abstaining from hormone replacement therapy. However, the heart and the major blood vessels do possess oestrogen receptors (Grohé *et al.*, 1997) and it is claimed that oestrogen is cardioprotective (Channer and Jones, 2003; Grohé *et al.*, 1998; London *et al.*, 1995; Scuteri *et al.*, 2001)

10.3.2 The Effects of Habitual Endurance Exercise in Women

In comparison to healthy sedentary age-matched women, the $\dot{V}O_{2\max}$ of the female athletic sub-populations were 81%, 60% and 64% greater at twenty-five, sixty and seventy years of age, respectively. This data also illustrates that the age-related decline in $\dot{V}O_{2\max}$ occurs at a faster rate in the athletic women (Fig. 39). This finding has been reported by other studies (Fitzgerald *et al.*, 1997; Hawkins *et al.*, 2001; Tanaka *et al.*, 1997). However the aerobic power of an endurance-trained sixty year old was still greater than that of a twenty-five year old healthy sedentary woman (Fig. 39). Therefore it can be concluded that women who habitually engage in long-term endurance exercise do significantly improve their cardiorespiratory fitness and exercise capacity by offsetting the normal age-related decline. Nonetheless, ageing still takes its toll.

The measured improvement in $\dot{V}O_{2\max}$ which occurred as a consequence of endurance-training was not the result of an adaptation in maximum overall cardiac function. None of the groups of female athletes showed any significant increase in CPO_{\max} or CR in comparison to the age-matched sedentary control groups (Figs. 40 and 41).

In the youngest group of highly trained and competitive women \dot{Q}_{\max} did show a small increase which was the result of a similar sized increase in SV_{\max} . Otherwise, none of the measurements of blood flow changed in women in response to the exercise stimulus. Therefore both the sedentary and athletic groups showed similar age-related decreases in \dot{Q}_{\max} , SV_{\max} and HR_{\max} (Table 14).

In terms of blood pressure generation engaging in long-term endurance-training had no effect. Maximum MAP showed a similar age-related increase in both the sedentary and trained groups, and there were no age-matched differences (Table 14).

The lack of a cardiac adaptation in women in response to an endurance-based exercise stimulus has been suggested by previous studies. Spina *et al.* (1993) reported no increase in \dot{Q}_{\max} in women, this was confirmed by Ehsani *et al.* (2003) with particular reference to older aged women. With specific reference to left ventricular adaptations, such as ejection fraction, end systolic and diastolic volume or stroke work index, Fleg *et al.* (1995) and Higginbotham *et al.* (1984) confirmed that cardiac function in women does not adapt in response to exercise, despite measured increases in aerobic power.

This increase in aerobic power in the endurance-trained women was primarily the result of improvements in the peripheral extraction and consumption of oxygen. This was confirmed by calculating the $a - \bar{v} O_{2\text{diff}_{\text{max}}}$ which was significantly augmented in comparison to all the age-matched sedentary populations (Fig. 42). This occurred despite the fact that the exercise regimen did not significantly increase total lean body mass in the youngest two age groups (Table 12). This conclusion is in agreement with that of Spina *et al.* (1993) who also attributed the increased $\dot{V}O_{2\text{max}}$ in trained-women to a skeletal muscle adaptation, in the absence of any improvement in cardiac function. Endurance exercise is known to increase the oxidative capacity of muscles. Hence, although not different in size, the 'trained' muscle possesses more mitochondria, and thus a greater capacity to extract and consume oxygen.

Finally, as with ageing *per se* CR in the all the groups of trained women was unchanged (Fig. 41). Therefore, this data illustrates for the first time that overall cardiac function in healthy women is remarkably resilient to both the effects of ageing and long-term endurance exercise, and contrasts markedly with the changes seen in the hearts of men.

10.4 Size-Independent Gender Comparison

As indicated, it appears that healthy male and female hearts respond very differently to the effects of ageing and long-term endurance training. However, it has been recognised for many years that body size can significantly affect heart size and hence the absolute values of cardiac function (Batterham *et al.*, 1999; Daniels *et al.*, 1995).

Over the past sixty years the most frequently used method for normalising the affect of body size is simply dividing a physiological variable by the measured body size. For example, $\dot{V}O_{2\max}$ (l/min) divided by total body mass becomes $\dot{V}O_{2\max}$ (ml/kg/min), or in cardiology left ventricular mass is divided by body surface area (Deague *et al.*, 1999). Fleg and Lakatta (1988) took this process one step further. They recognised the concomitant age-associated loss of metabolically active tissue (i.e. muscle) which occurs in tandem with the decline in $\dot{V}O_{2\max}$. Therefore they used urinary creatinine excretion as an index of muscle mass, and subsequently employed it to normalise total body oxygen consumption.

However, this simple division has two major flaws. Firstly it assumes that the relationship between the two variables is perfectly linear. Unfortunately such a relationship is rarely perfectly linear, and is often much more complex (Nevill *et al.*, 1992). Secondly, it assumes a causal relationship exists between the two measures. Clearly if a causal relationship doesn't exist then the scaling process is meaningless in physiological terms (as opposed to mathematical), and will result in erroneous data adjustments and interpretations.

The allometric scaling method has been shown to be theoretically, and more importantly physiologically and statistically superior to the traditionally used simple division approach (George *et al.*, 1997; Nevill *et al.*, 1992; Winter, 1992). Furthermore, previous work by the current investigators has proven this method to be effective in controlling the effects of body size and composition on CPO (Chantler *et al.*, 2005). This allometric technique was therefore used to normalise the impacts of body size and composition on aerobic power and

overall cardiac function, and thus allow a more meaningful sex-based comparison to be made.

Lean body mass proved statistically to be the best measure of body composition to scale too, both in terms of $\dot{V}O_{2\max}$ (Table 15), CPO_{\max} and CR (Table 17). This made good physiological sense as lean body mass is the major consumer of oxygen during exercise, and therefore demands the higher supply of blood. Once allometrically scaled, $\dot{V}O_{2\max}$ independent of body composition still declined significantly in both healthy men and women over the course of healthy ageing (Fig. 44c). The difference between the sexes that was present in the absolute measures (Fig. 44a) however was removed, and the rate of the age-related decline was no longer sex specific over the age range studied. These results are in close agreement with those of Fleg and Lakatta (1988). They reported that normalising aerobic power to lean body mass abolished the difference between the sexes, and reduced the decline observed in aerobic power between thirty and seventy years of age from 39% to 18%, and from 30% to 14% in men and women, respectively.

In terms of cardiac function, the sex-dependant difference in CPO_{\max} was somewhat reduced by allometrically scaling to LBM. However, the overall effect of ageing was still very much sex-dependant. Maximum overall cardiac function still declined significantly (22%) as a consequence of healthy ageing in sedentary men between nineteen and seventy-six years of age (Fig. 46). In contrast, there remained no age-related change in women (Fig. 46). Below forty-four years of age the body composition independent measure of CPO_{\max} was greater in healthy sedentary men than women. But, at this age point the

sexes became indistinguishable, after which healthy women continued to maintain their overall maximum cardiac function, whilst the significant decline in men continued.

This is the first time that the overall functional reserve of the human heart has been measured *in situ*, and allometrically scaled, therefore partition out the influence of changes in body composition. The result was that a sex-dependant difference was still present. The functional reserve capacity of the healthy male heart decreased by 19% between nineteen and seventy-six years of age (Fig. 47). While the female heart effectively retained its reserve capacity, and the heart of a healthy nineteen year old female is functionally indistinguishable from that of a healthy seventy-six year old.

The allometric process was also applied to all the groups of endurance-trained male and female athletes, but the process did not enhance or significantly change the age-related trends and conclusions already drawn and discussed. Therefore, male athletes have the ability to improve their cardiac function in response to a sufficient training stimulus independent of the concomitant changes in body composition. In contrast, long-term endurance-trained females exhibited no change in overall cardiac function when compared to healthy sedentary women.

This data shows that healthy ageing and endurance training have significantly different effects on the overall cardiac function of men and women. These differences are independent of changes which occur in body size and composition suggesting that intrinsically the male and female hearts respond

differently to ageing, with important public health and policy making implications. By engaging in long-term endurance exercise men improve their CR and hence can delay the age-associated decline in overall cardiac function. Healthy women show much less capacity to augment their overall cardiac function in response to an endurance based exercise stimulus. This seems strange considering they retain more cardiomyocytes, and would therefore seem to have a greater potential to respond to any such stimulus.

10.5 Future Research

As well as providing a new physiological insight into overall cardiac function, the data from this study have also confirmed that CPO is the best indicator of overall cardiac function (Nicholls and Riley, 2001). If only blood flow measurements had been made at maximal exertion, as has traditionally been the case in many previous studies on healthy ageing, the decline in function would have been overestimated in both healthy men and women, because the concomitant increases in blood pressure generation would have been ignored. Furthermore, if blood pressure had not been measured in the heart failure patients, the extent of the functional impairment which resulted from the disease process would have been underestimated.

Historically CPO has only been used in heart failure patients as a diagnostic and prognostic tool. The use of CPO when measuring cardiovascular function in healthy and diseased; young and older; trained and sedentary populations needs to be promoted and expanded beyond the scope of this study. This represents only a start in this direction. The use of this technique would provide a clearer picture as to what changes occur in overall cardiac function

and cardiac reserve in response to numerous preventative and therapeutic interventions in both clinical and exercise physiology.

Although some research has been done into the cellular mechanisms, and changes which occur with healthy ageing in the human heart more work is needed in this area. The aim should be to establish a definitive link between mechanistic adaptations and their impact on cardiac power output.

Finally, recent research has focussed on the dose-response relationship between endurance training and cardiovascular adaptations (Iwasaki *et al.*, 2003). Some authors suggesting repeated bouts of high intensity exercise may be as effective as longer duration lower intensity exercise in inducing cardiorespiratory improvements (Burgomaster *et al.*, 2005). These papers though are only focussing on the traditional measurements of individual components of cardiac and respiratory function, and tend to involve younger fitter individuals.

This study has established the adaptive changes, or lack of changes, which occur in overall cardiac function in long-term highly trained aerobic athletes. It would now be advisable to examine whether shorter-term bouts of exercise at different intensities could elicit similar adaptations in previously inactive individuals.

Chapter 11

Conclusion

11.0 Conclusion

The aims of this study were to examine what impact healthy ageing, long-term endurance exercise and heart failure had on overall cardiac function, and to do this in men and women under identical conditions. Previous studies have reported changes in the individual components of cardiac function, such as blood flow generation or myocardial contractility. But the main function of the heart is to act as a hydraulic pump ensuring adequate circulation of blood. To do this the heart generates kinetic energy thereby creating both blood flow and blood pressure. Therefore, to accurately measure its overall function regardless of the preload and afterload conditions both components must be measured in tandem. Cardiac power output does this by measuring and integrating both components. For this reason it represents the best measure of overall cardiac function (Nicholls and Riley, 2001) and was used throughout this study.

Initially, all the equipment to be used was tested to ensure its accuracy, and the protocols developed to ensure that all the data subsequently collected was valid and meaningful. Furthermore, all the subjects were thoroughly screened and tested to ensure the absence of any diseases, confounding medications or food supplements which could affect the measurements. This enabled us to study 'healthy ageing' in a fairly homogenous group of men and women.

In healthy sedentary men between seventeen and seventy-six years of age the advancing years resulted in the significant ($P < 0.001$) but progressive decline of $\dot{V}O_{2\max}$, CPO_{\max} and CR. However, engaging in long-term endurance based exercise effectively offset these negative effects by

increasing the reserve capacities. Despite this aerobic and overall cardiac function still decreased in the long-term endurance trained individuals. Even so, a seventy-year old endurance trained male has a $\dot{V}O_{2\max}$, CPO_{\max} and CR which is comparable to that of a twenty-year old healthy sedentary male.

In contrast, patients who were suffering from chronic heart failure exhibited severely impaired aerobic and cardiac function. This was known clinically, but it is crucial to quantify the exact levels of deterioration in such patients, i.e. to give more objective evidence of the level of dysfunction. Compared to healthy sedentary men, the $\dot{V}O_{2\max}$, CPO_{\max} and CR of these patients was significantly ($P < 0.0001$) reduced by 45%, 57% and 64% respectively, and their long-term prognosis without drastic intervention could be defined as very poor.

In healthy women $\dot{V}O_{2\max}$ also declined significantly ($P < 0.0001$) as a result of healthy ageing between nineteen and seventy-six years of age. But, in the same subjects there were no significant ($P > 0.05$) age-related changes in either CPO_{\max} or CR. Long-term endurance trained female athletes of twenty-five, fifty and sixty years of age significantly ($P < 0.05$) increased their $\dot{V}O_{2\max}$ by 81%, 60% and 64%, respectively. But the long-term training stimulus had no significant ($P > 0.05$) impact on either CPO_{\max} or CR. Therefore the increase in $\dot{V}O_{2\max}$ had to be attributable to an increased ability to extract and consume oxygen at the peripheries by the skeletal muscles. These represent very interesting gender differences in response to ageing and exercise that warrant greater study and explanation.

Previous studies have concluded that body size can significantly affect various indices of cardiac function (Batterham *et al.*, 1999; Daniels *et al.*, 1995), and that the best method to control for these differences is through the use of allometric scaling (George *et al.*, 1997; Nevill *et al.*, 1992; Winter, 1992). This scaling method was employed to derive body size and compositional independent measurements of overall cardiac function, thereby allowing the impact of healthy-ageing and long-term endurance training to be compared much more meaningfully between men and women.

After allometrically scaling the data relating to CPO_{\max} and CR, significant ($P < 0.01$) decreases as a consequence of healthy-ageing still existed in healthy men. In stark contrast there were still no significant ($P > 0.05$) changes in either CPO_{\max} or CR in healthy women, over the same age range.

Furthermore, the trends reported in the non-scaled data relating to the effects of engaging in long-term endurance exercise remained unchanged. Therefore, independent of changes in body size and composition long-term endurance trained men were able to significantly improve their overall cardiac function, whereas the women showed no overall central cardiac adaptation.

While our data correlates well with previous work on cardiomyocyte number in the hearts of both humans and animals, there is still vast scope for continuing research into the cardiovascular dose response relationship, and to establish a causal link between cardiac power output and events at the mechanistic cellular and molecular level.

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Appendix 1

Subject Questionnaire

Female Participant Questionnaire

**Liverpool John Moores University
Research Institute for
Sport and Exercise Sciences**

Project: Effects of Ageing on the Power Output of the Heart



Personal Details & Medical, Lifestyle and Dietary Assessment Questionnaires

Please Read Carefully

The main purpose of this questionnaire is to find out about your health status and lifestyle habits. Information that you provide will be used to determine your suitability to participate safely and effectively in this study

Please note: This questionnaire is an important part of the study. We request that you answer all questions as accurately and as honestly as possible. Most questions can be answered by either placing a circle around the appropriate response, a tick in the box provided, or a short written response.

Section One**Personal Information**

1. Name: _____

2. DOB: _____ Age: _____

3. Height: _____ Weight: _____

4. Address _____

5. Telephone number:

Home: _____

Mobile: _____

6. Email: _____

7. What is your ethnic group (please tick box)

Caucasian	Hispanic	Black	Asian	Chinese	Other
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Section Two**Personal Medical History Assessment****(circle answer)**

8. Has your doctor ever said that you have had a heart condition? Yes No

If yes, please give details, including dates _____

9. Have you ever been instructed to perform physical activity only
recommended by a doctor? Yes No

If yes, please give details, including dates

10. Have you ever had a real, or suspected, heart attack? Yes No

If yes, when did it occur _____

11. Have you ever experienced rapid heart beating or palpitations? Yes No

If so, please give details, including what you were doing at the time _____

12. Have you ever had angina or a sharp heavy pain in your chest as the result of physical activity? Yes No

If so, please circle level of activity: low moderate strenuous

13. Do you lose your balance because of dizziness? Yes No

14. Do you ever lose consciousness? Yes No

15. Have you ever had a resting or exercise ECG taken? Yes No

If yes, was the ECG normal? Yes No

16. Have you ever been severely breathless as a result of low / moderate level exercise? Yes No

17. Do you suffer from high or low blood pressure? Yes No

If yes, which one? Low High

18. Are you currently taking prescribed medication to control your blood pressure? Yes No

If yes, give name and dosage _____

19. Have you ever been told your blood cholesterol is too high? Yes No

If yes, please state your cholesterol level (if known) _____

20. Are you currently taking prescribed medication to control your cholesterol ? Yes No

If yes, state name and dosage _____

21. Do you suffer from any kidney problems now or in the past? Yes No

If yes please specify condition and medication _____

22. Do you suffer from diabetes? Yes No

If yes, how is it controlled (please tick)

- a) Dietary means ☐
- b) Insulin injection ☐
- c) Oral medication ☐
- c) Uncontrolled ☐

23. Do you suffer from asthma, or any respiratory disorders? Yes No

Please give details of condition and any medication taken including inhaler

Is the breathing condition made worse by exercise? Yes No

If yes, what level of exercise (please circle) low moderate strenuous

24. Do you have any musculo-skeletal problems that could be made worse by a change in physical activity? Yes No

If so, please give details of condition

What level of exercise can you do without making your condition worse? (please circle) low moderate strenuous

25. Do you know of any other reason why you should not undertake physical activity? Yes No

If yes, why

26. Do you suffer from any of the following: -

HIV/AIDS	Yes	No
Hepatitis B or C	Yes	No
Or any other disease transmitted by blood	Yes	No
Haemophiliac	Yes	No
Chron's disease	Yes	No
Thyroid Problems	Yes	No
Adrenal Problems	Yes	No
Pituitary Problems	Yes	No

27.Do you smoke? Yes No

If yes,

What do you smoke (please circle) cigarettes cigars pipe

How long have you smoked for? _____

How many per day? _____

28. Have you ever smoked? Yes No

If yes,

How long did you smoke for? _____

How many per day? _____

When did you stop? _____

Section Three

Hormonal Status.

29. Have you ever menstruated (had a period) before? Yes No

If YES, how old were you when you first menstruated? _____

30. Are you using hormone contraceptives? (the pill, progesterone injection, patch) Yes No

If YES, please continue (Q.31)

If NO, go to question 33

If YES, please state what type you use, it's hormonal contents and dosage, if known

31. How long have you been using hormone contraceptives?

- ☐ Less than 1 year.
- ☐ 1-2 years.
- ☐ 3-5 years.
- ☐ More than 5 years. Please state how long

32. Why do you use them? _____

-
- ☐ Contraception alone.
 - ☐ Contraception and regulation of the menstrual cycle.
 - ☐ Contraception and regulation of menstrual cycle symptoms (depression, pain, back ache etc.)
 - ☐ Other reasons, please describe
-

33. If you do not currently use hormone contraceptives, have you ever used them in the past? Yes No

If YES, please continue (Q.34)

If NO, go to question 37

34. How long were you using them?

- ☐ Less than 1 year.
 - ☐ 1-2 years.
 - ☐ 3-5 years.
 - ☐ More than 5 years. Please state how long
-

35. How long ago did you stop using hormone contraceptives?

- ☐ Less than 1 year ago.
 - ☐ 1-2 years ago.
 - ☐ 3-5 years ago.
 - ☐ More than 5 years ago. Please state how long
-

36. Why did you stop using them?

- ☐ Irregular bleeding.
 - ☐ Side effects (cycle irregularities, weight gain, mood disturbances).
 - ☐ Planning a pregnancy.
 - ☐ Other reasons. Please state
-

37. Have you reached the menopause?

- ☐ Yes, surgical hysterectomy.
- ☐ Yes, naturally, confirmed by my doctor.
- ☐ Yes, naturally, unconfirmed by my doctor.
- ☐ Unsure.
- ☐ No.

If YES, please continue (Q.38)

If NO, go to section four

38. At what age did you reach the menopause?

39. Are you taking any Hormone Replacement Therapy (HRT)? Yes No

If YES, please continue (Q.40)

If NO, go to question 43

40. Please list what HRT name, hormonal contents and dosage

41. Why do you use HRT?

- ☐ Treatment of short term symptoms (hot flushes, night sweats, vaginal dryness)
- ☐ Prevention or treatment of osteoporosis.
- ☐ Prevention of heart disease.
- ☐ Other. Please describe.

42. How long have you been taking HRT?

- ☐ Less than 1 year
- ☐ 1-2 years
- ☐ 3-5 years
- ☐ Longer than 5 years, please state how long

43. If you are not taking HRT now, have you ever used it in the past?

Yes No

If YES, please continue (Q.44)

If NO, go to section four

44. When did you stop taking HRT?

- ☐ Less than 1 year
- ☐ 1-2 years
- ☐ 3-5 years
- ☐ Longer than 5 years, please state how long

45. How long did you take HRT for?

- ☐ Less than 1 year
- ☐ 1-2 years
- ☐ 3-5 years
- ☐ Longer than 5 years, please state how long

46. Why did you stop taking HRT?

- ☐ Side effects (headache, acne, bloating, breast discomfort)
 - ☐ Worried about health risks (cancer, hypertension, blood clots, etc.)
 - ☐ No longer needed.
 - ☐ Other. Please describe.
-

Section Four

Physical Activity Assessment

47. Considering a typical **7-day period** (week), how **many times** do you do the following kinds of exercise for during your free time (write on each line the appropriate number).

	Times Per Week	Duration (to the nearest 5mins)
a) Strenuous Exercise (Heart beats rapidly)		
(e.g. running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous longer distance cycling)	_____	_____

b) Moderate Exercise (Not Exhausting)

(e.g. fast walking, baseball, tennis, easy cycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____	_____
--	-------	-------

c) Mild Exercise (Minimal Effort)

(e.g. yoga, archery, fishing from river bed, bowling, horseshoes, golf, easy walk)	_____	_____
--	-------	-------

48. Considering a typical **7-day period** (week), during your leisure time, how often to do you engage in regular activity long enough to work up a sweat with your heart beating rapidly?

OFTEN
☐

SOMETIMES
☐

NEVER/RARELY
☐

49. Are you currently engaged in moderate or intense training? Yes No

If yes, over the course of a typical week please could you detail below your current training schedule.

Day	Intensity	Duration	Description
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

How long have you been training for? _____

50. If you compete in any event please could you provide some details regarding personal best times. Please list them in chronological order with the most recent first.

Distance / Event	Time	Date Completed (Month & Year)

51. Have you ever previously engaged in moderate or intense training?
Yes No

If yes, please give details of your schedule:

Intensity	Number of times per week	Duration of each session (to nearest 5mins)
-----------	-----------------------------	--

_____	_____	_____
-------	-------	-------

What year did you start training? _____

How long ago did you stop training? _____

Section five

Diet Assessment
(please circle)

52. Are you a vegetarian Yes No

53. During a typical day what do you eat/drink

54. Do you take any food supplements Yes No

If yes, please specify _____

55. Please detail any further information you would like to tell us

Participant signature: _____

Thank you for completing this questionnaire

Appendix 2

Subject Consent Form

All Information Given to the Researcher Will Be Treated As Confidential

I,agree to take part in the above named project/procedure, the details of which have been fully explained to me and described in writing, along with the demands, risks and benefits of the study. I am aware of the risks involved and understand that I can withdraw from this study at any time without penalty.

Signed (Subject) Date

I,certify that the details of this project/procedure have been fully explained and described in writing to the subject named above and have been understood by him/her.

Signed (Researcher) Date

I,certify that the details of this project/procedure have been fully explained and described in writing to the subject named above and have been understood by him/her.

Signed (Witness)..... Date

Appendix 3

Peer Reviewed Research Communications

Papers

Chantler PD, Clements RE, Sharp L, George KP, Tan LB & Goldspink DF (2005). The influence of body size on measurements of overall cardiac function. *American Journal of Physiology Heart and Circulatory Physiology* **289**, H2059 – H2065.

Chantler PD, Goldspink DF, Clements RE, Sharp L, Schlosshan D & Tan LB. (2006). Congestive heart failure: extent of cardiac functional changes due to ageing and organ dysfunction. *Heart*, in press.

Published Oral Presentations

Chantler PD, Clements RE, Sharp L, Tan LB & Goldspink DF (2004). Cardiac power output in ageing sedentary and endurance trained men. *Journal of Physiology* **C120**, 555.

Clements RE, Chantler P, Sharp L, Tan L B & Goldspink DF (2004). Effects of Ageing and Long-Term Endurance Exercise on Cardiac Power Output. *Journal of Sports Science* **23**, 145, Ab147.

Sharp L, Clements R, Chantler P, Patwala A, Goldspink D & Tan LB (2004). Cardiac power output and age-related changes in healthy women. Excellence in health and performance. *Journal of Sports Science* **23**, 145, Ab148.

Published Poster Presentations

Chantler PD, Clements RE, Sharp L, Tan LB & Goldspink DF (2004). Blood pressure generating capacity is a component in measuring overall cardiac function. *Journal of Molecular and Cellular Cardiology* **37**, 172, AbA29.

Chantler PD, Clements RE, Sharp L, Tan LB & Goldspink DF (2004). Cardiac power in the ageing, trained and failing heart. *Journal of Molecular and Cellular Cardiology* **37**, 172, AbA30.

Chantler PD, Sharp L, Clements RE, Tan LB & Goldspink DF (2004). Age-and gender-related changes in cardiac power. *Journal of Molecular and Cellular Cardiology* **37**, 172 AbA31.

Clements RE, Chantler P, Goldspink DF, Sharp L & Tan L B (2004). Effects of ageing, exercise and heart failure on cardiac power output. *Heart* **90**, A1-56, Ab 26.

Clements RE, Chantler PD, Sharp LJ, Tan LB & Goldspink DF (2004). The impact of age and endurance training on cardiac power output in men. *The Physiologist* **47**, 287, Ab7.3.

Sharp L, Chantler P, Clements R, Goldspink D & Tan LB (2004). Age-related changes in cardiac power output in healthy women. *Heart*, 90, A1-56, Ab 6.

Sharp LJ, Chantler PD, Clements RE, Patwala A, Tan LB & Goldspink DF (2004). Age-related changes in cardiac power output and $\dot{V}O_{2\max}$ in healthy women. *The Physiologist* 47, 287, Ab 7.4.

Non- Published Oral Presentations

Chantler PD, Tan LB, Clements RE, Sharp L & Goldspink D (2004). The power output of the ageing and failing human heart and the benefits of endurance training. *9th European College of Sports Science*. July, Clermont-Ferrand, France.

Clements R, Chantler P, Sharp L, Tan LB & Goldspink D (2004). Age- and gender- related changes in maximum oxygen consumption and cardiac power output. *9th European College of Sports Science*. July, Clermont-Ferrand, France.

Clements R, Sharp L, Chantler P, Tan LB & Goldspink D (2004). Efficacy of long-term endurance exercise in ameliorating the age-related decline in cardiac power output. *Young Physiologists Symposium in Association with The Physiological Society*. August, Leeds, UK.

Clements RE, Sharp LJ & Goldspink DF (2005). The effects of ageing and long-term endurance exercise on overall cardiac function and maximal oxygen consumption in women. *10th European College of Sports Science*. July, Belgrade, Serbia.

Sharp L, Clements R, Chantler P, Goldspink D & Tan LB (2004). Age-related changes in cardiac power output and $\dot{V}O_{2\max}$ normalised to lean body mass in healthy females. *Young Physiologists Symposium in Association with The Physiological Society*. August, Leeds, UK.

Sharp L, Clements RE, Patwala A, Tan, L-B & Goldspink D (2005). The effects of 1 year of endurance training on cardiac power output in healthy post-menopausal women. *10th European College of Sports Science*. July, Belgrade, Serbia.

Non- Published Poster Presentations

Chantler PD, Clements RE, Tan LB & Goldspink DF (2004). Endurance training ameliorates the age-related loss of cardiac power in man. *Aging Heart & Vessels. International Society for Heart Research*. Melbourne, Australia.

Sharp L, Chantler P, Clements R, Patwala A, Tan LB & Goldspink D (2004). Age-related changes in cardiac power output in healthy women. *9th European College of Sports Science*. July, Clermont-Ferrand, France.

**THESIS
CONTAINS
CD/DVD**