AGE-AND EXERCISE-RELATED EFFECTS ON CARDIAC POWER OUTPUT

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Abstract

Ageing is an inevitable process characterised by a progressive deterioration in the function of a number of organs and systems, ultimately reducing the individual's quality of life of. Despite its obvious importance, our understanding of the basic age-related changes in cardiac function remains poor. In part because past studies, describing the changes in cardiac function with age, have not always adequately controlled for different lifestyles or superimposed diseases, while using less than complete measures of overall cardiac function and appropriate scaling models. The aim of this thesis was to determine the changes in overall cardiac function associated with healthy ageing, using the comprehensive, non-invasive method of cardiac power output (CPO).

After identifying that CPO was not affected by circadian rhythms, 149 sedentary men and women (19-75 years) and 60 active men were investigated. All were free from cardiovascular diseases and medications. The findings indicated that healthy ageing, in all subject populations, was associated with an ~17% decline in CPO_{rest}, ~15% in CPO_{max}, and ~14% in CR. Age for age, sedentary men had greater CPO values than women, both at rest (~19%) and at maximal exercise (~25%). In addition, cardiac function was greater in the active men, compared with age-matched, sedentary controls, with values ranging from 11-30% greater.

It was also found that body composition had a significant impact on the interpretation of CPO data. For example, when scaled allometrically for fat free mass (FFM^b), absolute sex-related differences in CPO disappeared, as did the age-related decline in CPO_{rest}. Also, in women no age-related changes in CPO_{max} were found once normalised to FFM^b even though in men, CPO_{max} and CR still declined with age.

Clearly, how these data are normalised relative to body composition is crucial to the interpretation of the effects of ageing or an active lifestyle. These are novel findings and indicate that healthy ageing is associated with reductions in overall cardiac function, as represented by significant declines in CPO_{max} and CR in men, but not women. In addition, endurance training improved aerobic capacity while attenuating the changes in cardiac function.

Contents

Methods

Results

Results continued...

List of Tables

List of Figures

List of Figures continued...

List of Figures continued...

List of Figures continued...

Abbreviations

a-v O_2 difference	Arterial-Mixed Venous Oxygen Difference
Act	Active
BM	Body Mass (the sum of the body fat mass, fat free mass and bone)
BP	Blood Pressure
BSA	Body Surface Area
Ci	Cardiac Index Corrected for Fat Free Mass
CO	Cardiac Output
CPi	Cardiac Power Index Corrected for Fat Free Mass
CPO	Cardiac Power Output
CPO_{rest}	Resting Cardiac Power Output
CPO_{max}	Maximal Cardiac Power Output
CR	Cardiac Reserve
CRi	Cardiac Reserve Index Corrected for Fat Free Mass
CRT	Cardiac Resynchronisation Therapy
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EDVI	End Diastolic Volume Index Corrected for Body Mass
ESVI	End Systolic Volume Index Corrected for Body Mass
FFM	Fat Free Mass (the non-adipose tissue of body mass and the non-fat component of adipose tissue)
FM	Fat Mass (the quantity of triglyceride fat in the body)
HF	Heart Failure
HT	Height
HR	Heart Rate
LVEDV	Left Ventricular End-Diastolic Volume
LVM	Left Ventricular Mass
LVV	Left Ventricular Volume
MAP	Mean Arterial Pressure
PCr	Phosphocreatine

PetCO2	End Tidal Partial Pressure of Carbon Dioxide
PNS	Parasympathetic Nervous System
PP	Pulse Pressure
PWT	Posterior Wall Thickness
RER	Respiratory Exchange Ratio
RES	Linear Regression Standards
RS	Per-ratio Standard
r, X, *Y*	Person's Product Moment Correlation
SBP	Systolic Blood Pressure
Sed	Sedentary
SEM	Standard Error of the Mean
SNS	Sympathetic Nervous System
SV	Stroke Volume
SVi	Stroke Volume Index Corrected for Fat Free Mass
SVR	Systemic Vascular Resistance
SVRi	Systemic Vascular Resistance Index Corrected for Fat Free Mass
SWT	Septal Wall Thickness
$\dot{V}CO_2$	Carbon Dioxide Production
$\dot{V}O_2$	Oxygen Uptake
$\dot{V}O_{2max}$	Maximal Oxygen Uptake
VR	Venous Return
Vt	Tidal Volume

Chapter 1

Introduction

Ageing is characterised by an impaired ability to maintain homeostasis (Lakatta, 1993). This comes about because of a progressive deterioration in the functional capacity of various organs and systems. Superimposed on the ageing process is an increase in the prevalence of diseases, such as atherosclerosis, obesity, diabetes, and ischaemic heart disease. The severity of these conditions usually increases with age. Such diseases may affect the process of ageing, highlighting the importance of demarcating the pathological condition from healthy ageing. In practice, it is difficult to differentiate between healthy ageing and the presence of specific diseases (Olivetti *et al.*, 1995), especially with advancing years. This issue is further complicated by the fact that age-related changes are not uniform in nature. Some physiological functions may fail to show impairment with ageing, whereas other functions may be paradoxically enhanced, which makes this line of research a demanding one.

As the average life expectancy increases, the importance of understanding the physiological changes and associated mechanisms that occur with ageing, have become a higher priority than ever before. Improving the health and quality of life is relevant to all age groups, but in particular to the increasing number of older people. This increased longevity places extra demands on any country's financial resources. Increased demands on health care resources have lead to the realisation that maintaining physiological function through increased physical activity can be a positive intervention from which the NHS may reap financial benefits. As well as these financial rewards, older people should have the opportunity to improve their quality of life by remaining fitter, and therefore more able to perform daily activities and retain their independence for longer. The improvement in physiological function may be brought about by changes in the function of the heart, through increased physical activity. Ageing is inevitable. However, understanding the physiological changes brought about by the process of healthy ageing, particularly in defining how the performance of the heart changes and precisely when the heart begins to deteriorate, can help to formulate appropriate regimens or interventions to delay, and in some cases reverse, the consequences of ageing.

Past research has tended to cloud the issue of ageing per se because of a failure to acknowledge, or control for interactions among age, disease and lifestyle, thus

complicating the interpretation of the process of ageing. It is important to determine the changes in cardiac function that occur during the process of healthy ageing, only then will we be able to distinguish the underlying process of disease.

1.1. Ageing

Ageing is a non-specific term that has been applied to a spectrum of life periods, e.g. stages surrounding perinatal, neonatal, maturational, adulthood, and old age. Thus development or ageing can be defined as that which happens over a period of time, thus encapsulating changes that can be beneficial, detrimental, or no change in function. In this thesis, ageing relates to the physiological changes that occur to an organism throughout the process of post pubertal, adult lifespan.

1.1.1. Definitions of Ageing

For scientific clarity it is important to provide the correct terminology that describes the process of ageing. A number of terms have been used which refer to the process of ageing in the presence or absence of disease. For example, normal ageing refers to senescence in the absence of disease (Masoro, 2001). This term has been criticised because it is thought that ageing in the absence of disease is a rare occurrence. It is therefore atypical (Masoro, 2001). In addition, normal ageing goes against the evolution theory of ageing, which predicts the occurrence of age-related disease is an almost inevitable and intrinsic component of senescence (Weinert and Timiras, 2003). Other terms used to describe the process of ageing include, 'Primary' and 'Secondary' ageing. Primary ageing relates to changes that occur in a population, but are not caused by disease or by environmental influences, whereas Secondary ageing refers to changes involving interactions of Primary ageing with environmental influences and disease processes (Busse, 1969). The validity of these terms has also been questioned. The process of senescence can be viewed as the result of the long-term accumulation of unrepaired cellular damage, the nature and site of this damage relating to genetic characteristics of the individual. Masoro (2001) concluded that it is immaterial whether the damage is caused by intrinsic (genetics) or extrinsic processes (environment and

lifestyle). Masoro (2001) went on to say that it is often the interaction between the biological system and environmental and/or lifestyle factors that result in damage, therefore all damage can be thought of as intrinsic. Two more widely used concepts are 'Usual' and 'Successful' ageing (Rowe and Kahn, 1987). Those individuals who exhibited a substantial deterioration in physiological functions with increasing age were categorised as Usual ageing and therefore are associated with a significant risk of disease and premature death. Whereas, those who exhibited minimal change in physiological function with advancing age were categorised as undergoing Successful ageing. The concept of Successful ageing implies that advancing age, ending in death, can be achieved without major deteriorations in physiological function. More often that not, individuals in the later stages of life suffer a marked deterioration in physiological function prior to death. Masoro (2001) suggested that it would simply be more appropriate to say that the process of ageing occurs more slowly in these individuals.

Within the context of this thesis the term 'healthy ageing' will be used to represent the process of ageing in individuals in the absence of overt clinical diseases, and in particular cardiovascular abnormalities or disease. This term allows us to measure the deterioration of cardiac function with increasing age, without the complication of superimposed disease

1.1.2. Theories of ageing

There are a number of theories, which attempt to explain how and why ageing occurs. A problem with ageing is that it is often synonymous with disease (Lakatta, 2000). One possible explanation for the aged-related increased prevalence of certain diseases is that there is an increased exposure time to risk factors, with increased severity and extent of pathophysiological manifestations in older individuals. A somewhat different view is that cardiovascular structures and functions change with time because of an "ageing process", and that over time specific pathophysiological disease mechanisms become superimposed on this process (Lakatta, 2002). This view suggests age-disease interactions which escalate as the organism becomes older.

The original search for a single gene or the functional deterioration of one major system in the body that is responsible for ageing has been replaced with the concept that ageing is the consequence of several complex and multi-factorial processes (Weinert and Timiras, 2003). Rather the theories that attempt to explain how organisms age have been grouped into several categories, with the 'programmed' and 'error' theories of ageing being the most widely used. According to the 'programmed' theory, ageing depends on biological clocks regulating life span through stages of growth, development, maturity, and old age. This regulation depends on genes sequentially switching 'on' and 'off' signals to the nervous, endocrine, and immune systems responsible for maintenance of homeostasis (Weinert and Timiras, 2003). The 'error' theory, relate to environment influences that induce progressive damage at various cellular or intracellular levels, e.g. mitochondria DNA damage, oxygen radicals accumulation, cross-linking etc (Medawar, 1952).

1.1.3. Age-related changes in cardiac structure

The average weight of the heart in men and women is considered to be approximately 320 and 280 grams, respectively (Olivetti *et al.,* 1995). It has been suggested that the human heart increases in weight by approximately 1 gram per year in men and 1.5 gram per year in women (Linzbach and Akuamoa-Boateng, 1973). However, these figures paid little attention to the pathophysiological states of the heart and major blood vessels upon analysis. More recent observations in the absence of disease, have reported that ageing, in men is associated with a consistent loss of myocardial mass, while the female heart remains essentially constant (Olivetti *et al.,* 1991, 1995). Hence, weight or mass alone is not very informative.

It is however generally believed that there is an increase in left ventricular wall thickness with age in both men and women (Gerstenblith *et al.,* 1977). However, in old age (80-100 years) the left ventricular mass (LVM) may decrease (Waller and Roberts, 1983), perhaps because of an extreme sedentary lifestyle. Most of the studies measure LVM through echocardiography, which samples only a single small area of the left ventricle posterior wall or ventricular septum and extrapolates this to represent the global left ventricle thickness; LVM is then estimated assuming a constant ventricular

geometry at all ages. So while providing useful non-invasive information on internal cardiac structures, there are technical limitations. Using magnetic resonance imaging Hees *et al.* (2002) identified that healthy ageing was associated with left ventricular remodelling, with a decrease in long axis length of the heart in both men and women. These changes resulted in a decrease in LVM in men. However an increase in wall thickness prevented any such loss in LVM in women.

Although the data on age-related changes in LVM are generally conflicting, it has been suggested that a major adaptation of the human heart in response to ageing is a progressive loss of cardiomyocytes (Olivetti *et al.,* 1991). In men between the ages of 18 and 70 years, up to 30-35% of the cardiomyocytes have been lost through apoptotic and necrotic cell death (Figure 1.1A). Interestingly, in women between 20 and 95 years-of-age, loss of cardiomyocytes is very much less (Figure 1.1C). In men, but not in women, some of the remaining viable cardiomyocytes undergo hypertrophy (Figures 1.1B and 1.1D). However, this adaptive response in the male heart does not fully compensate for the progressive decline in cardiomyocyte numbers (Olivetti *et al.,* 1991). The consequence of this natural attrition of contractile cells is a decrease in cardiac mass. Such data at the cellular level may explain why women live longer than men. However, there is mounting evidence that cardiac stem cells and some smaller cardiomyocytes may re-enter the cell cycle and develop into differential cardiomyocytes. This suggests that a potential for cardiomyocyte regeneration does indeed exist with the heart (Nadel-Ginard *et al.,* 2003; Sussman and Anversa, 2003). As it stands the work of Olivetti *et al.* (1991, 1995) suggests that myocyte death exceeds regeneration with a net loss of these contractile cells, at least in men. Whether this newly discovered regenerative capacity in the mammalian heart declines with healthy ageing is an important research question.

1.1.4. Age-related changes in resting indices of cardiovascular function

Resting cardiac output (CO_{rest}), the product of stroke volume (SV) and heart rate (HR), is an important component of cardiac function. Resting CO has been shown to either decline (Brandfonbrener *et al.,* 1955; Conway *et al.,* 1971; Julius *et al.,* 1967; Messerli *et al.,* 1981) or remain unchanged (Fleg *et al.,* 1990, 1995; Higginbotham *et al.,* 1984; Rodeheffer *et al.,* 1984, 1986) with increasing age. Differences have also been reported

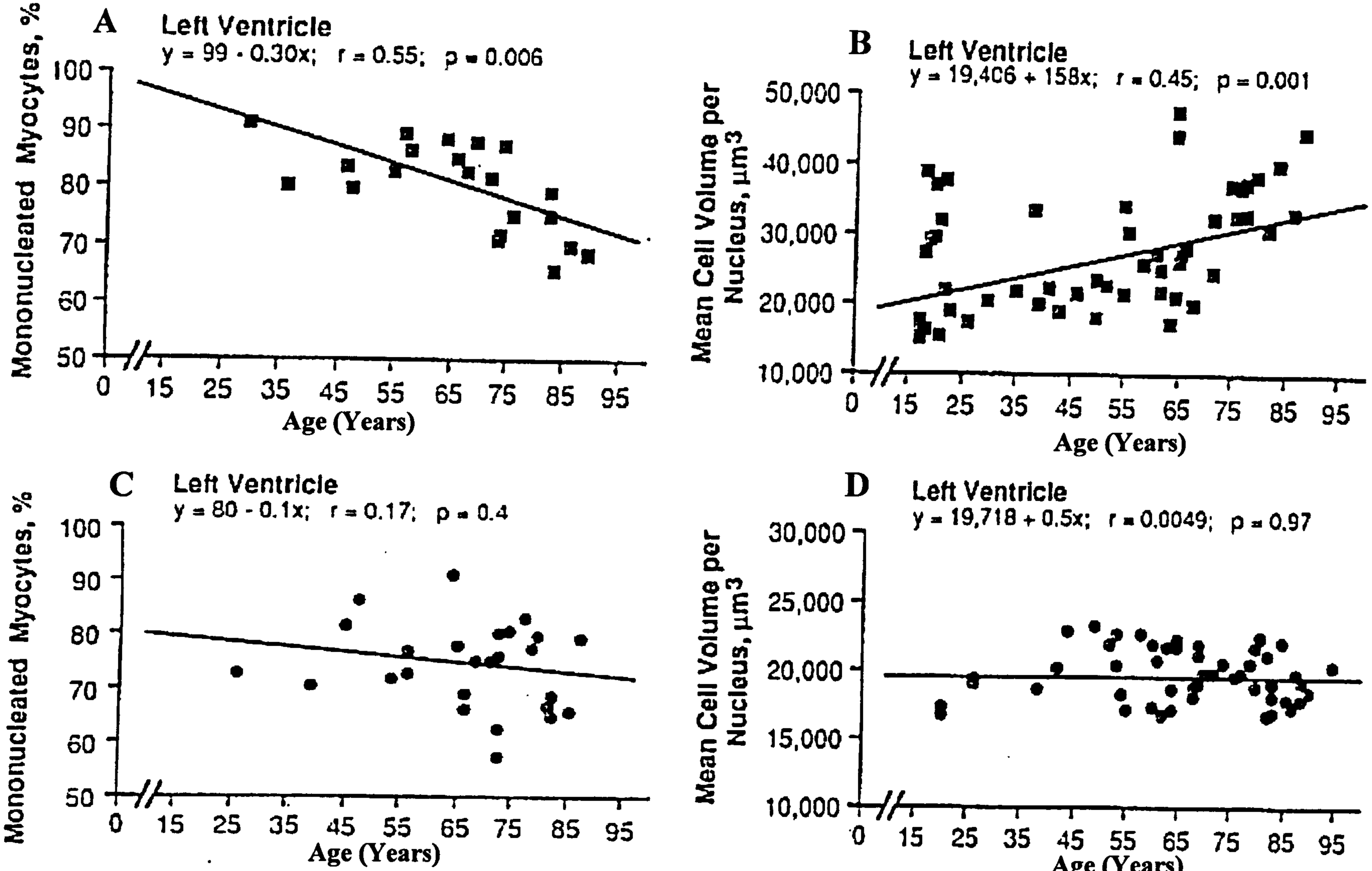


Figure 1.1 Age-related changes in myocyte number and size in the human heart.

Percentage change in myocyte numbers in male (A) and female (C) subjects, and changes in cell volume in male (B) and female (D) subjects, with age. All hearts were free of any signs of cardiovascular diseases. From Olivetti *et al.,* (1995)

between men and women, with women expressing a gradual decline in CO_{rest}, whereas no change was reported in men (Fleg *et al.*, 1990, 1995). In contrast, Rodeheffer *et al.* (1984) reported that men and women behave similarly with increasing age, with no change in CO. Some of this contradictory data can be attributed to the differences in the selection of subjects, protocols and techniques used, and body position when CO was measured.

Some of the conflicting evidence in resting CO may reside in the measurements of SV and HR, with age. Many studies have found no age-related change in SV, whereas resting HR declined, resulting in a corresponding decline in CO (Brandfonbrener *et al.*, 1955). A longitudinal study over 30 years by Arora *et al.* (1987) found that in men and women, HR_{rest} decreased from approximately 81 to 60 beats/min. This was subsequently confirmed in cross-sectional studies by Fleg *et al.* (1990 and 1995). In contrast, other studies found that SV increased with age to compensate for the decline in resting HR. For example, stroke volume relative to body surface area (i.e. stroke volume index; SVI) was shown to be augmented in men (Fleg *et al.*, 1990, 1995). This age-related increase in SVI was mainly due to an increase in end diastole volume index (EDVI), with no change in end systolic volume index (ESVI). In contrast, in healthy women EDVI and SVI have not been found to increase with age, and ESVI tends to decrease slightly (Fleg *et al.*, 1990, 1995). Conversely, no changes in either HR or SV have also been reported, with increasing age (Rodeheffer *et al.*, 1984).

Such conflicting findings may relate to the difficulty in attaining a truly basal resting state. However, it is generally believed that, in a sitting position, HR_{rest} declines, whereas SVI does not decrease with advancing age in both males and females (Fleg *et al.*, 1990, 1995; Rodeheffer *et al.*, 1984; Schwartz *et al.*, 1991; Simpson and Wicks, 1988). These results have been interpreted as indicating either a decline or no change in resting CO, and hence cardiac function with age.

Ageing is also associated with a progressive increase in blood pressure (BP), beginning in childhood and continuing into late adulthood (Kannel and Gordon, 1978). This trend during middle age is associated with a greater increase in systolic (SBP) than diastolic (DBP) blood pressure. Whereas SBP continues to rise, it is thought that DBP either remains constant or declines after the fifth or sixth decade (Franklin *et al.*, 1997). Such

changes increase pulse pressure (PP) and have been attributed to increased arterial stiffness (Lakatta, 1993). Women tend to follow a similar trend to the men. However BP starts off lower in women compared to men, but then catches up by the sixth decade and frequently becomes even higher thereafter (Franklin *et al.*, 1997). Mean arterial pressure (MAP), the steady component of pressure by which the variations in PP fluctuate, has been shown to increase gradually up to the fifth decade after which MAP_{rest} levels off (Franklin *et al.*, 1997).

Because the cardiovascular system at rest functions at only a fraction of its total capacity, age-related studies at rest do not adequately characterise changes in this system or its regulatory mechanisms (Lakatta, 1993). While subtle changes in cardiovascular function may be evident during acute stress, the major signs of adaptation in cardiovascular function between younger and older individuals will become evident at maximal exercise.

1.1.5. Cardiovascular function at maximal stress

Exercise provides a powerful research tool that permits the study of the regulation of the cardiovascular system, and its functional capacity under rigorously controlled and highly reproducible conditions (Rowell, 1974). Prior to reviewing some of the age-associated changes in the cardiovascular system some of the normal physiological responses to dynamic exercise will be described.

(A) *Normal responses to maximal exercise*

The transition from rest to maximal exercise is mainly facilitated by an increase in oxygen uptake ($\dot{V}O_2$) to support the increased metabolic demands of exercising skeletal muscles and to maintain cellular homeostasis. Oxygen uptake can be expressed using the following equation, which is based on the Fick principle,

$$\dot{V}O_2 = HR \times SV \times a\text{-}v\ O_2 \text{ difference},$$

where $\dot{V}O_2$ is oxygen uptake, HR is heart rate, SV is stroke volume, and a-v O_2 difference is the arterial-mixed venous oxygen difference.

The degree to which each of these variables can increase determines the upper limit for whole-body consumption. This limit is called maximal oxygen uptake ($\dot{V}O_{2max}$). The a-v O_2 difference is dependent on the efficiency of muscles to extract oxygen from the blood. This in turn is influenced by the muscle's metabolic rate and oxidative capacity, regional and peripheral distributions of blood flow, muscle capillary density and perfusion, changes in the oxyhaemoglobin dissociation curve etc (Jones *et al.,* 1985). In healthy individuals, at rest, a-v O_2 difference is normally 4.5 ml O_2 /100 ml of blood (~23% extraction) and at $\dot{V}O_{2max}$ this difference is closer to 16 ml O_2 /100 ml of blood, which represents approximately 80-85% extraction (Rowell, 1974).

To match this increased demand CO increases four-to five-fold from rest to maximal exercise in a near linear manner to increasing $\dot{V}O_2$ (Astrand *et al.,* 1964; Clausen, 1976; Epstein *et al.,* 1967). It is generally believed that a linear rise in HR with increasing exercise intensity has a greater contribution than SV to the increase in CO. Numerous studies have shown that after the initial increase in SV a plateau is reached at ~40% of $\dot{V}O_{2max}$, and that subsequent increases in workload do not further affect SV (Astrand *et al.,* 1964; Epstein *et al.,* 1967; Higginbotham *et al.,* 1986; Plotnick *et al.,* 1986). In contrast, to the above non-trained individuals, it has been reported that SV increases progressively throughout the incremental work rates in achieving maximal exercise in endurance trained men and women (Glendhill *et al.,* 1994; Wiebe *et al.,* 1998). In these trained individuals, this adaptation was attributed to a greater filling of the ventricles (i.e. venous return), thereby using the Frank-Starling mechanism more effectively up to $\dot{V}O_{2max}$ (Glendhill *et al.,* 1994; Krip *et al.,* 1997).

During exercise, SBP usually rises to around 200 mm Hg at peak exercise. In contrast, DBP remains essentially constant (Jones *et al.,* 1985). The rise in SBP is thought to be linearly related to the exercise workload (Rowell, 1991). The control of BP with exercise involves complex interactions between the peripheral vasculature and the heart. These are carefully modulated through the baroreceptors and the central nervous system via the sympathetic nervous system (SNS), as well as locally by factors that are

responsible for autoregulation at an arteriolar level (Schrager and Ellestad, 1983). Two major haemodynamic changes occur almost simultaneously with the onset of exercise. The resistance to blood flow through contracting muscles decreases and results in a fall in systemic vascular resistance (SVR). Various other perfusion beds in non-exercising areas vasoconstrict, thereby redirecting more blood to the exercising muscles. The SNS also constricts capacitance vessels aiding the return of blood to the heart, thereby increasing SV and CO by increasing preload. This action is of prime importance in enabling CO to rise in the face of reduced SVR (Guyton, 1981) and consequently the rise in MAP is comparatively small (Jones *et al.,* 1985).

(B) *Changes in maximal cardiovascular function in relation to ageing.*

It has been well documented that $\dot{V}O_{2max}$ declines with increasing age (Figure 1.2) in both men and women (Ehsani *et al.,* 1991; Hagberg *et al.,* 1985; Heath *et al.,* 1981; Ogawa *et al.,* 1992), with many studies reporting a 10% decline per decade (Drinkwater *et al.,* 1975; Inbar *et al.,* 1994; Jackson *et al.,* 1995; Toth *et al.,* 1994). In addition, $\dot{V}O_{2max}$ has been shown to decline in individuals who maintain endurance training throughout life (Figure 1.2). These deteriorations in $\dot{V}O_{2max}$ have been attributed to an age-associated decline in CO_{max} and a progressive decline in maximal a-v O_2 difference (Fleg *et al.,* 1990, 1995; Ogawa *et al.,* 1992).

Despite this, controversy exists regarding the age-related changes in maximal SV and CO. The vast amount of evidence suggest that CO_{max} declines with age (Ehsani *et al.,* 1991; Fleg *et al.,* 1990, 1995; Gerstenblith *et al.,* 1976; Hagberg *et al.,* 1985; Owaga *et al.,* 1992). However, some studies have reported that CO_{max} is maintained with increasing age (McGuire *et al.,* 2001; Rodeheffer *et al.,* 1984). These latter investigators identified that maximal SVI was increased at maximal exercise in older, compared to younger individuals, and that this was sufficient to compensate for the well recognised decline in HR_{max} (Fleg *et al.,* 1990, 1995; Lakatta, 1993; Owaga *et al.,* 1992). It is here were the controversy arises. An age-related decline in HR_{max} is unquestioned by all investigators. However, changes in SV_{max} remain equivocal. Numerous studies have found a decline in maximal SVI with increasing age (Julius *et al.,* 1967; Kuikka and Lansimies, 1982), whilst in other studies SVI remains essentially constant (Fleg *et al.,*

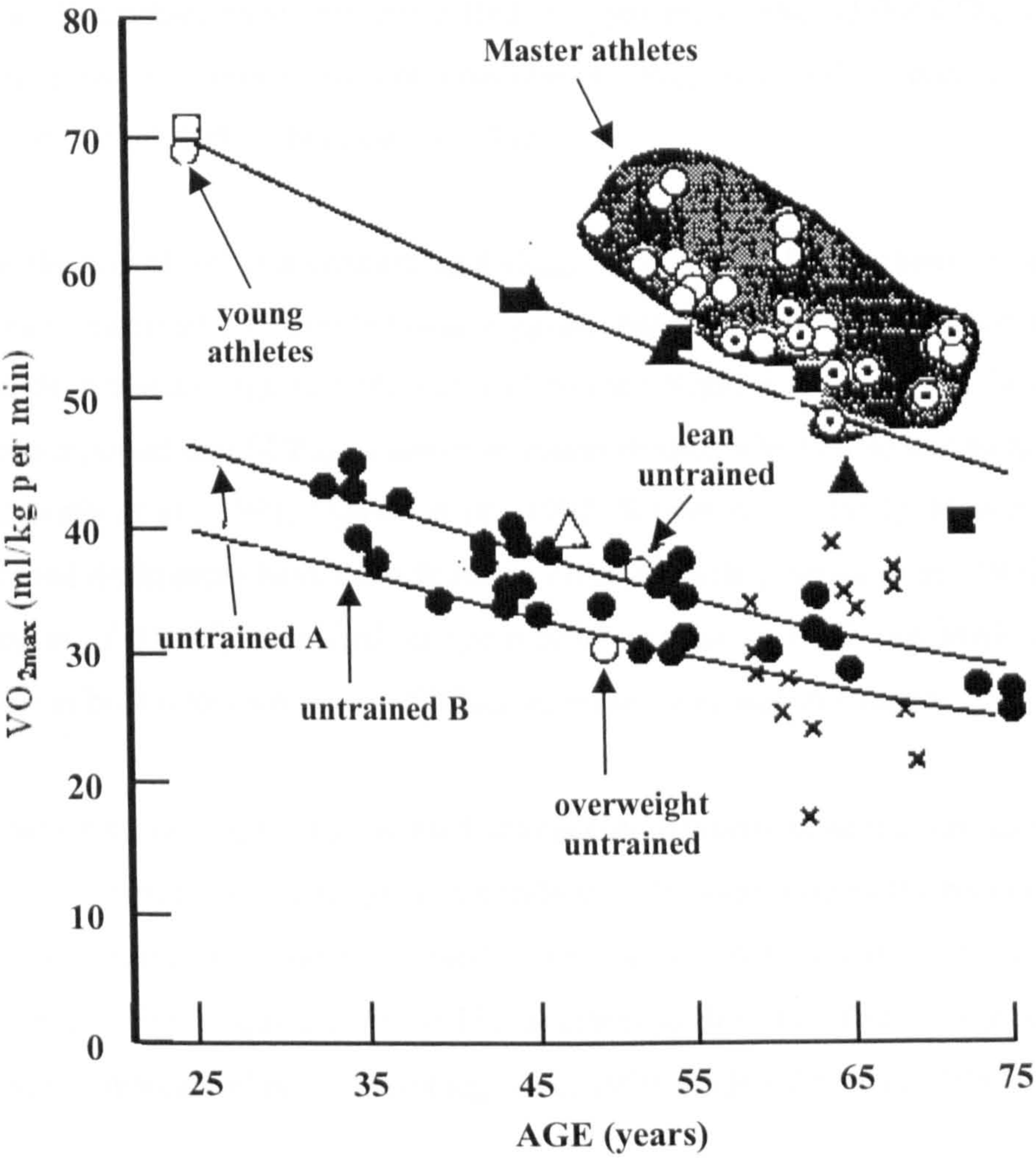


Figure 1.2. Maximal oxygen consumption ($\dot{V}O_{2max}$) in males of varying ages, fitness, and body composition (From Lakatta, 1993).

Data presented are for champion young athletes [○] (Health *et al.,* 1981) and [□] (Dill *et al.,* 1967); ex-champion athletes [△] (Dill *et al.,* 1967 and Robinson *et al.,* 1976); cross-country runners [▲] (Grimby and Saltin, 1966); runners [■] (Pollock *et al.,* 1974). Groups of untrained men from 9 studies [● and X] and master athletes [○ and ◉] are from Heath *et al.* (1981) and Fleg *et al.* (1988), respectively.

1990, 1995, Higginbotham *et al.,* 1984, 1986; Younis *et al.,* 1990). The lack of clarity may result from differences in the extent to which coronary artery disease is present among subjects, or from differences in fitness status, heart size, and body composition. When such variables have been controlled, it is generally believed that CO declines with increasing age, as a prime result of a decline in HR_{max}, with SVI_{max} remaining constant (Fleg *et al.,* 1990, 1995; Owaga *et al.,* 1992).

Unlike the wealth of data concerning CO_{max}, very little is know about the age-related changes in maximal BP. Limited data suggests that both SBP and DBP and thus MAP, rises with increasing age in both men and women (Ogawa *et al.,* 1992). In addition, it has been reported that SBP_{max} is lower in young women when compared to age-matched men (Martin *et al.,* 1991; Ogawa *et al.,* 1992; Wiebe *et al.,* 1998). However no such sex-related differences have been found in older subjects (Ogawa *et al.,* 1992). A study by Fleg *et al.* (1995) identified an age-related increase in DBP and MAP at maximal exercise in both sexes while only SBP_{max} increased with age in women.

Information regarding the age-related changes in maximal systemic vascular resistance (SVR_{max}) in normotensive subjects is conflicting. In some studies the reduction in SVR that occurs during exercise was noted to be less in older than in younger individuals (Julius *et al.,* 1967; Ogawa *et al.,* 1992). In others studies this effect of age was minimal in men, but substantial in women (Fleg *et al.,* 1990; Rodeheffer *et al.,* 1984).

Such conflicting evidence on the age-related changes in blood flow and pressure has lead to confusion concerning how ageing effects maximal overall cardiac function. This is especially likely to be true when combing flow and pressure generating capacities of the heart as in the studies described here.

1.2. Cardiac function

Cardiac function is a complex integration of electrical, biochemical and mechanical processes, which is also dependent on the preload and afterload imposed on it by the vascular system (Braunwald, 1971). Whilst there have been a number of methods developed to measure cardiac function, many are either invasive or tend to examine

only specific aspects of cardiac function, rather than overall cardiac function. For example, CO and ejection fraction has been used as markers of cardiac function. Cardiac output has been claimed to be an accurate measure of the heart's ability to perform its function (Braunwald, 1971) and therefore has been shown to be prognostically important in relation to the survival of patient (Chomsky *et al.*, 1996). Therefore, CO plays a vital role in the measurement of cardiac function. However, it must be remembered that the heart generates pressure as well as blood flow. Myocardial contractility (maximum left ventricular rate of pressure rise at end systolic resistance etc) has been used as a marker of cardiac function, as it is considered that only myocardial contractility originates from 'central' factors (i.e. the heart itself), whereas other determinants, HR, preload, and afterload are considered 'peripheral' factors (Braunwald, 1971). Although, contractility is a major contribution to cardiac function, it is by no means equal to the overall cardiac pump function. That is, contractile force is closely linked to the 'peripheral factors'. Alterations in the vasculature invariably affect cardiac performance. To date the ability to separate the central from the peripheral factors have been untenable. Therefore, a measure of overall cardiac function, which is sensitive to the way the heart is coupled with the vasculature, must be considered. In addition, the heart should not be represented by the performance of any one of its component parts alone (Tan, 1991).

Another important aspect in the measurement of overall cardiac function is whether cardiac function is evaluated at basal resting states or at maximal stimulation e.g. maximal exercise. Although, basal resting measures are easy to perform, no information is gained on the pumping reserve of the heart and critically how the heart responds to stress. That is, the heart, like the cardiovascular system, at rest functions at only a fraction of its total capacity. As such these basal measurements are very poor at discriminating between subject populations. However, once the heart is maximally stimulated such differences between populations can be readily identified. This was appreciated by Lakatta (1993) who indicated that differences in cardiovascular function between young and older individuals manifest themselves during situations of stress, such as exercise.

1.2.1. Cardiac power output and cardiac functional reserve

Cardiac power output (CPO) has been used as a marker of overall cardiac function (Tan *et al.,* 1989). Measuring CPO is a relatively novel technique that measures both the pressure and flow generating capacities of the heart, and has been independently judged to be the best overall indicator of heart function (Nicholls and Reilly, 2001). The product of flow output and systemic arterial pressure is the rate of the useful work done, or power output. The relationship between flow and pressure in the circulation has long been known to involve the concept of hydraulic power. By converting ATP into mechanical energy, the function of the heart is to supply adequate hydraulic energy to maintain the circulation (Tan, 1991). Without this energy the circulation would come to a standstill. Cardiac power output is therefore the rate at which the heart imparts hydraulic energy into the arterial system to maintain the circulation of blood and can be defined as the work of the heart per cardiac cycle multiplied by its frequency (Tan, 1991). Thus the ability of the heart to generate energy and perform external work encompasses not only its ability to generate flow, but also its ability to generate pressure. In addition to the prognostic value of CO, a number of groups have also shown the importance of the pressure generating capacity of the heart and have concluded that the measurement of maximal BP to be independently predictive of prognosis (Ghali *et al.,* 1992; Osada *et al.,* 1998; Pousset *et al.,* 2000). Thus, the incorporation of pressure into exercise haemodynamic assessment is crucial. Cardiac power output does this and is therefore a true measure of overall cardiac function. Furthermore, because the measurement of CPO is not derived from studies that isolate the heart from the rest of the circulation (i.e. in vitro). It is sensitive to all aspects of cardiac function, including central factors such as contractility, but as well as peripheral effects such as loading and HR (reviewed by Tan, 1991).

The measurement of the mechanical energy of the heart is by now means new (Bergel *et al.,* 1969) and indeed, left ventricular minute work presents similar information combining flow and pressure. However, CPO is viewed as providing information on the overall function of the heart rather than simply an index of contractility, and, is based on fluid dynamics rather than muscle mechanics (Tan, 1991). Furthermore, CPO is viewed as a better indicator of overall cardiac function than CO and left ventricular minute work (Tan, 1987). At rest a mean CPO of approximately 1 Watt is required to generate a

flow rate of 5 l/min and a MAP of 90 mm Hg in an average healthy adult male (Tan, 1995). Both components increase during exercise, with CPO_{max} increasing up to 4 Watts in healthy young but untrained subjects, and 8 Watts in elite athletes (Tan, 1991). These differences in CPO_{max} mainly result from cardiomyocyte hypertrophy, highlighting the beneficial effects of physical training.

It is strongly believed that the heart is a flow generating organ with arterial pressure presumed to be a by-product of CO and SVR (Braunwald, 1997). However, recent data have suggested otherwise (Schlosshan *et al.*, 2004). If arterial pressure is a by-product of CO and SVR, then any improvement in cardiac function should manifest itself as primarily a greater cardiac flow generating capacity leading secondary to higher BP. However, recently Schlosshan and colleagues (2004) challenged this theory in severe heart failure patients who had undergone cardiac resynchronisation therapy (CRT). The authors were able to measure cardiac functional reserve without directly affecting SVR. In a randomly controlled cross-over study, CPO was measured at rest and at peak exercise when either the CRT device was switched on or off. It was found that at maximal exercise, when the CRT device was switched on, there was an improvement in CPO_{max}. This improvement was due entirely to a significant increase in MAP_{max}, as no change in maximal CO or SVR was evident. The authors therefore concluded that cardiac pressure-generating capacity was a primary manifestation of improved cardiac function. This highlights the importance of including the pressure generating capacity of the heart to provide meaningful measurements of overall cardiac function.

There are two aspects to the overall assessment of cardiac performance, first the maximal pumping capacity which is the performance of the heart when maximally stressed (CPO_{max}). Second, the cardiac pumping reserve (CR) represents the difference between maximal stimulation and resting cardiac performance (CPO_{rest}) i.e. $CR = CPO_{max} - CPO_{rest}$. Each heart has its own upper limit for maximal pumping performance (CPO_{max}); a ceiling point that is physically impossible to exceed. This value will change if the heart's intrinsic conditions are changed, for example with myocardial hypertrophy, contractility and a reduction in afterload or after damage by a myocardial infarction. The theoretical maximum value for CPO is obtained when all the cardiac settings (including loading conditions, inotrophy, rhythm, and rate) are optimised. When comparing these maximal measures i.e. CPO_{max}, cardiac function is a

direct indicator of how functionally effective or impaired the heart is as a hydraulic pump (Figure 1.3). How good the heart is in fulfilling its function as a representative and flexible pump depends on the maximal value in relation to the baseline resting value i.e. its functional reserve capacity. For the same ceiling value, a subject with a high baseline resting CPO (high output state, due to metabolic disorders, hypertension etc), will have less CR to call upon.

The measurement of CPO has originated from a clinical setting, mainly through the work of Dr Tan (1987). Initially, this involved an invasive technique used to examine the prognosis of patients with heart failure (Tan and William, 1990). However, measurements of CPO have since been conducted non-invasively (Cooke *et al.,* 1998), after being successfully validated against the former invasive technique (Cooke *et al.,* 1998). The measurement of CPO_{max} has been identified as the most powerful predictor of prognosis in cohorts of patients with heart failure (Roul *et al.,* 1995; Tan, 1986; Tan and Littler, 1990; Williams *et al.,* 2001b). Furthermore, in a recent review, CPO was shown to give further prognostic power over $\dot{V}O_{2max}$ in the assessment of cardiac function (Nicholls and Riley, 2001). Heart failure patients who are unable to generate 1 Watt of power, i.e. those patients in cardiogenic shock, and have little or no pumping reserve (Figure 1.3), have a very poor prognosis. Cardiac functional reserve has been shown to be a useful method of determining exercise capacity in heart failure as well as healthy populations, from sedentary individuals to elite athletes (Cooke *et al.,* 1998). However, to date the emphasis on using CPO has mainly been directed as a diagnostic and prognostic tool for heart failure patients.

Various studies have identified the deleterious effects ageing has on physiological variables such as CO, early left ventricular filling (Fleg *et al.,* 1995), arterial systolic and diastolic pressure (Lakatta, 1989), and maximal aerobic capacity (Lakatta, 1990). However, the affects of ageing on the overall pumping performance of the heart have not previously been investigated. The beneficial effects of an active lifestyle and exercise training on endurance capacity (Hagberg *et al.,* 1998) and skeletal muscle force (Lemmer *et al.,* 2000) have been documented in populations of elderly people. While endurance training does little to counteract the age-related decline in skeletal muscle mass and force generation, it should be a useful intervention in inducing cardiomyocyte hypertrophy etc. It is therefore essential that the age-related changes in overall cardiac

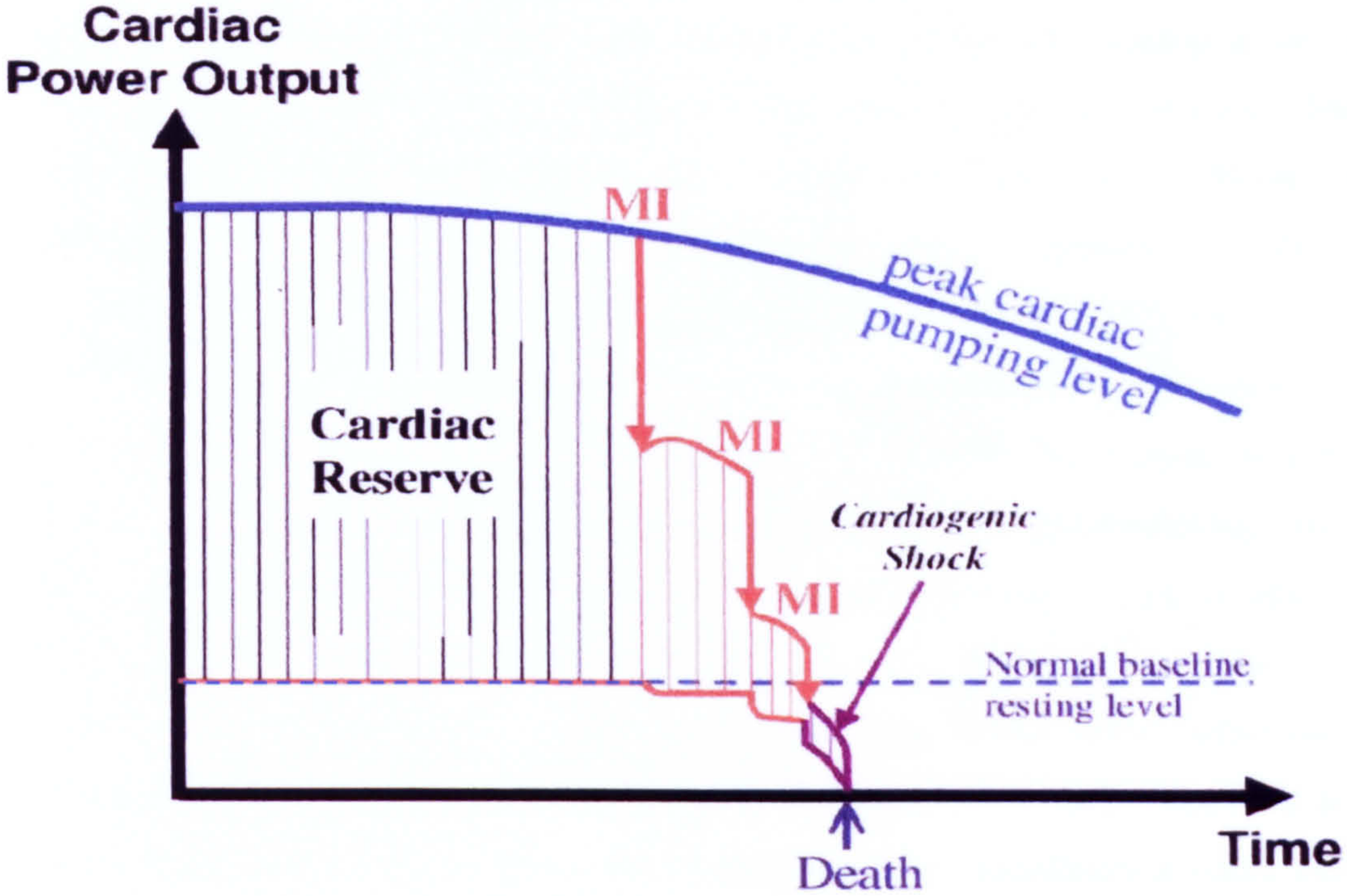


Figure 1.3. Schematic representation of the changes in cardiac reserve as a consequent of age, and ischaemic damage (Courtesy of Dr L-B Tan).

The lower dashed blue line represents resting CPO and the solid blue line maximal CPO. The hatched area between represents the reserve capacity of the heart. This can be affected by age or a myocardial infarction (MI). When the maximal performance of the heart is close to the resting CPO the prognosis is poor.

function (CPO) are examined and compare to studies looking purely at the flow or pressure generating capacities of the heart. In addition to what affect endurance training in older subjects has on CPO is unknown and therefore requires investigating.

1.3. Pump-load interactions

The performance of the cardiac pump, as indicated above, is influenced by its interaction with the load imposed on it. The afterload on the left ventricle is identified physiologically as the impedance by which the ventricle has to overcome. This is determined by the physical properties of the systemic vasculature and the blood, and is independent of myocardial performance. Aortic input impedance is the best representation of systemic afterload on the cardiac pump (Milnor, 1975), and is the ratio of aortic pressure to flow measured at the aortic root. The ratio of mean pressure to flow gives the resistive terms, and is often referred to as the SVR. An increase in afterload would lead to a decrease in ventricular emptying and myocardial shortening, and vice versa. At either extreme of the spectrum of vascular impedance, there is little or no hydraulic energy output from the heart (Figure 1.4). Given an extreme of total vasoconstriction with infinite vascular resistance (e.g. aortic valve occlusion), the pressure generating capacity will be maximal, but flow will be zero. Thus CPO is zero (Tan, 1986, 1987). Conversely, at the extreme of total vasodilatation (zero vascular impedance), flow is maximal, but the pressure generating capacity is zero and CPO is again zero. In between these two extremes is an optimal point, in which CPO is maximal (Figure 1.4). The cardiovascular system usually functions at the point where the pump and load are matched (Wilcken *et al.*, 1964; van der Horn *et al.*, 1985) to ensure the production of optimal power output. Optimal coupling of the cardiac pump and the arterial system at this point is presumably the most conductive to yield normal physiological cardiac reserve and exercise capacity (Williams *et al.*, 2001a). At rest in a healthy heart, the left ventricle normally functions at this optimal point (Wilcken *et al.*, 1964). However, in a diseased heart this operational point is shifted towards higher resistances, due to compensatory mechanisms causing vasoconstriction (Cotter *et al.*, 2003). Consequently, the cardiac pump is functioning at a mechanical disadvantage and therefore is less efficient.

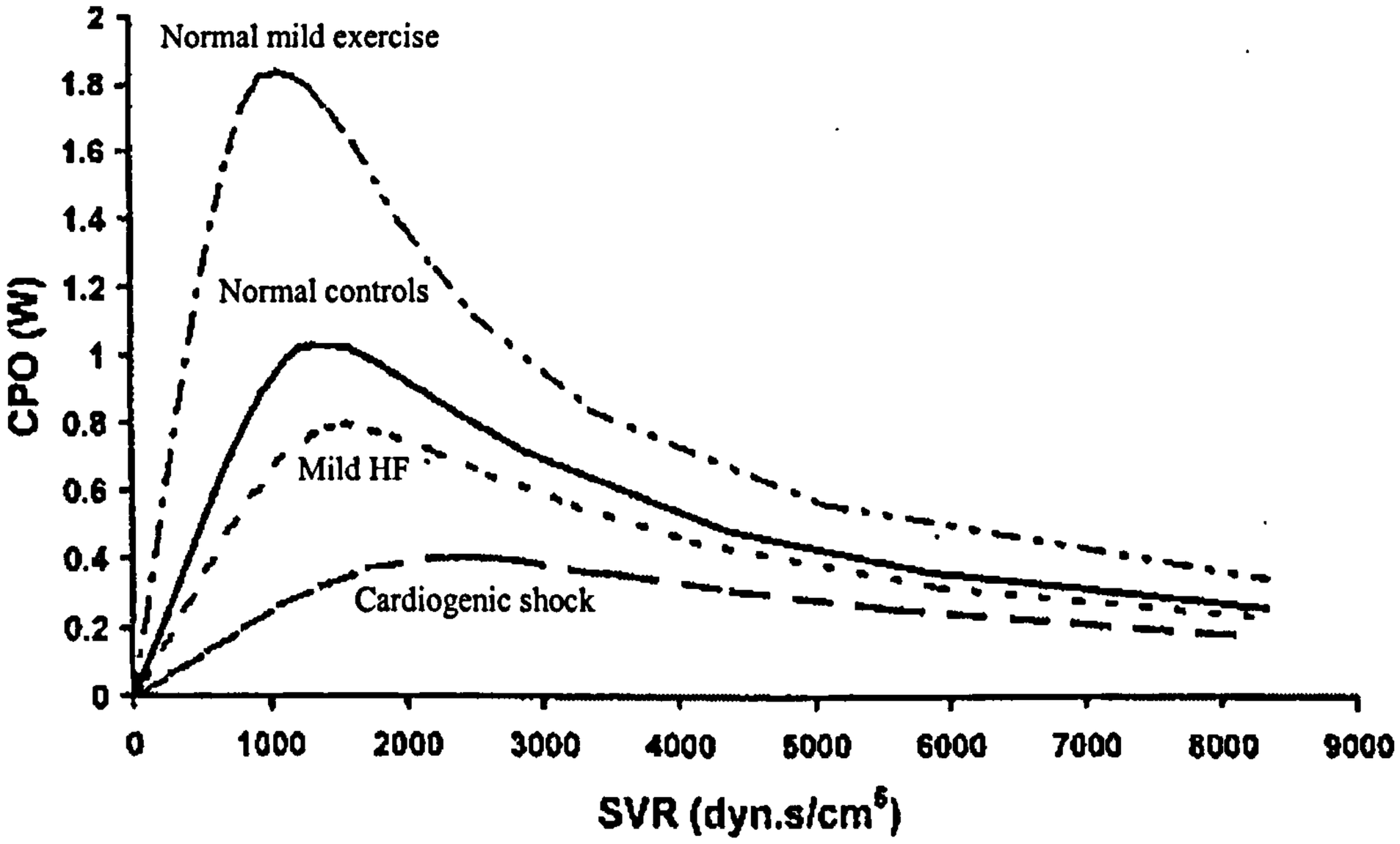


Figure 1.4. A schematic diagram depicting a family of ventriculo-arterial function curves (From Tan *et al.*, 2003).

The optimal operating points of normal ventriculo-arterial function curves (VAFCs) are at the zenith of the curves. However in pathophysiological states i.e. patients with mild heart failure and cardiogenic shock, the operating point may be shifted to higher resistance levels in different extents of heart failure, or to lower resistance states in vasodilative conductions. Additionally exercise can affect the operating point i.e. mild aerobic exercise.

When examining overall cardiac function, the influence of pump afterload must be taken into account to fully comprehend the changes associated with cardiac function.

1.4. Circadian rhythms and physiological function

Biomedical sciences depend heavily upon good measurements of physiological functions. These need to be highly reproducible. Factors which affect the reproducibility can have significant consequences to the reliability of data and their interpretations. Chronobiological investigations have shown that numerous cardiovascular variables have a periodic dependency with time (Smolensky *et al.*, 1976). Circadian rhythms are thought to be a direct result of changes in the environment (exogenous), such as the changes from day to night (Reilly and Brooks, 1990). However, biological rhythms may also occur when the environmental conditions are held constant, i.e. endogenous sources (Reilly and Brooks, 1990). Research has identified that the human body clock is regulated endogenously by the suprachiasmatic nuclei in the hypothalamus (Waterhouse *et al.*, 1997). In addition, to this master clock there are local timekeepers which have been found within skeletal and cardiac muscles (Waterhouse *et al.*, 1997).

Many of the biological variables that change over a 24-hour period are thought to change in a circadian pattern as a consequence of variations in body temperature. Core temperature has been shown to impact on muscle performance (Saltin and Hermansen, 1966). Furthermore, temperature is considered to act as a secondary pacemaker for the periodicity of numerous other physiological variables, e.g. resting $\dot{V}O_2$, ventilation rate, etc (Refinetti and Menaker, 1992). The normal circadian curve for body temperature in men aged 21-27 years, reaches a nadir around 04:00 to 06:00 hours, and a peak at approximately 16:00 to 18:00 hours (Reilly *et al.*, 1997).

Circadian variations have been documented in relation to resting CO and MAP, and their component parts, HR and SV, and DBP (Cohen and Muehl, 1977; Cugini *et al.*, 1991; Deschenes *et al.*, 1998a; Wang *et al.*, 1991), all which could have confounding influences when it comes to measurements of resting CPO. However, the current scientific literature contains a great deal of conflicting evidence. Significant circadian variations in resting CO and SV have been documented, with both reaching a peak

around 17:00 hours and a nadir around 06:00 hours (Cugini *et al.*, 1991). Conversely, Wang *et al.* (1992) identified the acrophase for resting CO at 15:00 hours and at 16:00 hours for SV.

Once again the evidence is conflicting for HR, another vital component that determines CO. Reilly and Brooks (1990) identified a peak in resting HR at 14:00 hours, whereas De Scalzi *et al.* (1984) found the peak to be between 10:00 to 12:00 hours.

Blood pressure is another cardiovascular parameter that has been extensively investigated at rest (Atkinson *et al.*, 1994; Furlan *et al.*, 1990; Reilly *et al.*, 1984). Systolic and diastolic pressures have been shown to exhibit circadian variations (Millar-Craig *et al.*, 1978; Rodahl *et al.*, 1976). Furlan *et al,* (1990) have shown that in healthy subjects, resting BP peaks between 22:00 and 24:00 hours, with a nadir between 03:00 to 06:00 hours or 1 to 3 hours before awaking. Whereas, Zulch and Hossman (1967) identified that BP in some subjects rose in the morning, transiently declined in the afternoon and peaked again in the early evening. However, no changes in resting BP have also been identified (Deschenes *et al.*, 1998a). It has been reported that a circadian rhythm for resting BP was only observed when intra-arterial measurements were made and were not apparent with sphygmomanomtery (Reilly *et al.*, 1984). Additionally, the BP rhythm can be easily disrupted by the timing and termination of sleep (Reilly *et al.*, 1984).

When examining maximal values with respect to an influence of a circadian rhythm, it is imperative that measurements are made at the ceiling point of the physiological variable, otherwise erroneous conclusions can be made. Therefore, recognized criteria must be applied when measuring maximal capacities, otherwise data collected may merely reflect the reluctance of subjects to work at their maximum at night time or early morning. This may explain why there is a lot of conflicting evidence identifying whether a circadian rhythm is evident at maximal exercise, or not. For example, maximal oxygen uptake has been reported to vary by some investigations (Hill *et al.*, 1989; Wojtczak-Jaroszowa, 1974), while others (Reilly and Brooks, 1990; Torii *et al.*, 1992) failed to confirm such variations in $\dot{V}O_{2max}$. Reilly and Brooks (1990) stated that $\dot{V}O_{2max}$ is a stable function, independent of the time of day.

Past research examining whether a circadian rhythm influences maximal exercise for CO are few and far between. To my knowledge Davis and Sergeant, (1975) are the only investigators to examine CO_{max}, and they identified no such rhythm. Maximal HR has been more extensively reviewed than CO. However, the evidence in the literature is once again conflicting. Reilly *et al.* (1984) observing a positive time of day effect in HR_{max}, which contradicted the earlier work of Cohen (1980). Deschenes *et al.* (2002) also found that HR_{max} failed to differentiate across the time of day. One possible explanation for the lack of agreement for fluctuations in HR_{max} is that the rhythmicity of HR appears to be confirmed only when exercise is performed in the early hours of the morning (i.e. 02:00-06:00 hours) when HR values are at their nadir (Reilly and Brooks, 1990).

Similar data concerning changes in maximal BP are limited. Deschenes *et al.* (1998a, 1998b) established significant variations in MAP when measured at maximal exercise. On both occasions the changes in MAP were mainly related to significant variations in SBP, with no changes in DBP (Deschenes *et al.*, 1998a, 1998b). These changes were linked to similar variations in plasma adrenaline concentrations. Catecholamines are known to increase the contractility of the myocardium (Hedge *et al.*, 1987), with circulating adrenaline and MAP ebbing around 08:00 hours.

However it may be that the stimulus of exercise doesn't simply enhance any time of day effects even if past research has identified such effects at rest. This may explain the lack of convincing evidence to suggest that circadian rhythms have any impact at maximal exercise. Indeed, circadian rhythms are highly influenced by other exogenous factors such as sleep, posture, ingestion of food and activity patterns (Pickering, 1988). Such influencing factors question whether an endogenous component exists at all.

However, if such rhythms do impact on CPO, then the timing of such measurements will need to be standardised according to the optimal time. In practical terms this will prove difficult. The temporal optima could vary between individuals which would severely limit the number of subjects that can be tested each day and have a significant impact on the accuracy of cross-sectional studies.

The current discrepancies highlighted here and the lack of precise knowledge of how circadian rhythms may affect cardiovascular function and their potential implications, warrant further study.

1.5. The effects of body size on physiological function

A number of physiological variables (e.g. $\dot{V}O_{2max}$, CO etc) are influenced by body size, e.g. height, body mass, muscle mass etc. In these relationships an increase in body size is often associated with a general increase in a relevant physiological variable. Comparisons between group means, or between an individual's performance relative to that of their peers, are often confounded by differences in body dimensions. To obtain meaningful inter-or intra-group comparisons, the effects of body size need to be accounted for (Batterham *et al.*, 1999). This process is often referred to as scaling or normalisation of the data, i.e. the physiological variable (y) is normalised for differences in a variable of body size (x). However, normalisation of such biological variables needs to take into account the fact that the relationships between body size and structures or physiological functions are complex and often non-linear (Nevill *et al.*, 1992). If non-linear, simple ratio scaling (y/x) will either under-or over-correct for the impact of body size and lead to erroneous interpretations and conclusions.

Previous investigators have scaled certain structures of the heart to a variety of body dimensions, e.g. LVM to body size has helped in the detection of LV hypertrophy in both obese normotensive or hypertensive subjects (de Simone *et al.*, 1992, 1994; Malcom *et al.*, 1993) and increased the prediction of cardiovascular events in clinically hypertensive patients (de Simone *et al.*, 1995). The effect of scaling heart size to body size can be further extended to parameters of cardiac function. Inevitably, CO or the amount of work performed by the heart in a 120 kg man would be greater than that performed in a 60 kg woman. Since CO is an integral component of CPO, dimensional effects on CO could have implications on the interpretation of CPO. Strong positive correlations have been reported between CO and body size (de Simone *et al.*, 1997), due to the larger oxygen demand imposed by a larger body mass (Lakatta, 1993). In addition to CO, SV and certain cardiac structures are usually normalised for body surface area (BSA), to effectively assess their effects when independent of body size. For example,

de Simone *et al.* (1997) concluded that normalisation of CO and SV to BSA, raised to the power of 0.71, was pertinent when the effects of obesity needed to be accounted for, as a lack of normalisation obscured any impact of obesity.

The other important component of CPO is MAP, which has been reported to be physiologically independent of body size (Dobeln, 1956). Therefore, it is more likely that CPO would be affected by different body dimensions in a similar way to that reported for CO. If such a relationship is identified then it is important that the potential confounding influences of body size on CPO are accounted for, especially when intra- and inter-group comparisons are to be made.

1.5.1. Scaling models

Numerous scaling approaches have been used to correct for the influence of body size (x) from physiological functions (y). Traditionally, the per-ratio standard (RS) approach was used. This method assumes a proportional linear relationship between the physiological dependent variable (y) and the body dimension variable (x) with the line of best fit passing through the origin (Batterham *et al.,* 1999). That is,

$$y = bx \ ,$$

where b is a constant derived from the mean values of the physiological (y) and the body size (x) variables for the series of data it describes.

The construction of a simple RS model is assumed to "normalise" the data, i.e. remove the influence of body dimensions from subsequent analyses. However, theoretical and mathematical flaws in this approach were recognised by Tanner (1949) over 50 years ago. Tanner (1949), indicated that the use of the RS method was "theoretically fallacious and in practice misleading". Because, smaller individuals received an arithmetic advantage while larger individuals were penalised. Tanner also stated that only in special circumstances is the RS method valid, i.e. when the coefficient of variation (CV) for body dimensions (CVx) divided by the CV for the physiological dependent variable (CVy) is equal to the Pearson's product moment correlation (r,X,Y) between the two variables (i.e. CVx/CVy = r, X, Y). If the two values are not similar,

then either a linear relationship does not exist or the linear relationship has either a positive or negative intercept on the y-axis. Indeed, this special circumstance is rarely satisfied (Welsman *et al.*, 1996).

As an extension to the RS model we have the linear regression standards (RES) approach. The general form is,

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

where b represents the gradient of the line of best fit, a the intercept on the y-axis, and ϵ the additive residual error term. The difference between this and the RS model concerns the assumption of a y-axis intercept term (a). As a consequence the RES approach does not require that the least-squares regression line pass through the origin (Batterham *et al.*, 1999). Although, this model has been shown to provide a better statistical fit in terms of a reduction in the residual error associated with this analysis compared with the RS model, positive intercepts are common. The latter would indicate that someone with zero body mass (BM) would still exhibit a physiological response. Since extrapolation of the regression line beyond the actual data points must be avoided, the values at y-intercepts are at best approximates. More importantly, the RES model assumes a constant (additive) error term, i.e. that the spread of scores around the regression line is constant throughout the range of x and y variables, a property known as homoscedasticity. This assumption is unlikely to be achieved in subjects who vary greatly in body size (Nevill *et al.*, 1992). Rather the measurement error tends to be greater as the independent variable (x) increases, and therefore the error is said to be heteroscedastic. Therefore, the use of the RES model for the normalisation of physiological data may not be appropriate even when the least squares regression line provides a better fit to the data.

Because the assumptions of the RS and RES models are not always justified, the allometric model has also been used for scaling purposes. It has been reported that a number of physiological variables relate to body size according to the general allometric equation below (Bergh, 1987; Bergh *et al.*, 1991; Nevill and Holder, 1994),

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

where y is the physiological variable, x is the variable of body dimension, a is the proportionality coefficient (constant multiplier), b the scaling component (i.e. the power ratio for scaling body size), and ϵ the multiplicative error term (which takes into account the error around the regression line). Using this simple allometric equation, physiological dependent variables may be scaled for differences in body dimensions by constructing a power function ratio (see below), that is supposedly size-independent (Nevill *et al.*, 1992).

$$y / x^b$$

Although the allometric model may produce only a modest improvement in statistical fit to the data (i.e. with less residual error) compared with the RES model, its use is justified for two reasons. First, the allometric model assumes a multiplicative error term, which allows the model to control for spread in the data (heteroscedasticity) providing that the variables diverge at a constant rate (Nevill *et al.*, 1992). Second, the relationship is plausible as the line of best fit passes through the origin, thus providing a more valid method of producing a dimensionless physiological variable (Nevill *et al.*, 1992). A simple regression analysis then can be performed on the log-transformed y and x components, from which the slope of the log-linear plot of data determines the exact values of the allometric power function exponent b.

1.5.2. Scaling variables

The next important aspect of scaling is to determine which variables of body size should be used. The choice of the most appropriate variable should be based on the accuracy of its measurement and its biological relevance. In the cardiology literature, a variety of different variables of body dimensions have been proposed for the scaling physiological variables. For the scaling of heart size (e.g. LVM, chamber volume etc), BSA has been widely used as it incorporates both height (HT) and BM and therefore some element of body composition. In this way a single scaling variable can be used that would theoretically incorporate changes in HT and BM. Despite BSA seemingly being advantageous, this type of 'cardiac normalisation' has been criticised both on theoretical (Gutsegell, 1990) and mathematical grounds (Tanner, 1949). Body surface area is

actually never measured, but simply estimated via an equation (e.g. DuBois and DuBois, 1916), which introduces a degree of measurement error. Furthermore, BSA does not differentiate between the modifications in body composition, e.g. a large proportion of metabolically active muscle versus metabolically inert adipose tissue (Forbes and Welle, 1983). Due to the relative ease and accuracy by which they can be measured, other widely used scaling variables include HT, and BM.

Daniels *et al.* (1995) and Roman *et al.* (1997) suggested that fat free mass (FFM) might represent the optimal parameter for allometric normalisation of cardiac structures and functions. Fat free mass has been defined by Jensen *et al.* (1993) as the non-adipose tissue of body mass (i.e. skeletal muscle, brain, heart, liver, kidneys and gastrointestinal tract) and the non-fat component of adipose tissue (e.g. proteins in cellular and extracellular structures). Therefore, as the metabolic rate of adipose tissue is relatively inert, compared to FFM (Weinsier *et al.*, 1993), scaling for FFM will allow the independent isolation of body dimensions that relate to metabolically active tissues and hence, physiologically dependent variables. Given that CO (and therefore CPO) is known to response to the tissues' demands for oxygen (Lakatta, 1993), it would seem to be theoretically plausible to scale CPO to FFM. However, whether FFM will be the optimal parameter, will depend on the accuracy with which it is measured. The emergence of dual energy x-ray absorptiometry (DEXA) provides a definitive method of accurately determining FFM and adipose mass, allowing the investigation of their independent effects on CPO (Jensen *et al.*, 1993).

1.6. Dietary creatine supplementation and cardiac performance

Older people and patients with failing hearts are less able to respond to exercise and various daily stresses. Hence a nutritional or ergogenic aid, leading to a metabolic improvement in cardiac function, may be better suited to the elderly than exercise-based interventions. Creatine is a substance found in fish and meat. In addition to this exogenous source, de novo synthesis of creatine occurs in the liver from the amino acids, arginine, glycine and methionine (Persky and Brazeau, 2001). The skeletal muscles and the heart activity take up approximately 95% of newly synthesised

creatine. Once inside the myocytes, approximately 70% of creatine is phosphorylated (PCr) by creatine kinase, the remaining 30% existing as free creatine (Wyss and Kaddurah-Daouk, 2000). In all muscles PCr represents an immediate source of energy to replenish the immediate but limited concentrations of ATP.

It has been well documented that when creatine is supplemented in the diet, skeletal muscles increase their creatine and PCr contents (Harris *et al.*, 1992; Greenhaff *et al.*, 1994). Although not always universal accepted (Snow *et al.*, 1998; Smith *et al.*, 1999). This results in improved exercise performance (Balsom *et al.*, 1995; Vandenberghe *et al.*, 1997, 1999) and muscle force or power (Vandenberghe *et al.*, 1997), These performance-enhancing effects, when seen, would be especially useful to an elderly population, who are reported to have depleted creatine concentrations in their skeletal muscles (Balsom *et al.*, 1994; Moller *et al.*, 1980; Smith *et al.*, 1998). In addition, creatine concentrations in the human heart have been found to be depleted during ageing (Nascimben *et al.*, 1996), and also in the diseased heart (Smith *et al.*, 1998). As such reversing an age-related decline in creatine concentrations in the heart could represent a simple and inexpensive way of improving cardiovascular function. Furthermore, creatine supplementation, combined with exercise, may even produce additive benefits.

Studies examining changes in skeletal muscle force in older individuals have been inconclusive. Rawson *et al.* (1999) and Rawson and Clarkson (2000) examined healthy older men (60-82 years) and showed no significant changes in exercise performance or body mass. A further study by Bermon *et al.* (1998) examined 8 weeks of resistance training and creatine supplementation in older subjects (67-80 years), but found that the training regimen alone was sufficient to explain the increase in muscle force, with no additional effects of creatine. This was further confirmed by Eijnde *et al.* (2003) who found no added improvement in physical fit 55 to 75 year-old men, who took creatine supplementation in conjunction with exercise training. Therefore, these negative sets of data may suggest that older subjects may respond differently to creatine supplementation than young subjects.

In contrast to skeletal muscle, very little is known about the effects of creatine supplementation on cardiac performance. Indeed, Juhn and Tarnopolosky (1998) noted

that "to truly determine whether oral creatine supplementation has any effect on cardiac muscle concentration and function, long-term human studies are needed". A number of animal studies have examined the role of creatine in cardiac performance. It has been postulated that the creatine kinase /phosphocreatine system acts as an energy reservoir and may, in addition function as an energy shuttle between intracellular sites of ATP production and consumption, for the maintenance of normal cardiac performance (Neubauer *et al.*, 1999). A number of studies have examined this hypothesis, by depleting intramuscular PCr and free creatine concentrations, by chronic feeding with the creatine analogue β-guanidinopropionate. Most reports have found an impaired cardiac performance (measured via cardiac contractility) under severe creatine depletion by β-guanidinopropionate (Kapelko *et al.*, 1989; Mekhfi *et al.*, 1990; Zweier *et al.*, 1991). However, the above studies were performed on in vitro-perfused hearts. Neubauer *et al.* (1999) examined the role of chronic myocardial creatine depletion in both vitro and vivo rat hearts. The vivo analysis showed that at rest or during acute volume loading no alterations in cardiac haemodynamics occurred after β-guanidinopropionate, despite a 90% reduction in creatine kinase reaction velocity. These workers suggested that in the intact rat, cardiac and/or humoral compensatory mechanisms are sufficient to maintain normal haemodynamics. However, these compensatory mechanisms may not be sufficient when the heart is maximally stressed, i.e. at maximal exercise. Then the depletion of creatine may limit the heart's ability to perform external work. As mentioned earlier, the heart under resting situations operates at a fraction of its total capacity and therefore measurement of cardiac function at rest does not provided important information about the reserve capacity of the heart (Neubauer *et al.*, 1999).

A study by Brzezinska *et al.* (1998) examined 7 days of creatine loading in the rat and found that this dietary loading did increase cardiac muscle high energy phosphate reserves and its oxidative potential. Theses results conflict with those of Horn *et al.* (1998), who found no change in the high-energy phosphate content in myocardium of rats fed with a variety of creatine doses for 40 days.

Therefore, when added as a supplement to normal diets, creatine may improve the functional reserve of both ageing normal and failing heart. If so, this simple approach

may improve the power output of the heart, as well as that of skeletal muscles, and hence help frail elderly and heart failure patients too enjoy a more active life-style and improve their quality of life.

1.7. Aims of the following research

The major aim of this thesis was to examine the age-related changes in cardiac power output and cardiac reserve. However, there were a number of potential confounding factors which could affect the interpretation of the results. Such factors, therefore, needed to be addressed prior to meaningfully analysing the effects of ageing on CPO.

- This overall aim was approached by examining the following objectives:
    1. To investigate whether measurements of CPO were affected by the time of day at which they were measured.
    2. To determine the relationships between variables of body size and CPO, and where such relationships exist identify the best scaling model and variables to provide valid inter-and intra-group data set comparisons.
    3. To establish a temporal baseline of overall cardiac function, with respect to healthy ageing.
    4. To determine the effects of an active lifestyle and long-term endurance training on these age-related changes in CPO and CR.
    5. To investigate the potentially beneficial effects, if any, of orally ingested creatine on CPO in older men.

Chapter 2

Methods

2.1. Ethics and medical screening

Ethical approval was obtained from Liverpool John Moores University ethics committee. All subjects received verbal and written explanation of the procedures involved and filled in consent forms.

Prior screening for the suitability of the subjects was accomplished by completing a medical health questionnaire, which ascertained any past history of cardiovascular conditions and any other contradictions to testing (Appendix 1). Medical exclusion criteria for entry into the studies included a history of coronary artery disease (CAD), hypertension (blood pressure >140/90 mm Hg), diabetes mellitus, and use of any medications known to affect cardio-respiratory function. Subjects with evidence of CAD during screening on the exercise treadmill test were also excluded. To eliminate the confounding influence of severe obesity, only subjects with a body mass index less than 35 kg/m^2 were included in the studies.

Subjects were categorised based on their self-reported physical activity levels, which were obtained via a fitness questionnaire (Appendix 1). The questionnaire ascertained the frequency, duration and intensity of the physical activity performed. The validity of the answers to questions set in the questionnaire were ascertained through an interview with the subject. Furthermore, confirmation of the fitness of the subjects were ascertained through examination of their $\dot{V}O_{2max}$ (ml/min/kg) score (see below) compared to guidelines of physical fitness set by the American college of sports medicine (ACSM; 2000). Therefore, individuals were classified as sedentary if they performed no regular aerobic physical exercise on a weekly basis and if their $\dot{V}O_{2max}$ score was below average i.e. $<50^{th}$ percentile for their age according to the ACSM guidelines (Appendix 2). Conversely, individuals were categorised as physically active if they performed regular aerobic physical exercise three times per week, at an intensity that causes sweating. In addition, they achieved above average i.e. $>60^{th}$ percentile or their $\dot{V}O_{2max}$ for their age, according to the ACSM guidelines.

2.2. Measurements of body composition using Dual Energy X-ray Absorptiometry

Height (HT) was measured using a Harpenden stadiometer and body mass (BM), in light clothing, was measured to the nearest 0.1 kg using Avery balance beam scales. Height and BM measurements were then used to calculate body surface area (BSA), according to the formula of DuBois and DuBois (1916).

Whole-body and regional body composition were measured using Dual Energy X-Ray Absorptiometry (Hologic Inc, Horizon Park, Levensesteenweg, Belgium). The software (Delphi A S/N 70719) provided the mass of fat free tissue, fat tissue and bone. Appendages were isolated from the trunk and head by using DEXA regional computer-generated default lines, with possibility of manual adjustment. With the use of specific anatomical landmarks, the specific regions of the body (head, left and right arms and legs, trunk, and pelvis) were determined.

For this analysis all subjects wore light clothing, having previously removed any metal objects (jewellery, coins, under wire bra etc). The DEXA unit consists of a bed on which the subject lies supine, while a collimated dual energy x-ray fan beam, originating from a source under the bed, passes through the subject (Figure 2.1). The beam's attenuation is measured by the detectors above the subject. Both the source and detector move so that whether the whole body, or selected regions, of the subject are scanned. The dual energy of the beam allows quantification of two components in each pixel; i.e. fat and lean tissue components in boneless regions.

For this thesis, the body components were defined, as follows:

- Body mass (BM) equals the sum of the body fat mass, fat free mass and bone.
- Body fat mass (FM) equals the quantity of triglyceride fat in the body.
- Adipose tissue mass equals the storage form of body fat and its supporting cellular and extracellular structures.
- Lean body mass (LBM) equals the non-adipose tissue of body mass and bone mineral-free constituents.

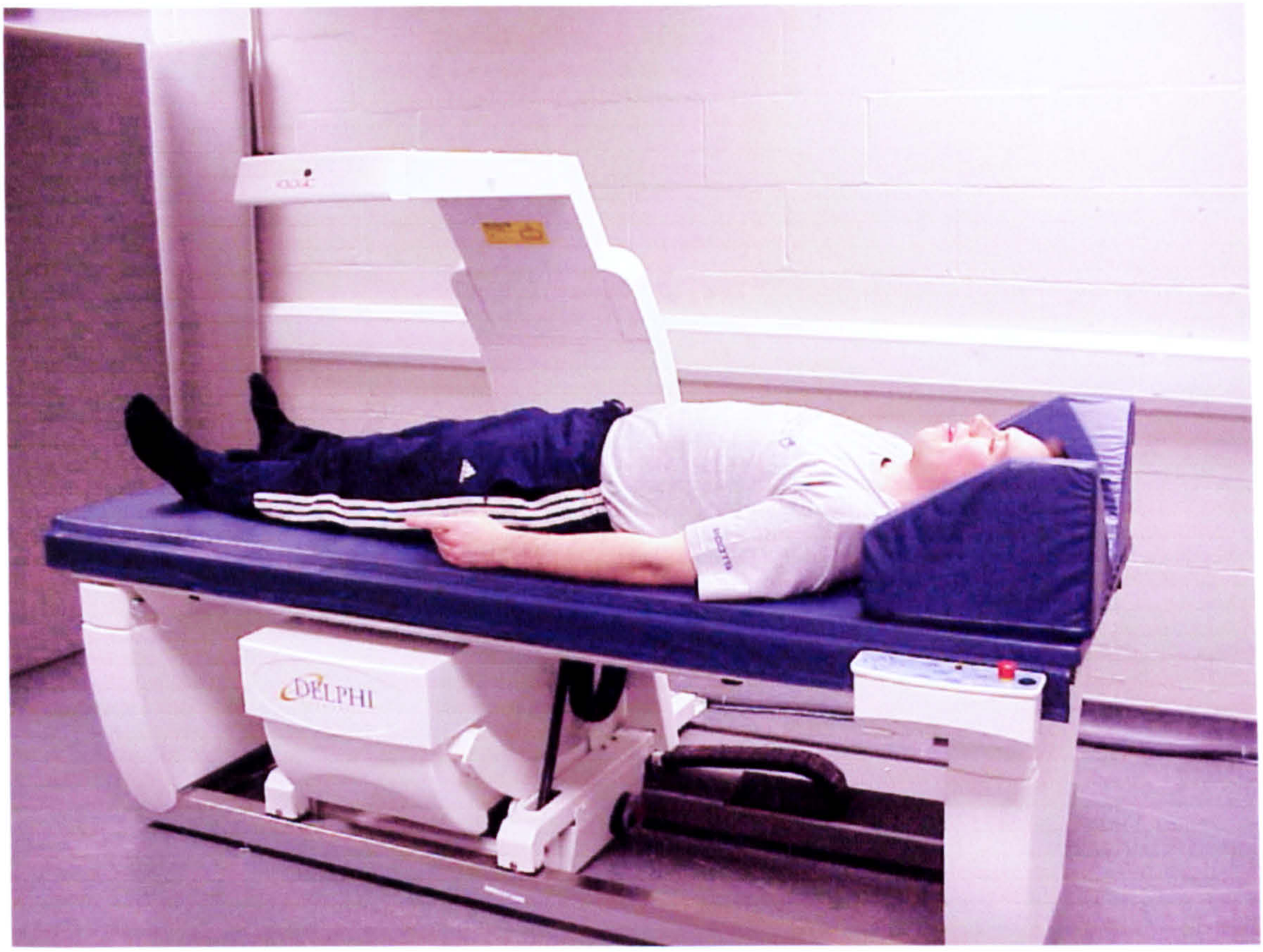


Figure 2.1. Dual Energy X-ray Absorptiometry (DEXA).

- Fat free mass (FFM) equals the lean body mass (e.g. skeletal muscle, brain, heart, liver, kidneys and gastrointestinal tract) and the non-fat component of adipose tissue (e.g. proteins in cellular and extracellular structures). This definition also excludes the bone mineral-free constituents and the head.

The calibration of the DEXA was performed on a daily basis using a spine phantom to test the system's calibration and its precision of imaging. In addition, a step phantom was used. That has known concentrations of soft and lean tissue. In order to obtain a subject's body composition, the dual energy attenuation values of the subject were compared to those produced by the step phantom.

2.3. The measurement of cardiac power output

To determine cardiac power output (CPO) the pressure and flow generating capacities of the heart need to be measured. This process can be achieved non-invasively by measuring mean arterial pressure (MAP) and cardiac output (CO), both at rest and at maximal exercise (Cooke *et al.,* 1998). This involves a three-stage procedure:

i) An incremental exercise test to exhaustion to measure maximal oxygen consumption ($\dot{V}O_{2max}$), carbon dioxide production, and maximal heart rate.
ii) Measurement of CPO at rest (CPO_{rest})
iii) Measurement of maximal CPO (CPO_{max}), i.e. when subjects are exercising at their previously established $\dot{V}O_{2max}$ (determined in stage i).

2.3.1. Breath- by-breath gas sampling and analysis

Continuous breath-by-breath sampling of the respiratory gases were obtained during the incremental exercise test, and during the measurement of resting and maximal CPO, using the Medgraphics cardiopulmonary exercise testing system (CPX-D system; Medgraphics Corporation, St Paul, Minnesota, USA). This is an integrated module system incorporating a flow/waveform module, a gas analyser, 12-lead electrocardiograph and a dedicated host computer with the appropriate software to calibrate and to analyse the respiratory gases.

A pink sample line connected to the pneumotachograph draws the respiratory gases and passes them through a drying sample line (to remove moisture), via a vacuum system before entering the gas analyser. The drying sample line helps to increase the accuracy of the measurement of these gases.

The measurement of respiratory gas flow was obtained through a disposable (pre Vent ™) pneumotachograph (Medgraphics Corporation), which was attached to the flow analyser via an umbilical tube (double lumen). Flow was measured indirectly as a pressure differential by the patented tube-style pneumotachograph.

Oxygen (O_2) concentrations were measured by a patented zirconium fuel cell, which was divided into an inner chamber containing the sample gas and an outer chamber containing a reference gas. With a reference gas on one side of the cell and sample gas on the other, a voltage is created by the movement of O_2 molecules and this is measured by the cell.

The carbon dioxide (CO_2) concentrations in the same samples were measured by an infrared analyser. Carbon dioxide absorbs more infrared light at the 4.3 μm wavelength than any other gas. The amount of light absorbed in the sample chamber was compared to the amount absorbed in the reference cell and the relative amount of CO_2 in sample gas quantified.

Prior to each test, both the pneumotachograph and gas analyser were calibrated. Initially, environmental factors such as ambient temperature, barometric pressure and relative humidity were measured and entered into the system as such factors can affect the results. Then the pneumotachograph was calibrated using a 3 litre syringe, having established a baseline "zero" without any flow. Five injections and withdrawals of the syringe were performed at varying speeds, in order to represent fluctuations in respiration. The gas analyser was calibrated using precise concentrations of reference gases (21% O_2 and balanced N_2) and calibration gases (12% O_2, 5% CO_2, and balanced N_2).

2.3.2. Measurement of maximal oxygen uptake($\dot{V}O_{2max}$)

All exercise tests were conducted in specialised cardiopulmonary exercise laboratories. The environmental conditions within the laboratory were controlled; temperature and humidity were maintained around 20°C and 40-60%, respectively. All subjects attended the laboratory after a minimum 3-hour postprandial period, having abstained from caffeine in the preceding 3 hours. On arrival, a 12-lead electrocardiogram (ECG) (Cardio-perfect, Atlanta) was attached with the electrodes positioned on to the chest of the subject.

Irrespective of the subject population, a single exercise protocol was used to determine their $\dot{V}O_{2max}$. All subjects were tested on a programmable treadmill (Cosmos, Nussdorf-Traunstein, Germany) using a modified version of the Bruce (1971) protocol (Table 2.1). The protocol contained two preliminary 1-minute stages of 2.2 kph at 0% incline. The protocol then increased in both speed and gradient every minute, until exhaustion was reached. From stage 4 onwards of the protocol, every alterative stage corresponded to a stage in the Bruce (1971) protocol (Table 2.1). The reason for adopting the 1-minute incremental protocol was to obtain a more linear rise in the $\dot{V}O_2$ and HR relative to the workload and to avoid the fluctuations apparent with the Bruce (1971) protocol. Additionally, maximal exercise would be achieved within approximately 10 minutes, in keeping with the recommendations of Buchfuhrer *et al.* (1983). Figure 2.2 illustrates a symptom limited exercise test performed by a sedentary 50 year-old male.

Throughout the exercise test a 12-lead ECG was monitored and the HR was derived from it. Blood pressure (BP) was measured by an experienced investigator using a manual sphygmomanometer before starting the test, at two-minute stages during the exercise test, at maximal exercise and immediately at the end of the exercise test (refer to section 2.33 for further detail). Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), end tidal partial pressure of carbon dioxide ($P_{ET}CO_2$), tidal ventilation ($\dot{V}E$) and respiratory rate were measured breath-by-breath using the Medgraphics CPX-D system (Medgraphics Corporation, St Paul, Minnesota, USA). Breath-by-breath data ($\dot{V}O_2$ and $\dot{V}CO_2$) were averaged from 5 breaths.

Table 2.1. Exercise protocol.

One minute incremental programme for treadmill, adapted from Bruce (1971)

Protocol							
Bruce, 1971				1-minute incremental programme			
Stage	Duration (min)	Speed (km/h)	Gradient (%)	Stage	Duration (min)	Speed (km/h)	Gradient (%)
				1	0-1	2.2	0
				2	1-2	2.2	0
				3	2-3	2.7	5
1	**3**	**2.7**	**10**	**4**	**3-4**	**2.7**	**10**
				5	4-5	3.3	11
2	**3**	**4.0**	**12**	**6**	**5-6**	**4**	**12**
				7	6-7	4.8	13
3	**3**	**5.5**	**14**	**8**	**7-8**	**5.5**	**14**
				9	8-9	6.2	15
4	**3**	**6.8**	**16**	**10**	**9-10**	**6.8**	**16**
				11	10-11	7.4	17
5	**3**	**8.0**	**18**	**12**	**11-12**	**8**	**18**
				13	12-13	8.4	19
				14	13-14	8.8	20
				15	14-15	9.2	21
				16	15-16	9.6	22

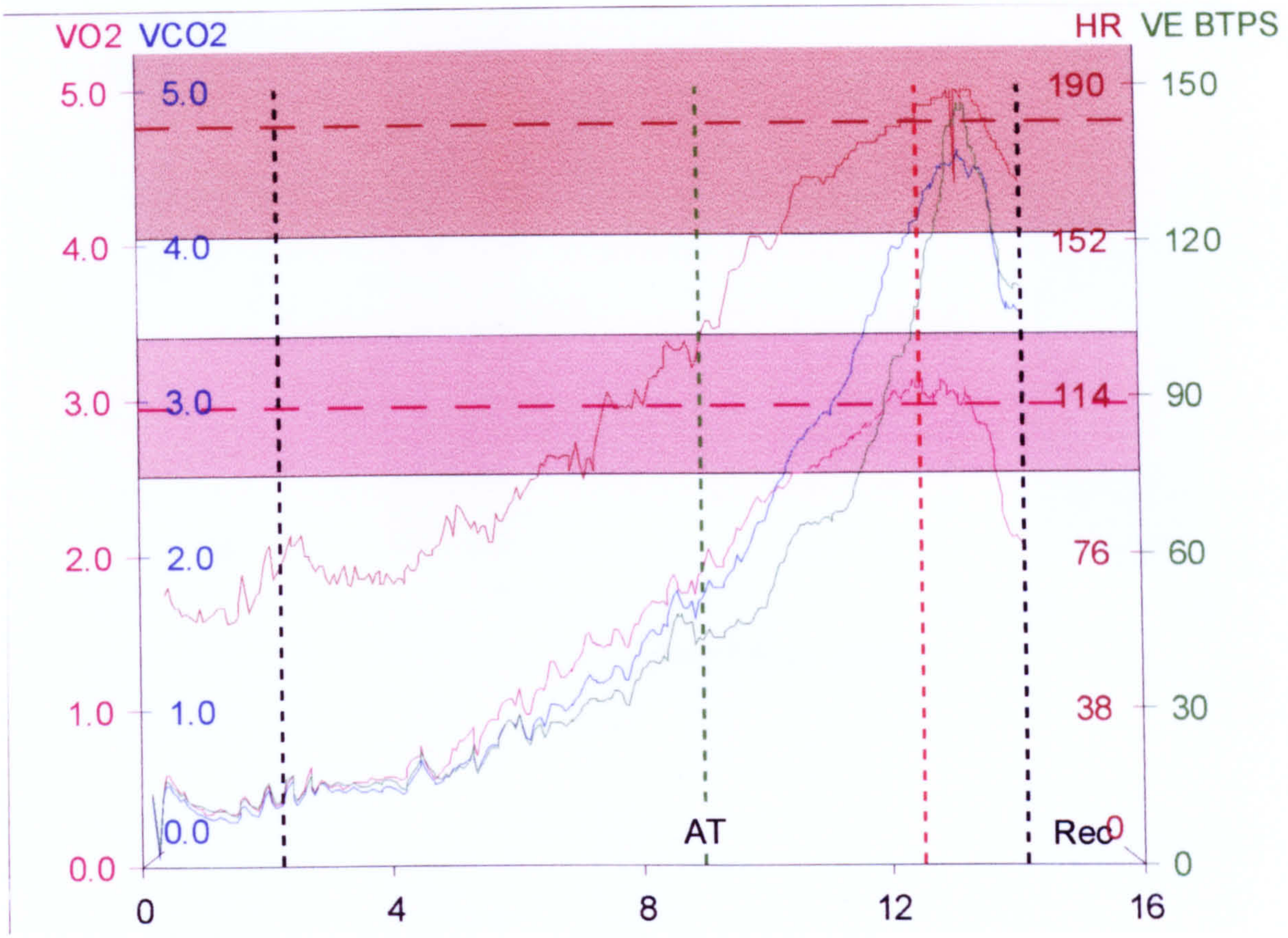


Figure 2.2. Graphical representation of the changes that occurred during an incremental exercise test.

Changes in oxygen consumption [$\dot{V}O_2$ (l/min); pink line], carbon dioxide production [$\dot{V}CO_2$ (l/min); blue line], heart rate [HR (b/m); red line] and the volume of expired gas [$\dot{V}E$ (ml BTPS); green line] during the 1-minute incremental exercise test. The subject began to exercise at approximately 2 minutes and reached exhaustion around 13 minutes, with $\dot{V}O_{2max}$ achieved at 12 minutes.

Maximal oxygen consumption was considered to be reached when two out of the following three criteria were satisfied; $\dot{V}O_2$ levelling off despite further increase in workload, heart rate greater than 95% of their age-predicted maximal value (220-age), and a respiratory exchange ratio greater than 1.10. All subjects were given verbal encouragement to achieve the criteria outlined above.

Any premature termination of the incremental exercise test consisted of any evidence of ECG ischaemia or arrhythmia, and a rise in systolic blood pressure (SBP; >230 mm Hg) and/or a rise in diastolic blood pressure (DBP; >115 mm Hg).

The main purpose of the exercise test was to obtain the subject's maximal HR, $\dot{V}O_2$, $\dot{V}CO_2$, and Vt values. These values were then used as benchmarks to ensure that subjects re-attain their maximal levels during the measurement of maximal CPO (i.e. stage iii). Therefore, the $\dot{V}O_{2max}$ test acted as a familiarisation session for the subjects, while to excluding any silent ischaemia or latent exercise induced hypertension, and determining their exercise capability prior to the crucial measurement of maximal CPO.

2.3.3. Measurements of arterial blood pressure at rest and during dynamic exercise

The measurements of resting and maximal blood pressure (BP) were performed manually, using a mercury sphygmomamater and a stethoscope. The measurement of BP conformed to the recommendations of American Heart Association (Frohlich *et al.*, 1988). The correct size of BP cuff (i.e. bladder width and length = 40-50% and 80% of upper arm circumference, respectively) was fitted to the subject's left arm, positioned over the brachial artery (Figure 2.3). The drum of the stethoscope was positioned over the brachial artery, and the cuff was inflated 40 mm Hg beyond the disappearance of the Korotkoff sound, this phase represented the point at which the blood flow in the brachial artery was occluded. The cuff was then deflated by approximately 3 mm Hg per second. During the deflation of the BP cuff, systolic blood pressure (SBP) was taken as the appearance of the first Korotkoff sound (faint, clear tapping sound) and diastolic blood pressure (DBP) was taken as the 5th Korotkoff sound (the pressure level when the last sound is heard, and after which all sounds disappear).

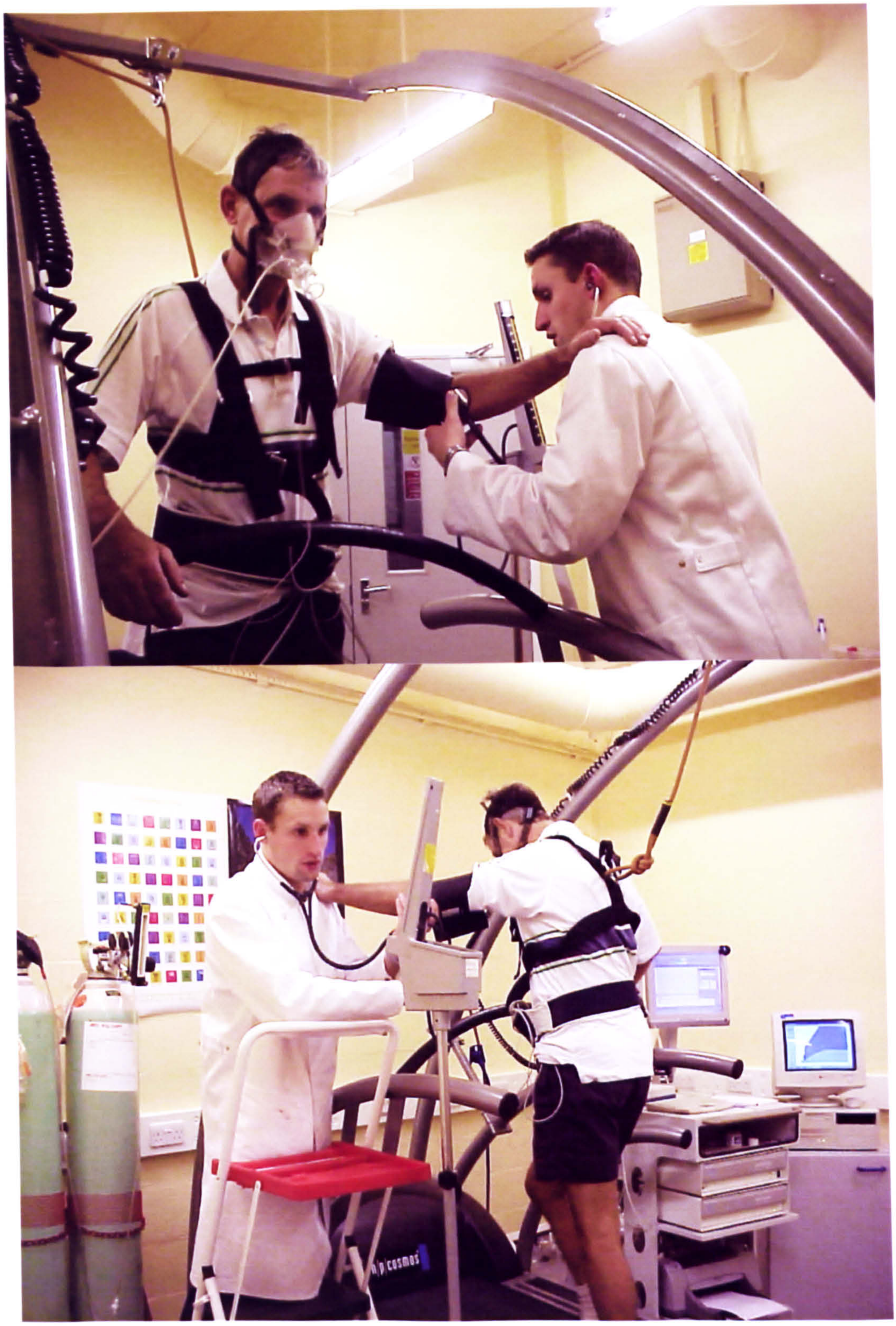


Figure 2.3. Determination of blood pressure using the auscultation method during an incremental exercise test.

2.3.4. Measurement of cardiac output using the carbon dioxide (CO_2) rebreathing technique

The measurement of CO was determined using the CO_2 rebreathing methods of Collier (1956) and Defares (1958), and calculated using the indirect Fick equation. The indirect Fick equation requires measurements of respiratory gases to obtain $\dot{V}CO_2$, arterial ($Caco_2$), and venous ($Cvco_2$) concentration of CO_2. This was achieved using the Medgraphics CPX-D system. The Fick equation (see below) was programmed into the software, which accompanied the gas analyser and was used to calculate CO,

$$CO = \dot{V}CO_2 / (Cvco_2 - Caco_2),$$

where $Cvco_2$ is the venous and $Caco_2$ the arterial concentrations of CO_2 (mm Hg).

The $\dot{V}CO_2$ component of the Fick equation was obtained from the inspiratory and expiratory gas volumes. The content of CO_2 in arterial blood ($Caco_2$) was derived from the logarithmic version of the CO_2 dissociation curve (Jones, 1988) of the partial pressure of CO_2 in the arterial blood ($Paco_2$; mm Hg). Partial pressure of CO_2 in the arterial blood was estimated from the end-tidal Pco_2 ($P_{ET}CO_2$), assuming normal lung function, using the following equation (Jones, 1988),

$$Paco_2 = 5.5 + 0.9\ P_{ET}CO_2 - 0.0021 \times Vt\ (BTPS),$$

where Vt – tidal volume (ml BTPS) and $P_{ET}CO_2$ is the average taken over the 30 seconds preceding the commencement of the rebreathing manoeuvre.

The $Cvco_2$ component of the Fick equation was measured by obtaining the partial pressure of CO_2 in the venous blood ($Pvco_2$; mm Hg). The $Pvco_2$ can be determined using one of two rebreathing methods, the equilibrium (Collier) or the exponential (Defares) rebreathe techniques.

However, when converting partial pressures to content, two assumptions are made. First, the haemoglobin concentration is at 15 g/100 ml, and second, the mixed venous oxygen saturation was > 95% during rebreathing (Jones, 1988).

(A) The Equilibrium (Collier) CO_2 rebreathing technique

To determine $Pvco_2$ the Collier (1956) method and hence CO, was used at rest, as past research has shown that this method was more accurate and reproducible than the Defares (1958) method (Auchincloss *et al.,* 1980; Franciosa *et al.,* 1976; Zeidifard *et al.,* 1972). For this procedure the subjects breathed through a low resistance three-way rebreathe valve (Hans Rudolph, Model 2870 Series). This valve allowed rapid switching from breathing room air to breathing a known concentration of gases from a 5 litre-rebreathe bag. Attached to the outflow of the valve, was a pre-vent pneumotachograph to measure the flow of breathing. Also a gas sampling line was fitted near to the mouthpiece, and connected to the gas analyser (Figure 2.4).

At rest, the rebreathe bag was filled with 10% CO_2 (35% O_2 and balanced N_2) in a known volume, which corresponded to approximately twice the subject's resting tidal volume (VT). A table relating flow rate to bag volume was constructed by the author to facilitate easy of flow. Under or overfilling of the bag can lead to falsely high or low CO, respectively. At the end of a normal tidal breathe the three-way valve was closed manually by the investigator. This switched the subject's breathing from room air to that of the rebreathe bag. The subject was then instructed to take a deep inspiration, inhaling the full volume of the bag. The subject continued to rebreathe from the bag at a rate of approximately 30 breaths/min, ensuring the bag was completely emptied each time. This procedure lasted approximately 11 seconds, until a plateau in the percentage of CO_2 concentrations were achieved and maintained for at least two breaths. The valve was then switched back to room air. Figure 2.5, illustrates such an equilibrium breathing pattern.

A satisfactory capnograph plot met the following criteria:

- The CO_2 equilibrium was reached after 2 to 3 breaths.
- The equilibrium was maintained for at least 2 breaths.
- This equilibrium was reached within 12-15 seconds, to avoid problems with recirculation.

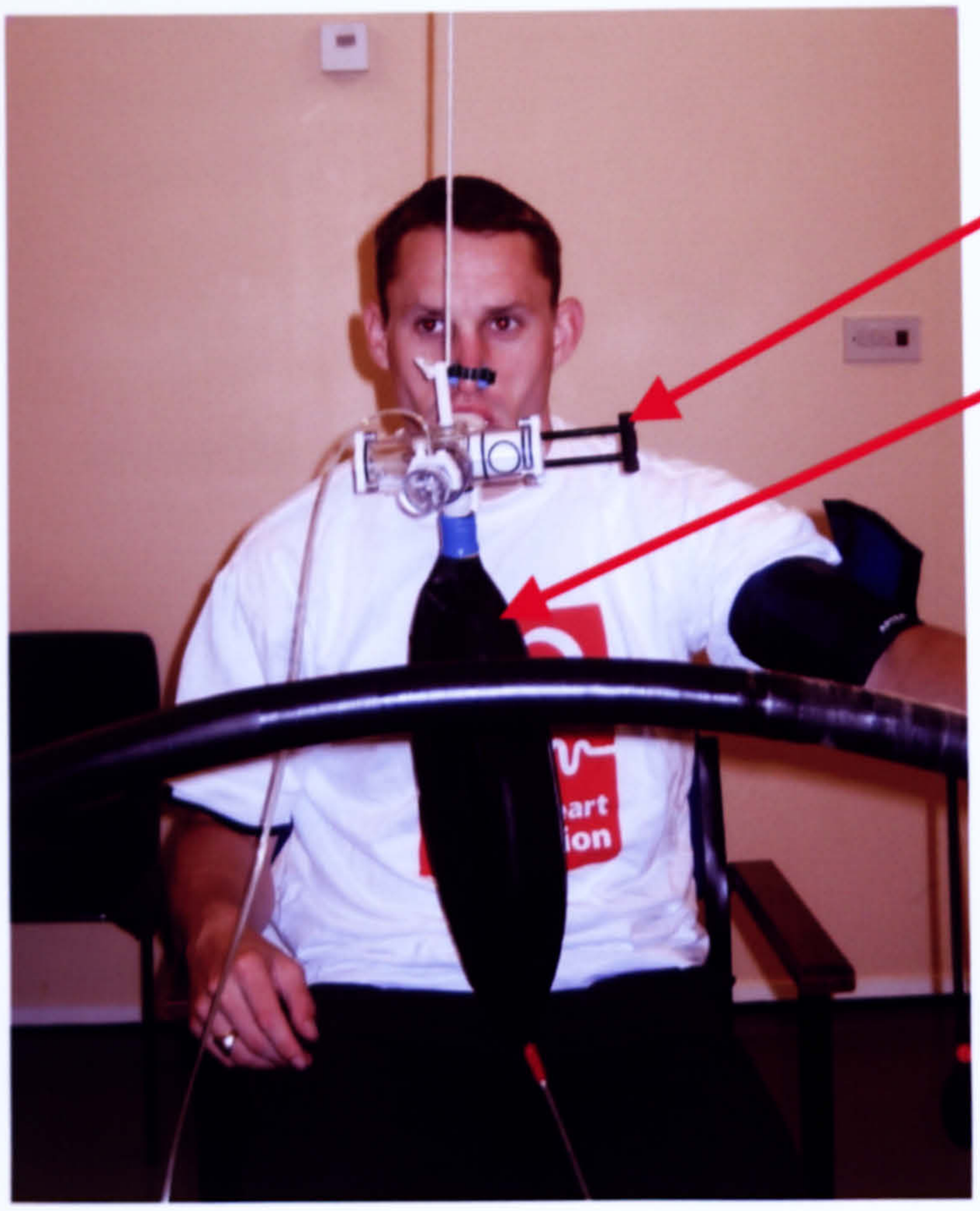


Figure 2.4. Measurement of resting cardiac output using the carbon dioxide rebreathe technique.

As illustrated above the black 5-litre rebreathe bag, filled with appropriate concentrations of CO_2, O_2 and N_2 is attached to a 3-way rebreathe valve. The manual plunger allows the switching of breathing from room air to the rebreathe bag in a closed circuit.

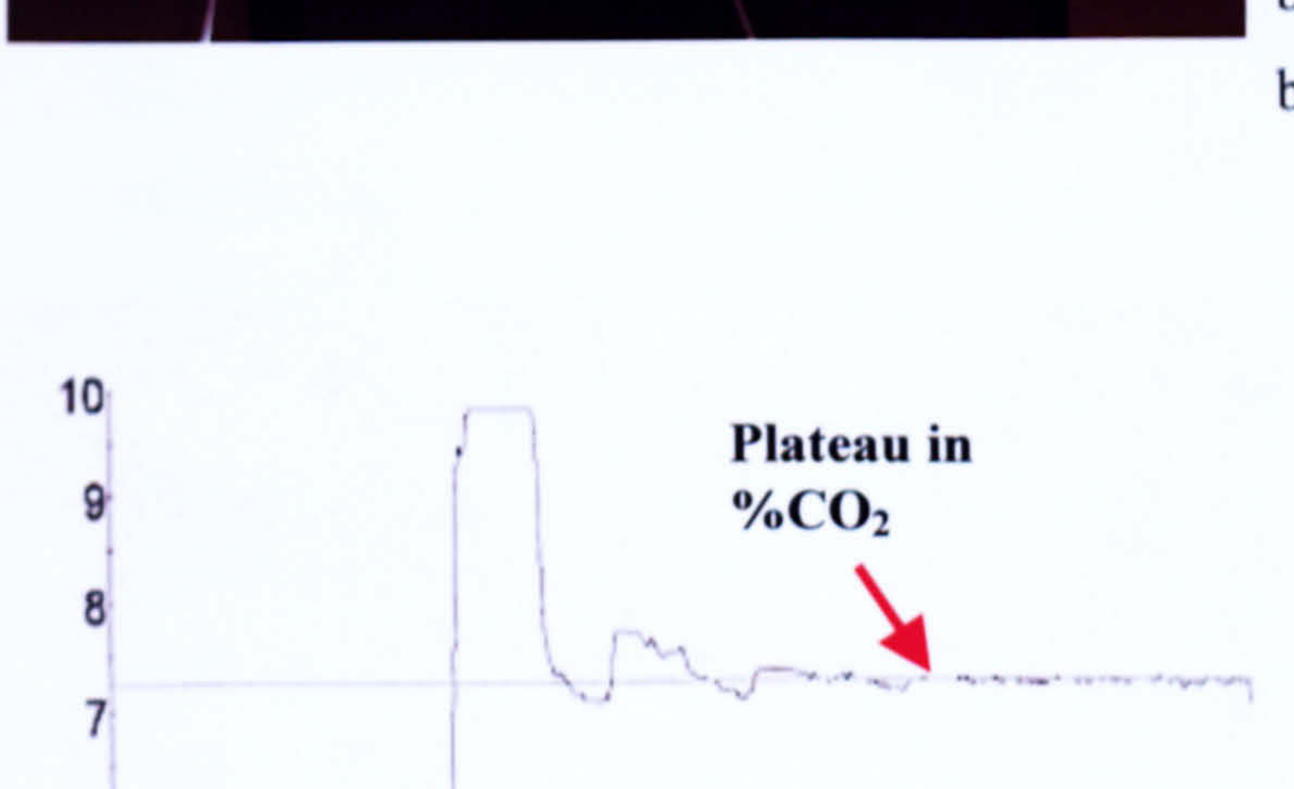


Figure 2.5. Capnograph plot taken from a healthy sedentary 50 year-old subject.

The graph shows the change in tidal CO_2 concentration, which occurs during the rebreathe manoeuvre. Normal tidal breathing can be seen initially. Then at the end of the second expiration (arrow) the subject began to rebreathe from the bag. A plateau (arrow) in $\%CO_2$ had occurred after the third breath and was maintained for two breaths.

As recommended by Jones (1988), the empirically derived 'downstream correction' equation was applied to the equilibrium method to correct for the alveolar to arterial Pco_2 difference observed during this method. This equation is present in the software and it follows,

$$Pvco_2 \text{ (mm Hg)} = P_{eq}co_2 - (0.24 \times P_{eq}co_2 - 11) \text{ (Jones } \textit{et al.}\text{, 1972),}$$

where $P_{eq}co_2$ = the equilibrium Pco_2 before correction.

(B) Exponential (Defares) CO_2 rebreathing technique

At maximal exercise the Defares method was employed to measure CO_{max}, as past research has established that this method provides the most accurate and reliable measurement of CO (Ferguson *et al.*, 1968). Once again the subjects breathed through a three-way rebreathe valve (Hans Rudolph) as described for the equilibrium method. Attached to the rebreathe valve with a specialised accessory to connect a facemask (Hans Rudolph). Connected to the mask was a seal gel, which moulded to the shape of each subject's face. Once the valve was closed this seal gel ensured that the subject was breathing into a closed system. The weight of the rebreathe valve was balanced by attaching the value to a specialised head support device (Hans Rudolph, Model 2785 Series), which allowed the subjects to walk/run with little hindrance (Figure 2.6).

Once the subjects reached 100% of their predetermined $\dot{V}O_{2max}$ values, the valve was manually closed and the subject began to breathe the gas mixture (4% CO_2, 35% O_2 and balanced N_2) in the rebreathe bag, the volume of which equalled each subject's maximal Vt (as determined during the $\dot{V}O_{2max}$ test). The subject rebreathed from this bag at a rate of approximately 40 breaths/min, for approximately 8-10 seconds. The valve was then opened to allow the subject to breathe room air. Figure 2.7 shows the exponential rebreathe pattern, taken from a healthy male subject. As described by Da Silva *et al.* (1985), the first breath was rejected because of incomplete mixing of the gases in the lung. All $P_{ET}CO_2$ points were then analysed, using an iterative technique that was solved for t = 20 seconds. Only $P_{ET}CO_2$ values up to 8 seconds were analysed, i.e. only

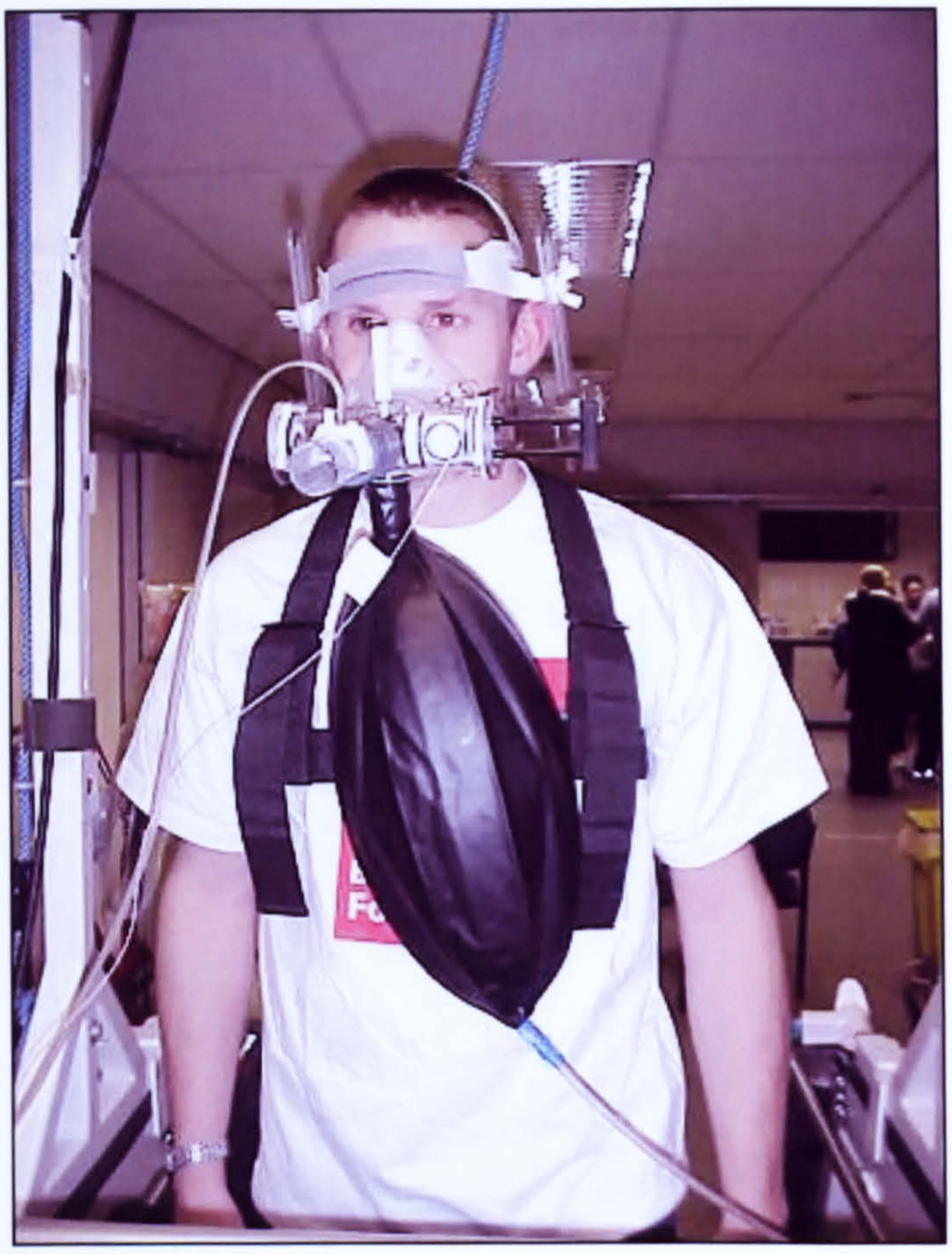


Figure 2.6. Measurement of maximal cardiac output using the Defares carbon dioxide rebreathe technique.

The figure illustrates the 3-way rebreathe valve attached to Hans Rudolph face mask and support device. The face mask and seal gel produces a comfortable seal around the contours of the face allowing complete gas collection. The device helps to balance the weight of the valve, while the subject is walking or running.

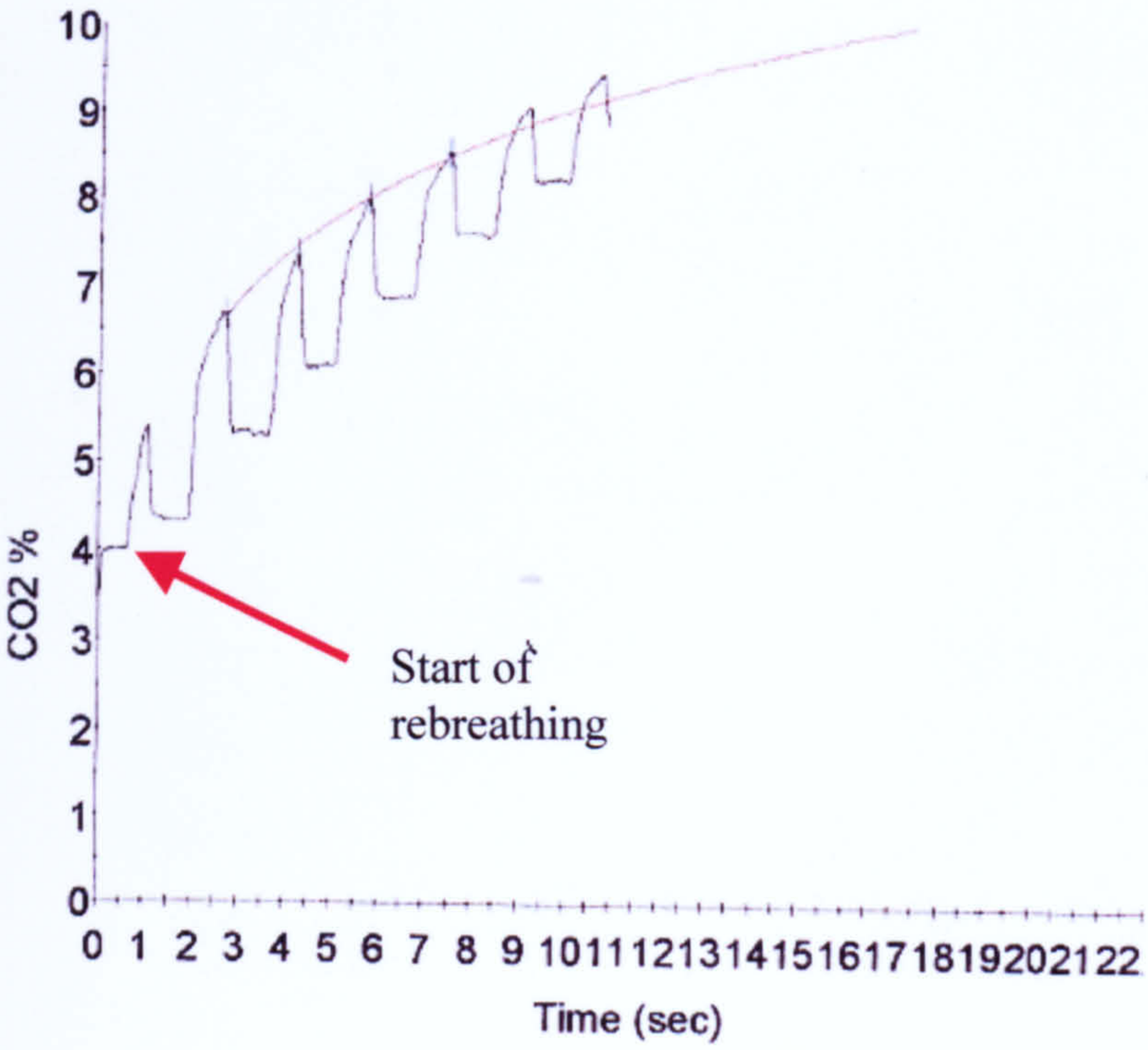


Figure 2.7. Capnograph plot taken from a healthy sedentary 50 year-old subject.

The graph shows the exponential change, in tidal CO_2 concentration, which occurs during the CO_2 rebreathe at maximal exercise. It can be seen from the graph that with each breath the concentration of tidal CO_2 increases.

3 to 6 breaths were used. This was to ensure that no $P_{ET}CO_2$ were taken after recirculation of blood through the lungs had occurred.

For both the Collier (at rest) and Defares (at maximal exercise) methods a 3-minute wash out period was left between successive (duplicate or triplicate) measurements, during which time the preceding respiratory values were re-established.

2.3.5. Measurement of resting cardiac power output

Resting CPO (CPO_{rest}) was performed after the subjects had rested (seated position) for approximately 20 minutes. During that time ventilatory gases were measured and standardised. Blood pressure was measured on three occasions, with each measurement separated by 2 minutes. Cardiac output was measured using the CO_2 rebreathing technique of Collier (1956), with at least three resting measurements separated by 4 minutes to allow for a complete wash out of CO_2 from the circulating blood. The average of three CPO_{rest} values were calculated. The day to day reproducibility of the average measurement of CPO_{rest} had a coefficient of variation of 7.7% (equating to approximately 0.1 W), which is below the acceptable level of 10% (Atkinson and Nevill, 1998).

2.3.6. Measurement of maximal cardiac power output

The protocol to measure the subject's maximal CPO was as follows;

The speed and gradient of the treadmill (based on the values obtained during the $\dot{V}O_{2max}$) were adjusted manually by the investigator to obtain maximal respiratory and haemodynamic values within 6-9 minutes. By this time all subjects were exercising at 100% of the values that they attained during the $\dot{V}O_{2max}$ test. Once maximal $\dot{V}O_2$, $\dot{V}CO_2$ and HR were reached BP and CO (Defares method) were measured. Duplicate or triplicate CO_{max} were made, each separated by 2 to 3 minutes of recovery at a low intensity of exercise. An average value was then calculated.

The day to day measurements of CPO_{max} corresponded to a coefficient of variation of 7.3%. Again this was below the acceptable level of 10%.

2.3.7. Calculations

- Mean arterial pressure (MAP) was calculated from the following equation (Meaney *et al.*, 2000),

$$MAP = DBP + 0.412 \times (SBP - DBP),$$

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

- Cardiac power output (expressed in Watts) was calculated from the equation (Cooke *et al.*, 1998),

$$CPO = (CO \times MAP) \times K,$$

where CO is cardiac output (l/min) and K the conversion factor (2.22×10^{-3}) into Watts.

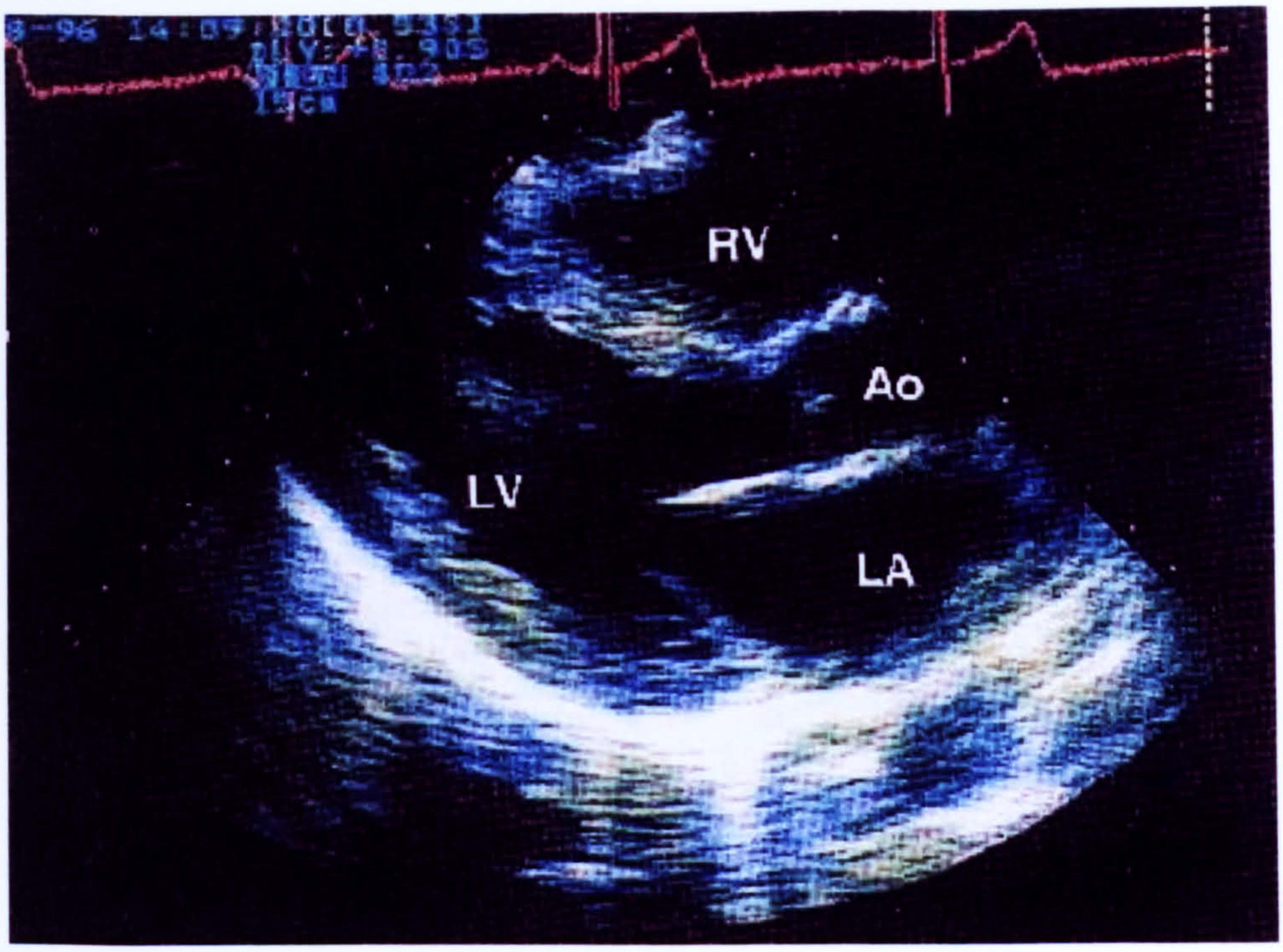
- Cardiac reserve (CR; expressed in Watts) was calculated from the equation

$$CR = CPO_{max} - CPO_{rest}$$

2.4. Measurements of cardiac dimensions using echocardiography

Echocardiographic measurements were performed in the supine position, using an Acuson Cypress Echocardiography System (Siemens Ltd, Hertfordshire) with simultaneous ECG recordings. Ultrasound images of the left ventricle were obtained with the subject lying in the left lateral decubitus position. Placement of a 2.5-MHz transducer at the parasternal window allowed the production of a two-dimensional image of the left ventricle in the long axis (Figure 2.8A). M-mode recordings were taken at the tip of the mitral valve leaflets (Figure 2.8B). All measurements were taken

A



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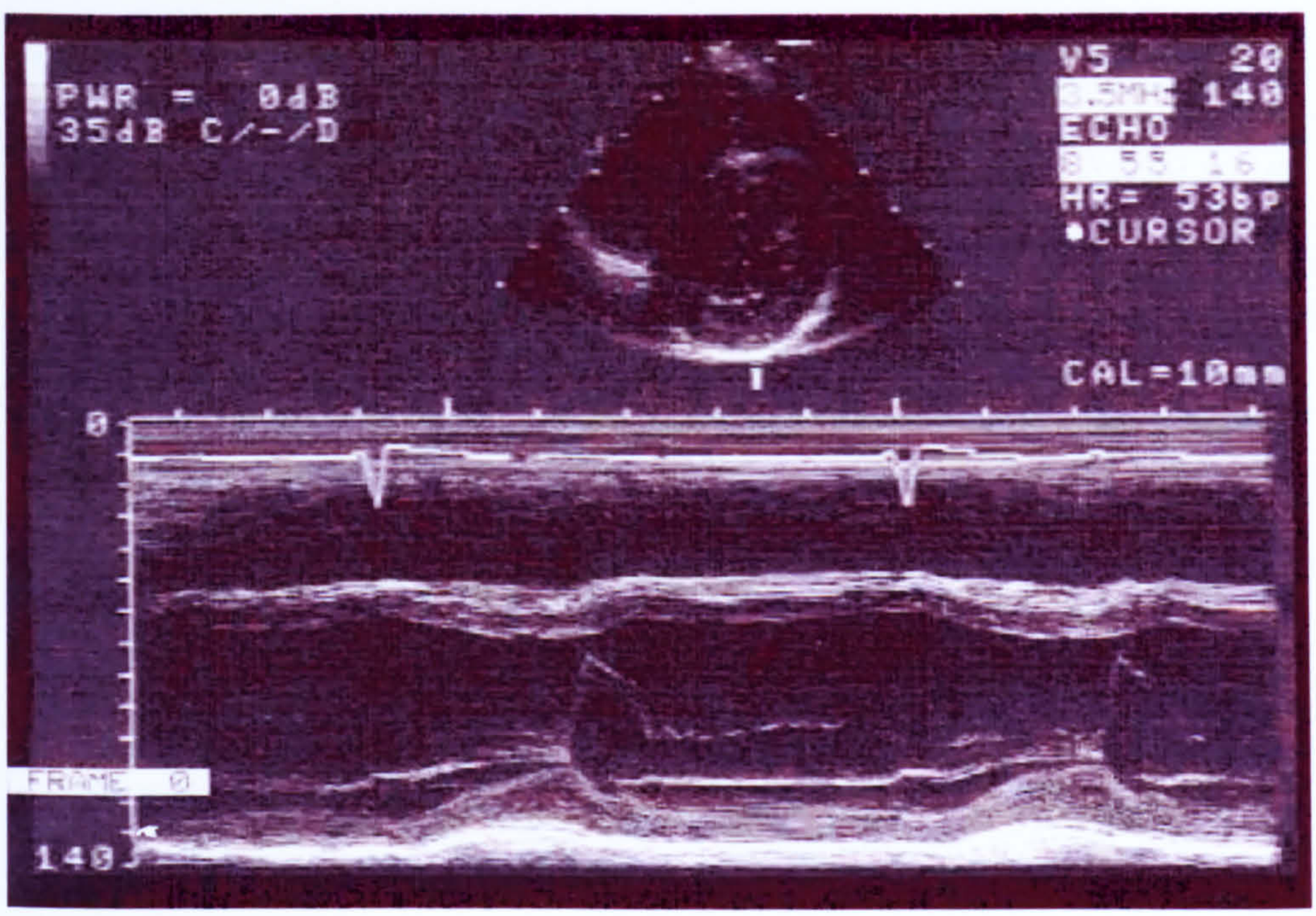


Figure 2.8. Cardiac dimensions using echocardiography

(A) 2-D image of the heart, with the transducer positioned on the parasternal long-axis. (B) M-mode image of the left ventricle at the level of the mitral valve, from which septal wall thickness (SWT), posterior wall thickness (PWT), left ventricular internal diameter in diastole (LVIDd) and systole (LVIDs) can be measured.

in accordance with the guidelines set by the American Society of Echocardiography (Sahn *et al.,* 1978). Three to five consecutive measures were made and the average was taken. From the concomitant ECG trace septal wall thickness (SWT), posterior wall thickness (PWT) and left ventricular end-diastolic dimension (LVIDd) were digitised at the peak of the R-wave, according to Penn convention guidelines (Devereux and Reichek, 1977). Left ventricular end-systolic dimensions (LVIDs) were measured as the minimum separation of the septal and posterior walls. Left ventricular mass (LVM) was determined via a regression-corrected "cube-formula" (Devereux and Reichek, 1977).

2.5. The Process of Scaling

In order to establish the best scaling procedure and to identify the most appropriate scaling variable, the following processes were implemented. All data from males and females subjects were grouped together into one large population. The relationship between various variables representing body size (e.g. body mass, height, body surface area, and fat free mass) and CPO were checked using Pearson's correlation. If a relationship was identified, then by using Tanner's (1949) calculation for 'special circumstances' their relationships were analysed for linearity with a zero intercept. In this procedure the correlation coefficient (r,X,Y) for each variable representing body size and CPO were compared with the ratio of the coefficient of variation (CV) for body dimensions (CVx) divided by the CV for the physiological dependent variable (CVy) i.e. CVx/CVy. Where r,X,Y is either equal to or roughly equivalent (arbitrarily chosen as ± 0.05 in this study) to CVx/CVy, a linear relationship with an intercept at zero is likely to be true. Conversely, if these two terms are not similar (the difference between CVx/CVy and r is >0.05), then either a linear relationship does not exist or the linear relationship has a non-zero intercept on the y-axis.

Subsequently, the allometric modelling technique was investigated to describe the relationship between each combination of body size and the physiological variables. Allometric relationships were derived from natural log transformations (base ϵ) of the absolute data. The general curvilinear allometric equation can be log-transformed into linear relations (Nevill *et al.,* 1992),

$$\log y = \log a + b \log x + \log \epsilon ,$$

where the exponent ***b***, is the slope of the regression line when comparing the log transformed variables of body size and CPO on the log linear plot, and ***a*** is derived from the antilog of the intercept on the y-axis. All exponents were calculated as means, with 95% confidence intervals (CI). Statistical significances of the coefficients were tested at an α-level of 0.05.

First, it was important to determine the viability of a common power function ratio (y/x^b) for both male and females, across the age range studied. Only in this way can CPO, when normalised for body size throughout different populations, be compared directly. For this, the slopes of the regression lines for male and female data were tested to see if they were parallel, as equality of slopes across all age groups must be satisfied for ANCOVA to proceed. This was achieved by including a gender (males coded 0, females coded 1) times log BM (or log HT, BSA and FFM) interaction term in a multiple log-linear regression model (Nevill *et al.*, 1992).

$$\log \mathrm{CPO}_{\mathrm{rest}} = \log a + d(\mathrm{sex} \bullet \log \mathrm{BM}) + c \bullet \mathrm{sex} + b \log \mathrm{BM} + \log \epsilon$$

Clearly, the above equation can be changed to include the remaining variables of body size and CPO, to examine a sex-related interaction. If the interactive term is not significant (P>0.05), commonality of slopes in the disparate groups is then confirmed. An inclusive 'best compromise' exponent ***b*** can then be derived by removing the interaction term, but including sex as a predictor variable alongside the body size variable in a multiple allometric regression model (see below) (Nevill *et al.*, 1992).

$$\log \mathrm{CPO}_{\mathrm{rest}} = \log a + c \bullet \mathrm{Sex} + b \log \mathrm{BM} + \log \epsilon$$

This model provides a solution for a single exponent ***b***, isolating the "sex independent" influence of body size on $\mathrm{CPO}_{\mathrm{rest}}$. Furthermore, the above equation allows for the derivation of adjusted values of the proportionality coefficient ***a***, isolating the effects of sex on $\mathrm{CPO}_{\mathrm{rest}}$. With a common exponent ***b***, the ***a*** value can be statistically analysed to test for size-independent sex differences in CPO. Alternatively, using the best compromise exponent ***b***, the power function ratios $\mathrm{CPO}_{\mathrm{rest}}/\mathrm{BM}^b$, $\mathrm{CPO}_{\mathrm{rest}}/\mathrm{HT}^b$,

CPO_{rest}/BSA^{b} or CPO_{rest}/FFM^{b} can be compared statistically. Similarly, CPO_{rest} can be replaced with CPO_{max} or CR and the exponent ***b*** statistically analysed.

After the generation of the exponent ***b***, it was possible to check whether this allometric approach produced a size-independent physiological parameter by correlating the power function ratio with the variables of body size. If the influence of body size were corrected for, then this correlation would not be significantly different from zero (Batterham *et al.*, 1999).

$$(CPO/BM^{b}) / BM = zero$$

Information regarding the optimal body dimension was obtained by comparing the model R^2 (i.e. the ratio of the variance due to treatment and the total variance) and root-mean-squares-error from separate regression models, together with the relative width and stability of the confidence intervals surrounding the mean size exponents. The root-mean-squares-error indicates the variation not explained by the regression line, so it is a measure of the 'goodness-of-fit' of the line in the units of the measurements made.

2.6. Creatine supplementation prior to measurements of cardiac power output.

To examine the possible effects of dietary creatine supplementation on CPO in older sedentary and active male subjects, a double blind cross over experiment was performed, with all tests randomised to ensure that no bias was involved. All subjects ingested either placebo (control) or creatine drinks. The placebo drink contained 15g of maltodextrin with no creatine, whilst in the creatine trial 5g of creatine and 10g of maltodextrin (SIS, Blackburn) were dissolved and ingested. Both the placebo and creatine drinks contained flavouring to make them more palatable and to disguise the presence of creatine from the subjects.

The contents of each sachet, was dissolved in warm water before ingestion and the equivalent of four full sachets (i.e. 20 g of creatine) were ingested each day, for 5 days. The $\dot{V}O_{2max}$ exercise test was performed in the morning on the sixth day after the

contents of a sachet had been taken prior to attending the laboratory. The resting and maximal CPO was performed on the seventh day, this time after the contents of the last sachet had been taken. At least four weeks were allowed between the 1st and 2nd trial, to allow for an adequate wash out period and to ensure that a complete restoration of the initial concentrations of creatine were obtained.

2.7. Statistical analysis

All data are presented as Means ± SEM. Data from each experiment were first tested for normality (Kolmogorov-Smirnov test). Normally distributed data were analysed for statistically significant differences using parametric tests. Simple comparisons between two independent cases were analysed using Student's two-tailed independent *t*-test. Comparisons between the same data sets were analysed using Paired Sample *t*-test. More complex comparisons were conducted using one-way analysis of variance followed by Tukey's HSD *post-hoc* analysis.

Linear regression analyses were performed to determine the association among variables. In all cases, age was used as the predictor variable. Pearson product-moment correlation coefficients were used to indicate the magnitude and direction of relations among variables. The slopes of the regression lines (comparing men and women or sedentary and active men) were compared using analysis of covariance which included an interaction term. Significant differences were expressed as $P \leq 0.05$.

Chapter 3

Results

3.1. The effects of time of day on the measurement of cardiac power output

Previous research has established a circadian rhythm in cardiac output (CO), a principal component of cardiac power output (CPO), and also diastolic blood pressure (DBP), which is a component of mean arterial pressure (MAP) (Cugini *et al.*, 1991; Deschenes *et al.*, 1998a). However, this circadian rhythm in CO and MAP has only been observed at rest. It is therefore conceivable that CPO may be influenced by the time of day at which it is measured. If such a pattern does exist, the implications on the measurement of CPO would be considerable. For example, in cross-sectional studies measurements of CPO would need to be standardised according to the optimal time of day. In practical terms this would be limiting, with fewer subjects tested each day. Therefore, before investigating how ageing effects CPO, it was necessary to ascertain whether a circadian pattern exists for CPO.

For this purpose nine male subjects, with a mean age of 22 ± 1.1 years, performed the CPO protocol on two separate occasions, at 04:30 (morning) and 16:30 (afternoon) hours. These times reflected the points at which resting core temperature reaches its nadir and peak (Refinetti and Menaker, 1992; Reilly *et al.*, 1997). The only change from the protocol was that the $\dot{V}O_{2max}$ test was performed a week prior to the start of the experiment, to obtain the subjects maximal exercising limits.

Past research has identified that many biological functions follow a circadian pattern, similar to that of the fluctuations in resting core temperature (Reilly *et al.*, 1997). In the present study, although not significantly different, core temperature, measured via rectal temperature, was lower (37.2°C) in the morning than in the afternoon (37.5°C), under resting conditions. In addition, no significant differences were measured in core temperature attained at maximal exercise between the morning and afternoon. In contrast, significant ($P<0.001$) increases in core temperature were measured when comparing resting to maximal exercise, whether undertaken in the morning (37.6°C) or afternoon (37.9°C) trial.

When examining the resting haemodynamic data for CPO, CO and MAP, no significant differences were measured in relation to morning or afternoon sessions (Table 3.1). Similarly, no differences were established for the same variables when measured at maximal exercise (Table 3.1). As expected from these findings, the component parts of CO and MAP, i.e. SV, HR, SBP and DBP, were also unaffected by the time of day whether they were measured at rest or at maximal exercise (Table 3.1).

To be absolutely sure that trends relating to the time of day were not obscured by averaging these data from the nine subjects, measurements for CPO (Figure 3.1), CO (Figure 3.2) and MAP (Figure 3.3) were examined within each individual subject. No consistent trends were evident when comparing the data obtained in the morning or afternoon trials.

The lack of significant changes determined between morning and afternoon trials for CPO_{max} were also evident in the measurement of maximal oxygen consumption ($\dot{V}O_{2\,max}$). The values attained in the morning (46.1 ± 1.8 ml/min/kg) and afternoon (45.0 ± 1.7 ml/min/kg) trials were not significantly different from each other. Furthermore, these values were not different from the initial $\dot{V}O_{2max}$ (45.1 ± 1.2 ml/min/kg) test performed a week prior to the start of the investigation. This also confirmed that all subjects exercised at their maximum when CPO_{max} was measured.

Collectively, these results indicate that CPO is not affected by the time of day at which it was measured. Therefore, CPO can be measured accurately and the results collected, at different times of day, from various subjects in cross-sectional studies averaged with confidence.

Table 3.1. The measurement of resting and maximal cardiac power and its component parts, during morning and afternoon trials.

	Time of Day		
	Morning	Afternoon	P Value
Heart Rate (b/m)			
At Rest	65 ± 3.3	66 ± 3.1	0.65
At Maximal Exercise	187 ± 2.5	188 ± 2.9	0.57
Stroke Volume (ml)			
At Rest	79.6 ± 4.8	84.8 ± 3.0	0.16
At Maximal Exercise	121.0 ± 6.9	120.1 ± 5.6	0.72
Cardiac Output (l/min)			
At Rest	5.1 ± 0.3	5.6 ± 0.3	0.26
At Maximal Exercise	22.6 ± 1.1	22.5 ± 0.9	0.83
Systolic Pressure (mm Hg)			
At Rest	117.2 ± 3.0	118.7 ± 2.3	0.58
At Maximal Exercise	191.0 ± 4.4	192.1 ± 5.2	0.70
Diastolic Pressure (mm Hg)			
At Rest	74.6 ± 2.1	69.8 ± 2.3	0.06
At Maximal Exercise	58.6 ± 2.5	56.8 ± 2.1	0.51
Mean Arterial Pressure (mm Hg)			
At Rest	92.1 ± 2.0	89.9 ± 1.4	0.49
At Maximal Exercise	111.2 ± 2.5	118.2 ± 3.0	0.21
Cardiac Power Output (Watts)			
At Rest	1.0 ± 0.1	1.1 ± 0.1	0.42
At Maximal Exercise	5.6 ± 0.3	5.7 ± 0.3	0.74
Cardiac Reserve (Watts)	4.6 ± 0.3	4.6 ± 0.3	0.93

Data presented as mean ± SEM, for n = 9. Morning measures were taken between 04:15 and 05:30, with afternoon measurements taken between 16:15 and 17:30. The morning and afternoon sessions were separated by at least two days to prevent any fatigue and tiredness.

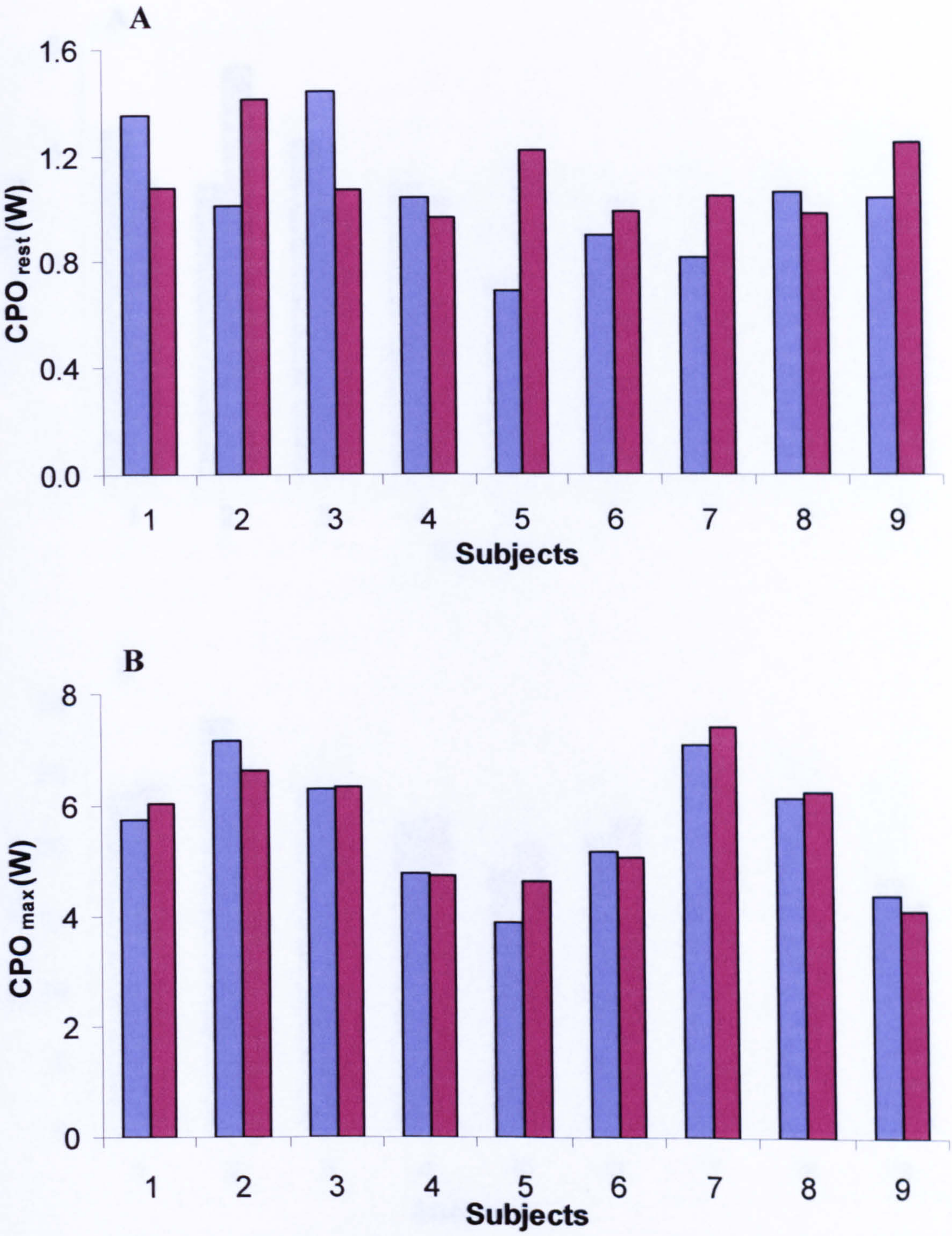


Figure 3.1. Cardiac power output (CPO) of individual subjects.

Measurements were taken at rest (A) and at maximal exercise (B), during the morning (■) and afternoon (■) trials.

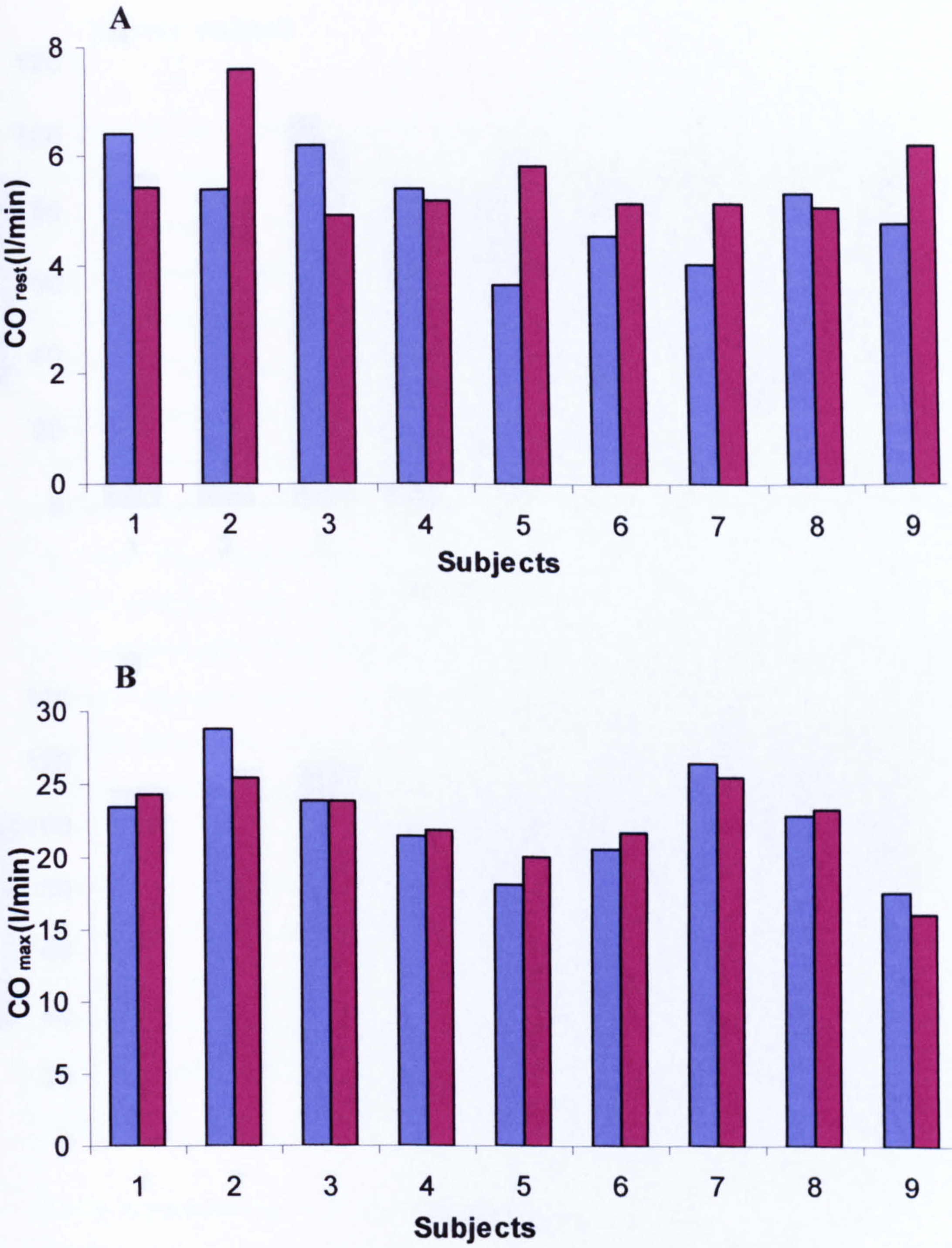


Figure 3.2. Cardiac output (CO) for individual subjects.

Measurements were made at rest (A) and at maximal exercise (B), during the morning (■) and afternoon (■) trials.

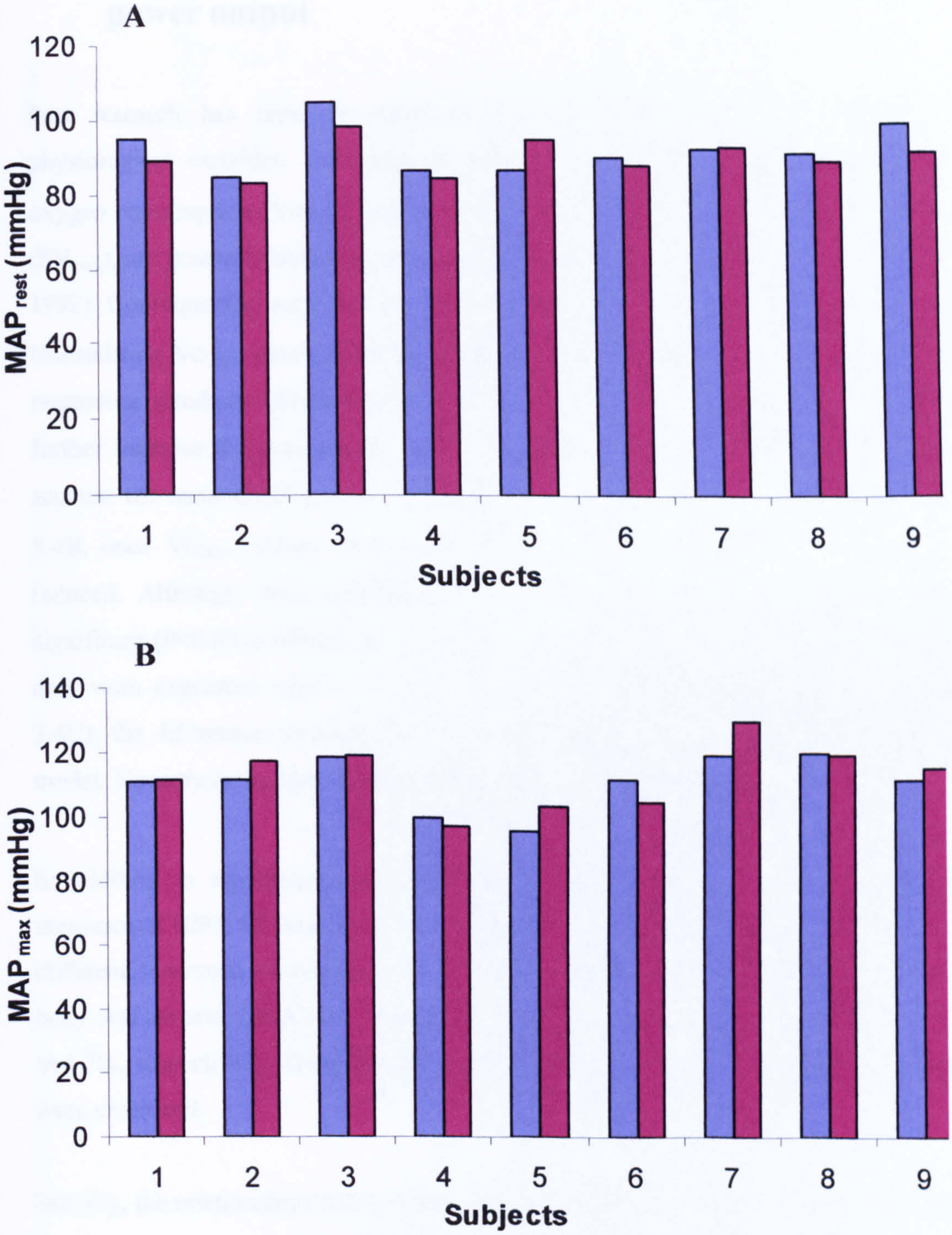


Figure 3.3. Mean arterial pressure (MAP) of individual subjects.

Measurements were taken at rest (A) and at maximal exercise (B), during the morning (■) and afternoon (■) trials.

3.2. The influence of body size on the measurement of cardiac power output

Past research has reported significant sex-related differences in a number of physiological variables. For example, when expressed in absolute terms maximal oxygen consumption ($\dot{V}O_{2max}$; Figure 3.4A), cardiac output (CO_{max}), and stroke volume (SV_{max}), are generally higher in men compared to women (Lakatta, 1993; Ogawa *et al.*, 1992). Consequently, such data are often expressed relative to a variable of body size. Normalising $\dot{V}O_{2max}$ data relative to body mass is a common procedure using the linear regression standards (RES) approach. However, scaling to fat free mass (FFM) can further improve the precision of the measurement because of its ability to take into account the metabolically active tissue (Toth *et al.*, 1994). As can be seen in Figure 3.4B, once $\dot{V}O_{2max}$ values were expressed relative to FFM the sex differences were reduced. Although, such normalisation reduces the differences between the sexes, significant ($P<0.001$) differences often still remain (Figure 3.4B). However, when such data were expressed relative to FFM using the allometric scaling approach (Figure 3.4C), the differences between the sexes were further reduced compared to the RES model. Nevertheless a significant ($P<0.01$) difference still remained.

In addition to significant sex-related differences for $\dot{V}O_{2max}$, resting and maximal measures of CPO, CO and SV (Table 3.2) were also found to be significantly ($P<0.05$) different. However, on average men had a larger body mass (BM), fat free mass (FFM), body surface area (BSA) and were taller, compared to the women by 24%, 28%, 15% and 7%, respectively. Therefore, the relationships between CPO and body dimensions were examined.

Initially, the relationships between body size and variables of CPO, for male and female data combined, were investigated. The results revealed highly significant ($P<0.01$) positive Pearson's correlations (r) with all variables of CPO and body dimensions (Table 3.3). However, FFM presented the strongest correlations, with CPO_{rest} ($r = 0.52$), CPO_{max} ($r = 0.75$) and CR ($r = 0.71$), compared to the other body dimensions.

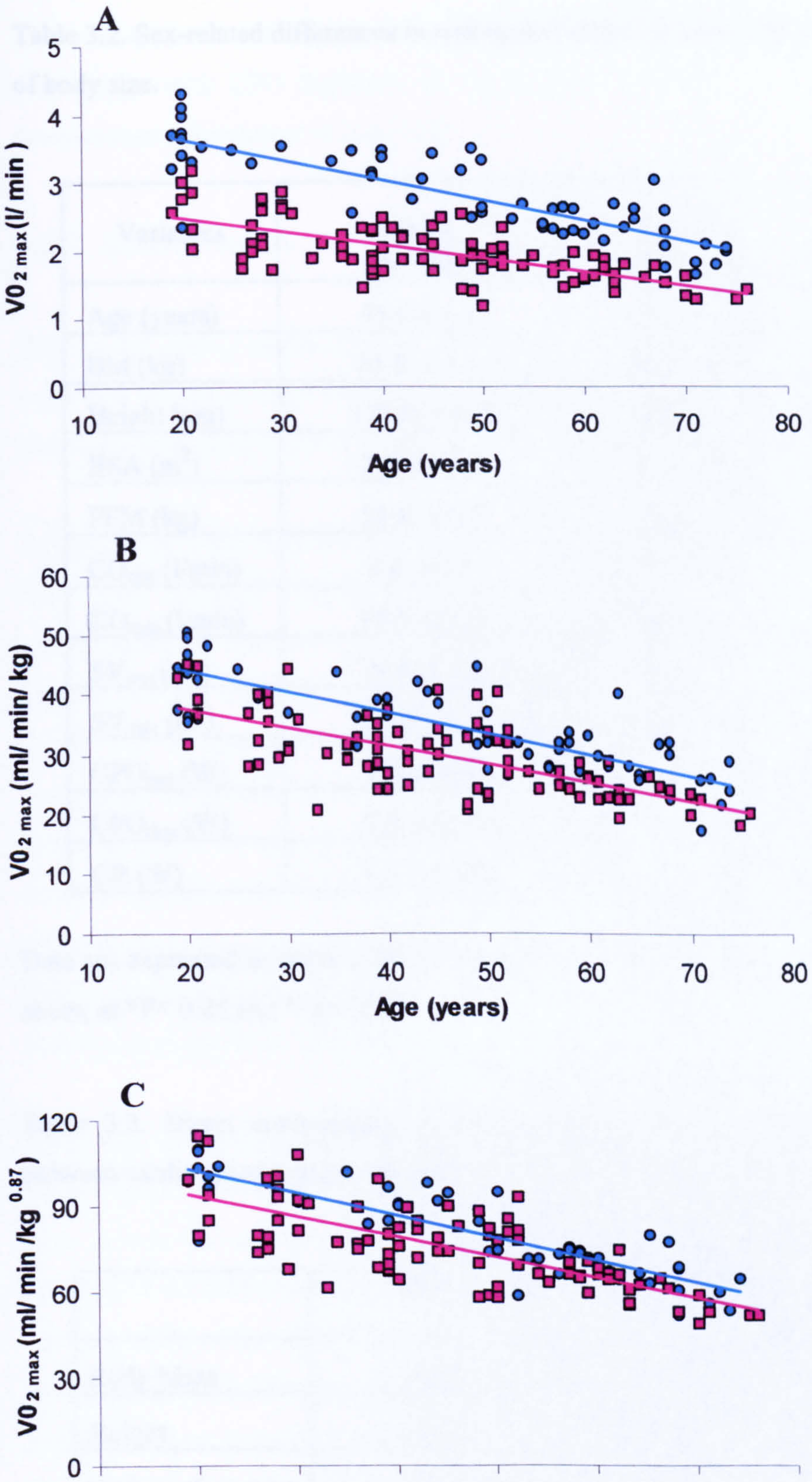


Figure 3.4. Age-and sex-related differences in maximal oxygen consumption.

Male (●) and female (■) measurements of $\dot{V}O_{2max}$ are expressed as absolute values (A), relative to fat free mass (FFM) using the linear regression standards approach (B), and relative to FFM^b using the allometric approach (C). n = 60 male and 89 women.

Table 3.2. Sex-related differences in resting and maximal haemodynamics and variables of body size.

Variables	Males (n = 88)	Females (n = 103)	% difference of women relative to men
Age (years)	45.4 ± 1.8	44.3 ± 1.4	-2
BM (kg)	81.5 ± 1.1	66.9 ± 1.0	-18*
Height (cm)	175.9 ± 0.7	164.0 ± 0.6	-7*
BSA (m^2)	2.0 ± 0.02	1.7 ± 0.01	-15*
FFM (kg)	59.6 ± 0.7	43.0 ± 0.5	-28*
CO_{rest} (l/min)	4.8 ± 0.1	3.8 ± 0.1	-21**
CO_{max} (l/min)	19.6 ± 0.3	15.1 ± 0.2	-23**
SV_{rest} (ml)	74.0 ± 1.9	57.5 ± 1.4	-22**
SV_{max} (ml)	114.2 ± 1.6	88.9 ± 1.3	-22**
CPO_{rest} (W)	1.0 ± 0.02	0.8 ± 0.02	-20*
CPO_{max} (W)	5.3 ± 0.09	4.0 ± 0.06	-25*
CR (W)	4.3 ± 0.08	3.2 ± 0.06	-26*

Data are expressed as mean ± SEM for n = 191. Significant difference between the two sexes, at *P< 0.05 and **P< 0.001.

Table 3.3. Direct comparisons of the correlation coefficients for all relationships between cardiac power and body size.

	CPO_{rest}	CPO_{max}	CR
Body Mass	0.43*	0.59*	0.55*
Height	0.41*	0.61*	0.58*
Body surface area	0.46*	0.65*	0.61*
Fat free mass	0.52*	0.75*	0.71*

Significant Pearson's correlations at *P<0.01. Male and female data are pooled together; n = 191.

These sex-related differences in body size and the associated highly significant correlations with CPO highlight the importance of scaling to provide meaningful comparisons independent of body-size.

3.2.1. Scaling models

The correct scaling model needs to be identified prior to determining which variable of body size should be used for scaling. This is to avoid the wrong scaling model being adopted thus leading to potential errors. This is highlighted below.

To determine if the ratio standard (RS) model correctly partitions out the influence of body size, linearity checks were performed. The special circumstance for RS normalisation of linearity and zero intercept was not satisfied for variables of CPO relative to body mass (BM), height (HT), body surface area (BSA) or fat free mass (FFM), as the ratio of the coefficient of variation (CV*x*/CV*y*) did not equal the correlation coefficient (*r,X,Y*) (Table 3.4). In some circumstances the differences between CV*x*/CV*y* and *r*,X,Y were as great as 0.37. However, a close similarity between the ratio of CV and r was noted between BSA and CPO_{rest} as the difference between the values were equal to 0.05 (i.e. 0.46-0.41; Table 3.4). Therefore, except for CPO_{rest} correlated to BSA, the use of the RS method for scaling CPO would distort the data in this study. This would probably lead to erroneous interpretations of these data.

Compared to the ratio standards (RS) approach, the linear regression standards (RES) scaling model improved the fit to these data and resulted in reductions in the residual error around the regression lines (Figures 3.5-3.7). However, positive intercepts were common in the RES model, as illustrated in Figure 3.5A. This suggests that for zero BM a resting CPO value of 0.36 W exists. Clearly, this is physiologically impossible. In contrast, Figures 3.5B-3.5C presented negative intercepts. Therefore extension of these regression lines should be avoided. The discrepancy between the RES line of best fit and the RS line of fit are highlighted in Figures 3.5-3.7. The occurrence of positive and negative intercepts further illustrates that the assumption of the RS model, with a zero intercept on the y-axis, has been violated. In addition, significant ($P<0.05$) correlations were calculated between the absolute residuals and the independent variables for all of

Table 3.4. Direct comparisons of the correlation coefficient (r) and the ratio of coefficient of variation (CV) data (*r,X,Y* : CV*x*/CV*y*).

	CPO_{rest}		CPO_{max}		CR	
	CV	r	CV	r	CV	r
Body Mass	0.71	0.43	0.80	0.59	0.72	0.55
Height	0.21	0.41	0.24	0.61	0.21	0.58
Body surface area	**0.41**	**0.46**	0.46	0.65	0.42	0.61
Fat free mass	0.84	0.52	0.94	0.75	0.64	0.71

Ratios are shown in **bold** if the difference between the values are ≤0.05. Based on same data (n = 191) as Table 3.3.

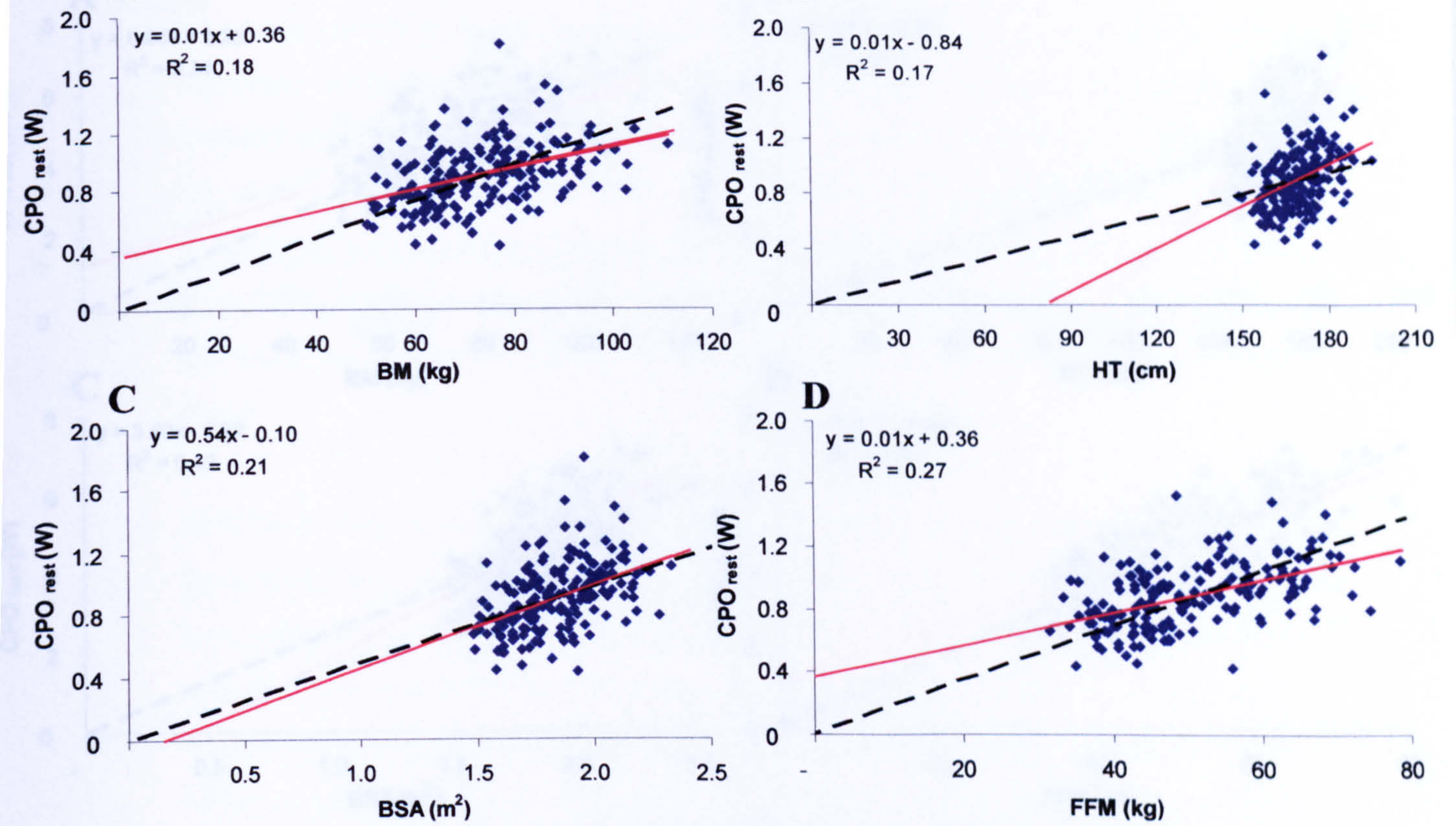


Figure 3.5. The relationship of resting cardiac power output to variables of body dimensions.

The variables of body dimensions are (A) body mass (BM), (B) height (HT), (C) body surface area (BSA) and (D) fat free mass (FFM) for all male and female data combined (n = 191). Superimposed on the figures are the dashed line ($y = bx$) with zero intercept and the solid lines of best fit ($y = a + bx + \varepsilon$), representing the ratio standard (RS) and linear regression standards (RES) scaling models, respectively.

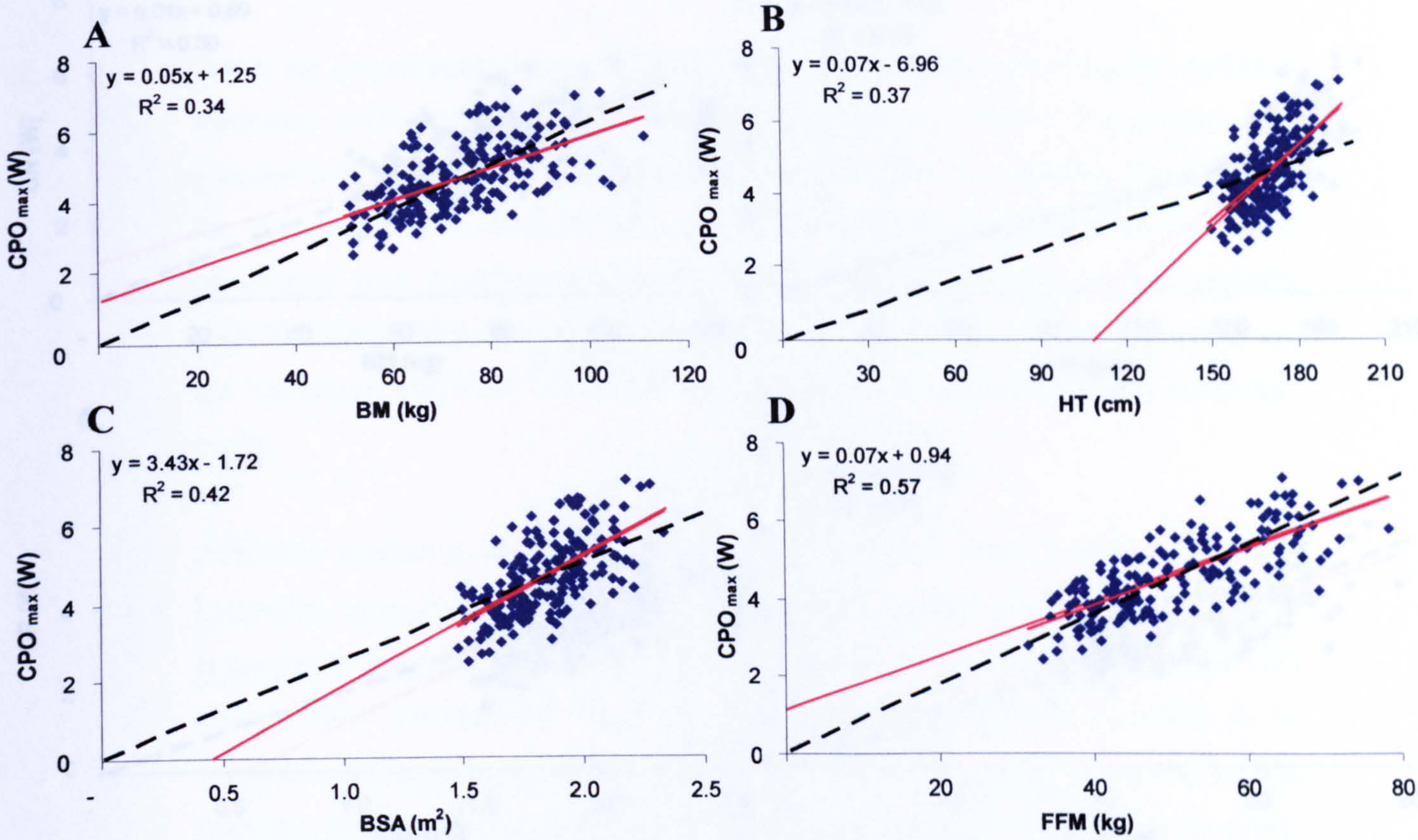


Figure 3.6. The relationship of maximal cardiac power output to variables of body dimensions.

The variables of body dimensions are (A) body mass (BM), (B) height (HT), (C) body surface area (BSA) and (D) fat free mass (FFM) for all male and female data combined (n = 191). Superimposed on the figures are the dashed line ($y = bx$) with zero intercept and the solid lines of best fit ($y = a + bx + \varepsilon$), representing the ratio standard (RS) and linear regression standards (RES) scaling models, respectively.

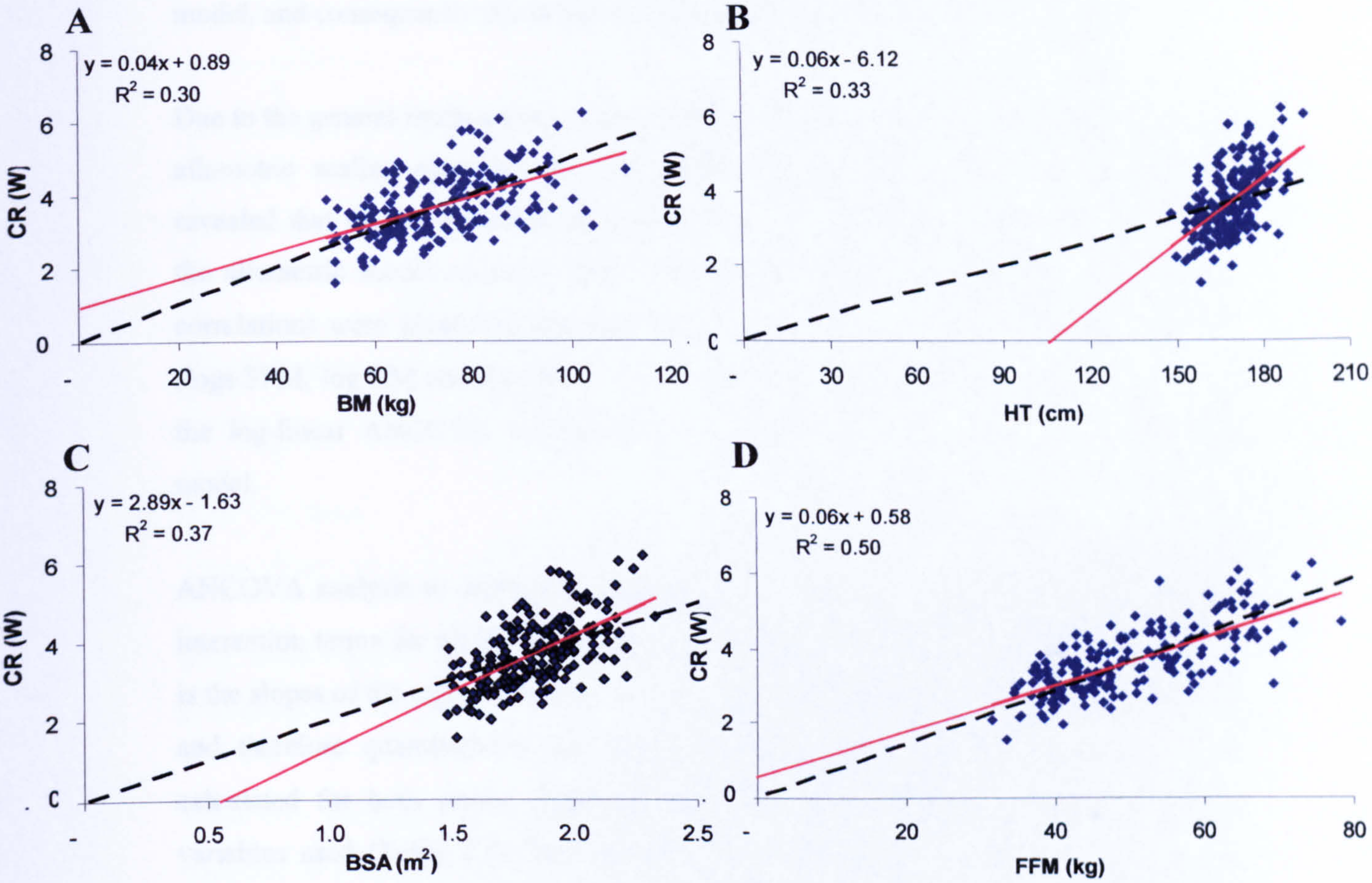


Figure 3.7. The relationship of cardiac reserve to variables of body dimensions.

The variables of body dimensions are (A) body mass (BM), (B) height (HT), (C) body surface area (BSA) and (D) fat free mass (FFM) for all male and female data combined (n = 191). Superimposed on the figures are the dashed line ($y = bx$) with zero intercept and the solid lines of best fit ($y = a + bx + \varepsilon$), representing the ratio standard (RS) and linear regression standards (RES) scaling models, respectively.

the RES model relationship analysed. This indicated that the error around the regression line was not constant, and therefore the assumption of homoscedasticity had not been satisfied. Rather the error around the regression line increased as the independent variable increased (i.e. heteroscedasticity). This is an important assumption of the RES model, and consequently this model should not be used for the scaling of CPO.

Due to the general inadequacies of the RS and RES approaches to scaling, the log-linear allometric scaling approach was examined. Kolmogorov-Smirnov one-sample tests revealed that the log-transformed dependent and independent variables, together with the allometric model residuals, were normally distributed. In addition, no significant correlations were identified between the absolute residuals and the predictor variable (logs FFM, log BM and log BSA). The absence of correlations between residuals from the log-linear ANCOVA confirmed the appropriate fit provided by the allometric model.

ANCOVA analysis to determine commonality of slopes produced non-significant sex-interaction terms for all body-size-CPO relationships, except those involving HT. That is the slopes of the regression lines for male and female data were similar (apart for HT) and therefore quantitatively the same, thereby allowing common exponents to be calculated for both sexes. However, the exponents will change depending on the variables used (Table 3.5). This would allow direct group comparisons to be made. However, because the ANCOVA results indicated that the relationship of CPO and HT were quantitatively different when comparing male and female data (i.e. a significant sex interaction term was established), different male and female exponents would be required. These individual exponents would preclude intergroup comparisons to be made; therefore HT was excluded from further data analysis.

By using the following equation [(CPO/BM^{b}) / BM = zero], it was possible to check whether the allometric models produced dimensionless physiological variables. The scaling of cardiac power to FFM^{b} resulted in non-significant Pearson's correlations (Figure 3.8). Conversely, significant ($P<0.01$) correlations remained when CPO was scaled to either BM^{b} or BSA^{b}. However, when men and women were analysed separately (but with the same exponent b) non-significant correlations were calculated for all variables of CPO relative to body dimensions (Table 3.6). In addition,

Table 3.5. Common group allometric exponents ***b***, for describing the relationships between variables of cardiac power and body dimensions.

	CPO_{rest}	CPO_{max}	CR
Body mass	0.33 ± 0.11 (0.11-0.54)	0.41 ± 0.08 (0.25-0.57)	0.44 ± 0.10 (0.25-0.62)
Body surface area	0.60 ± 0.21 (0.20-1.01)	0.81 ± 0.15 (0.52-1.10)	0.87 ± 0.18 (0.53-1.22)
Fat free mass	0.47 ± 0.13 (0.22-0.73)	0.71 ± 0.09 (0.53-0.89)	0.79 ± 0.11 (0.57-1.00)

Data are presented as mean exponents b ± SEM, with 95% confidence intervals in parenthesis for combined male and female data.

Table 3.6. Pearson's correlation check for the normalisation of cardiac power to variables of body dimensions for men and women.

	CPO scaled to the appropriate ***b*** exponent for body size					
	CPO_{rest}		CPO_{max}		CR	
	Male	Female	Male	Female	Male	Female
Body mass	-0.13	0.09	-0.08	0.03	-0.05	0.02
Body surface area	-0.09	0.06	-0.07	0.05	-0.06	0.03
Fat free mass	-0.05	-0.01	-0.01	-0.02	-0.01	-0.02

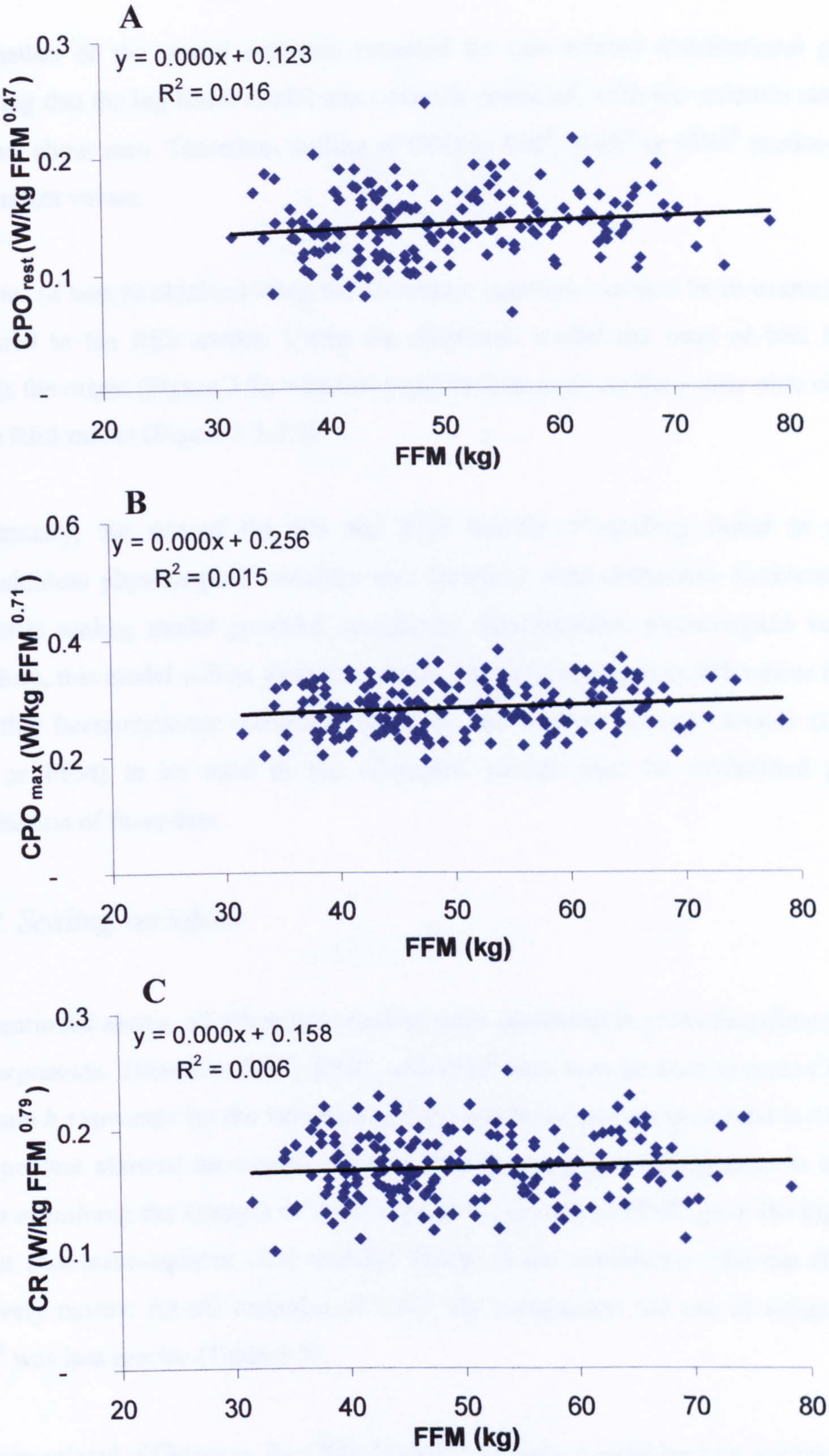


Figure 3.8. The relationship of scaled cardiac power output (CPO/FFM^{b}) correlated to fat free mass.

The variables of cardiac power were CPO_{rest} (A), CPO_{max} (B), and CR (C) for combined male and female data.

examination of the model residuals revealed no size related distributional pattern, indicating that the log-linear model was correctly specified, with the residuals randomly scattered about zero. Therefore, scaling of CPO to BM^b, BSA^b or FFM^b produced size independent values.

The lines of best fit obtained using the allometric equation can now be re-examined and compared to the RES model. Using the allometric model the lines of best fit pass through the origin (Figure 3.9), whereas negative intercepts on the y-axis were obtained for the RES model (Figure 3.5-3.7).

In summary, the use of the RS and RES models of scaling, failed to provide dimensionless physiological variables and therefore were dismissed. Conversely, the allometric scaling model provided completely dimensionless physiological variables. Therefore, this model will be used to examine inter-and intra-group differences for CPO and other haemodynamic variables. However, the optimal scaling variable (i.e. BM, BSA or FFM) to be used in the allometric model must be established prior to examination of these data.

3.2.2. Scaling variables

As mentioned above, all allometric models were successful in providing dimensionless size exponents. Therefore, BM^b, BSA^b, and FFM^b may now be used to scale CPO. The common ***b*** exponents for the variables of CPO and body size are presented in Table 3.7. This process allowed the comparisons of data from intra-or inter-groups to be made. When examining the strength of the ***b*** exponents, scaling to FFM^b gave the highest R^2, lowest root-mean-squares error and the width of the confidence intervals (CI) were relatively narrow for all variables of CPO. By comparison the use of either BM^b or BSA^b was less precise (Table 3.7).

The sex-related differences for CPO (Table 3.2) were re-analysed by scaling CPO to either BM^b, BSA^b or FFM^b to provide data that were body size-independent (Table 3.8). For all values of CPO, highly significant ($P<0.001$) sex-related differences remained once scaled for BM^b or BSA^b (Table 3.8). Furthermore, significant ($P<0.05$) differences

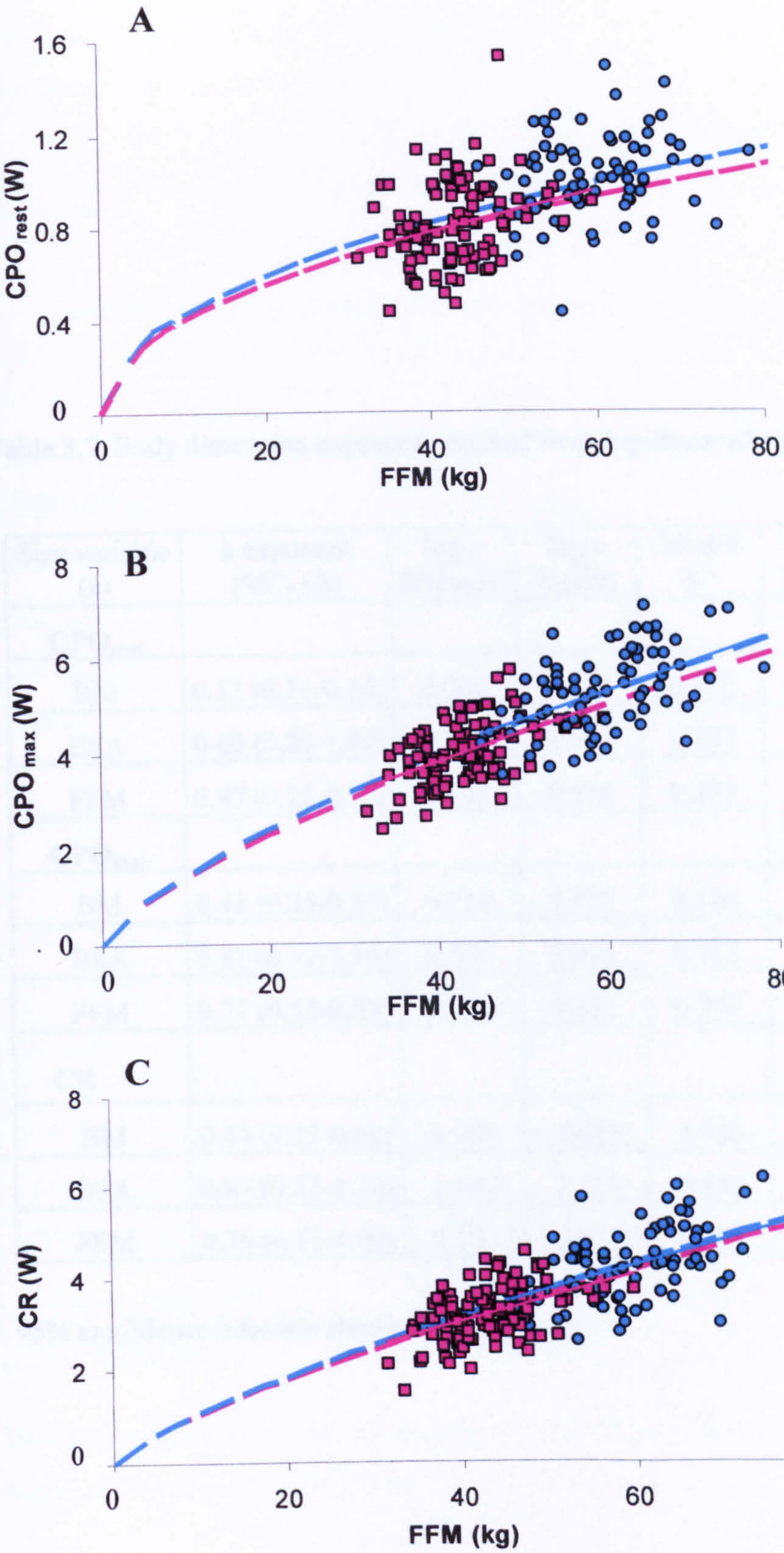


Figure 3.9. The allometric relationship between cardiac power and fat free mass.

The variables of cardiac power output were CPO_{rest} (A), CPO_{max} (B), and CR (C) for men (●) and women (■). Superimposed on these data are the allometric lines of best fit passing through the origin for men (—) and women (—).

Table 3.7. Body dimension exponents derived from log-linear allometric models.

Size variable (x)	b exponent (95% CI)	log a (Female)	log a (Male)	Model R^2	Model RMSE	P-value of size exponent
CPO_{rest}						
BM	0.33 (0.11-0.54)	0.201	0.239	0.278	0.043	0.001
BSA	0.60 (0.20-1.01)	0.566	0.664	0.277	0.043	0.001
FFM	0.47 (0.22-0.73)	0.143	0.134	0.275	0.040	0.001
CPO_{max}						
BM	0.41 (0.25-0.57)	0.714	0.872	0.504	0.023	0.001
BSA	0.81 (0.52-1.10)	2.532	3.013	0.513	0.022	0.001
FFM	0.71 (0.53-0.89)	0.272	0.285	0.567	0.020	0.001
CR						
BM	0.44 (0.25-0.62)	0.505	0.620	0.435	0.032	0.001
BSA	0.87 (0.53-1.22)	1.946	2.319	0.445	0.032	0.001
FFM	0.79 (0.57-1.00)	0.164	0.170	0.501	0.030	0.001

95% confidence intervals shown in parenthesis.

Table 3.8. Sex-related comparisons of cardiac power output once normalised.

	Males	Females	% difference of women relative To men
Age (years)	45.4 ± 1.8	44.3 ± 1.4	-2
Absolute data			
CPO_{rest} (W)	1.0 ± 0.02	8.0 ± 0.02	-20*
CPO_{max} (W)	5.3 ± 0.09	4.0 ± 0.06	-25*
CR (W)	4.3 ± 0.08	3.2 ± 0.06	-26*
CPO scaled to BM^b			
CPO_{rest} (W/kg BM $^{0.33}$)	0.24 ± 0.01	0.21 ± 0.01	-13**
CPO_{max} (W/kg BM $^{0.41}$)	0.88 ± 0.01	0.72 ± 0.01	-18**
CR (W/kg BM $^{0.44}$)	0.63 ± 0.01	0.51 ± 0.01	-19**
CPO scaled to BSA^b			
CPO_{rest} (W/m^2 BSA $^{0.60}$)	0.7 ± 0.01	0.6 ± 0.01	-14**
CPO_{max} (W/m^2 BSA $^{0.81}$)	3.1 ± 0.05	2.6 ± 0.04	-16**
CR (W/m^2 BSA $^{0.87}$)	2.4 ± 0.04	2.0 ± 0.03	-17**
CPO scaled to FFM^b			
CPO_{rest} (W/kg FFM $^{0.47}$)	0.15 ± 0.003	0.14 ± 0.003	-7*
CPO_{max} (W/kg FFM $^{0.71}$)	0.29 ± 0.004	0.27 ± 0.004	-7*
CR (W/kg FFM $^{0.79}$)	0.17 ± 0.003	0.17 ± 0.003	0

Data are expressed as means ± SEM for n = 191. Significant difference between the two sexes, at *P< 0.05 and **P< 0.001

remained once CPO_{rest} (7%) and CPO_{max} (7%) were scaled to FFM^{b}, with males presenting with higher values compared to females. Nevertheless, the percentage differences for CPO_{rest} and CPO_{max} between sexes were considerably reduced (i.e. previously 22% and 25%, respectively). Non-significant differences were obtained between the sexes for values of CR when scaled to FFM^{b}.

These results highlight the importance of scaling CPO while using the appropriate scaling model and body dimension. Therefore, the evaluation of the age, sex and fitness-related changes in CPO (section 3.3) will be examined relative to FFM^{b}. Similarly, other haemodynamic variables, i.e. CO and SV, will also be examined in this way.

3.3. Age-related changes in overall cardiac function

Past research examining the relationship between ageing and cardiac function has tended to either neglect the measurement of the overall functional capacity of the heart or have failed to take into account the confounding influences of body size, cardiovascular disease and/or fitness levels of the subjects. The following studies examine the age-related changes in overall cardiac function by measuring both the pressure and flow generating capacities of the heart, both at rest and at maximal exercise. In an attempt to remove the confounding influence of cardiovascular diseases, only healthy men and women were selected for these studies. In addition, subjects were separated into specific fitness groups (sedentary, active and endurance trained athletes). Furthermore, the influences of body size on measures of cardiac function were also accounted for.

3.3.1. The changes in body composition and cardiac function due to age in sedentary men and women

To examine the age-and sex-related effects on CPO, sixty men and eighty-nine women, who were healthy and sedentary were investigated. The female subjects consisted of fifty-two pre-menopausal, thirty-two post-menopausal, and five peri-menopausal women. The pre-menopausal women consisted of a variety of pill and non-pill users. Furthermore, the post-menopausal women consisted of a variety of women who were taking hormone replacement therapy and those who were not.

(A) Body Composition

Between 20 and 75 years of age, the sedentary men had significantly ($P<0.001$) 23% greater body mass (BM) and 37% greater fat free mass (FFM) values compared to sedentary women (Figures 3.10A and 3.10B). Fat mass (FM) was found to be similar between men and women (Figure 3.10C). However, the percentage of body fat was found to be significantly ($P<0.001$) greater (32%) in the sedentary women compared to their male equivalents (Figure 3.10D), this being attributed to a greater BM in the men.

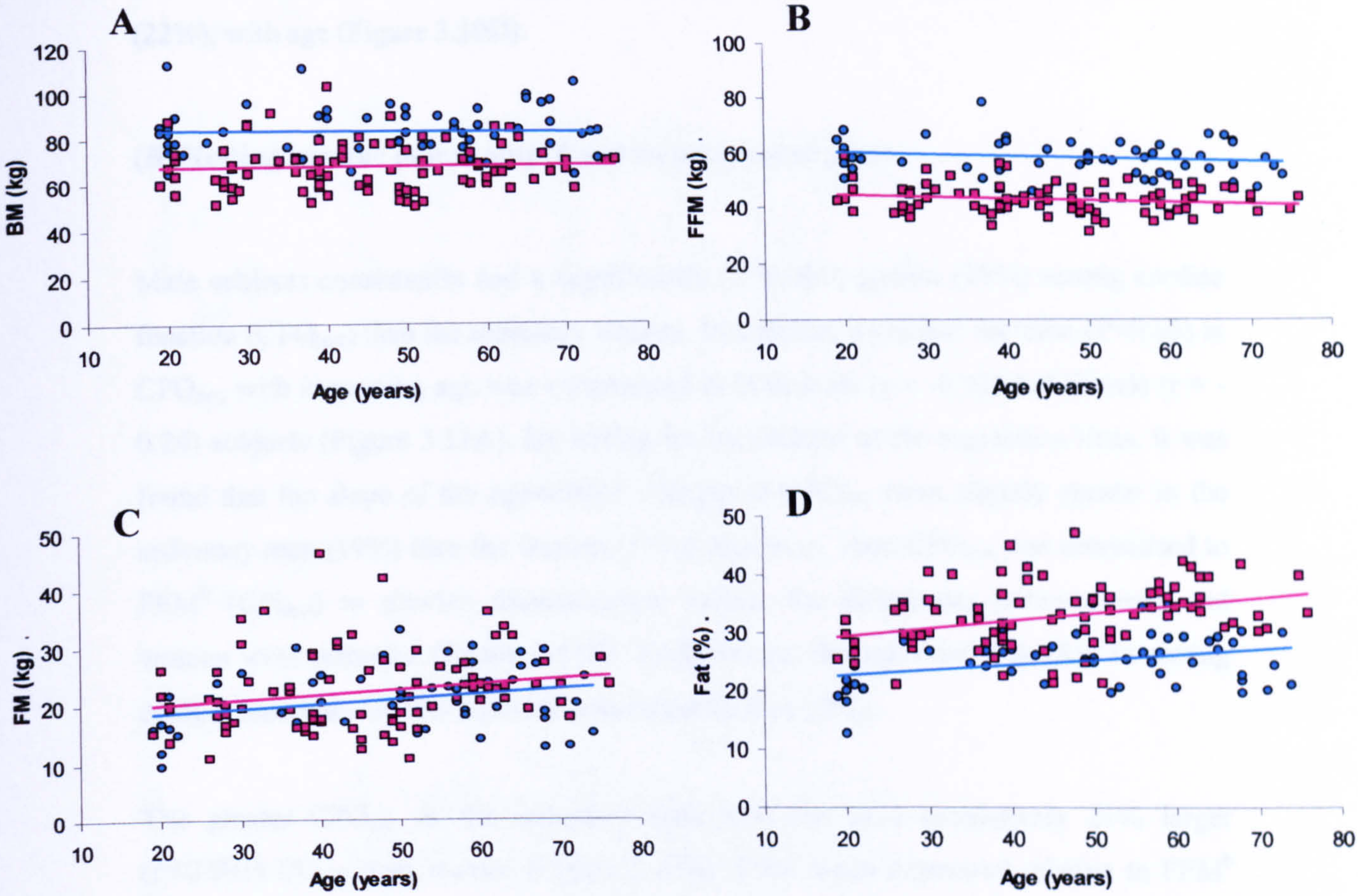


Figure 3.10. Changes in body composition in relation to age and sex.

(A) Body mass (BM), (B) fat free mass (FFM), (C) fat mass (FM) and (D) the percentage of body fat (fat) are shown for 60 sedentary men (●) and 89 women (■). The lines of best fit for men (—) and women (—) are shown. The same subjects were used for all subsequent figures.

Examination of the body compositional changes in association with increasing age indicated that BM (Figure 3.10A) did not change in both men and women. Furthermore, a non-significant decline of 6 to 7% in FFM was found with increasing age (Figure 3.10B). Due to the scatter of these data, FM was not found to be significantly different (Figure 3.10C) with age in either sex, despite a 21% increase. However, significant ($P<0.05$) increases in the percentage of fat were found in both men (20%) and women (22%), with age (Figure 3.10D).

(B) Resting cardiac power output and its component parts

Male subjects consistently had a significantly ($P<0.001$) greater (19%) resting cardiac function (CPO_{rest}) than the sedentary women. In addition, a gradual decrease ($P<0.05$) in CPO_{rest} with increasing age was experienced in both male ($r = -0.32$) and female ($r = -0.24$) subjects (Figure 3.11A). By testing for parallelism of the regression lines, it was found that the slope of the age-related changes in CPO_{rest} were slightly greater in the sedentary men (19%) than the women (17%). However, once CPO_{rest} was normalised to FFM^b (CPi_{rest}) to provide dimensionless values, the differences between men and women were removed (Figure 3.11B). Furthermore, the age-related decline in resting cardiac function was also removed once expressed as CPi_{rest}.

The greater CPO_{rest} in the sedentary men was due to a consistently 21% larger ($P<0.001$) CO_{rest} than women (Figure 3.12A). Even when expressed relative to FFM^b (Ci_{rest}) the significant sex-related difference remained (3.12B). The decline in CPO_{rest}, with age, was attributed to significant ($P<0.001$) decreases in CO_{rest} in both men (26%; $r = -0.55$) and women (27%; $r = -0.45$). Despite similar percentage decreases between 20 to 75 years in men and women, analysis of the slopes of the regression lines indicated that the decline in CO_{rest} was greater in the sedentary men than women (Figure 3.12A). Furthermore this age-related decline in CO_{rest} was still evident once scaled for FFM^b (Figure 3.12B).

Upon attempting to explain the sex-and age-related differences in CO_{rest}, its component parts were examined i.e. SV and HR. The sex-related differences in CO_{rest} were attributed to significantly ($P<0.01$) 23% greater resting stroke volumes (SV_{rest})

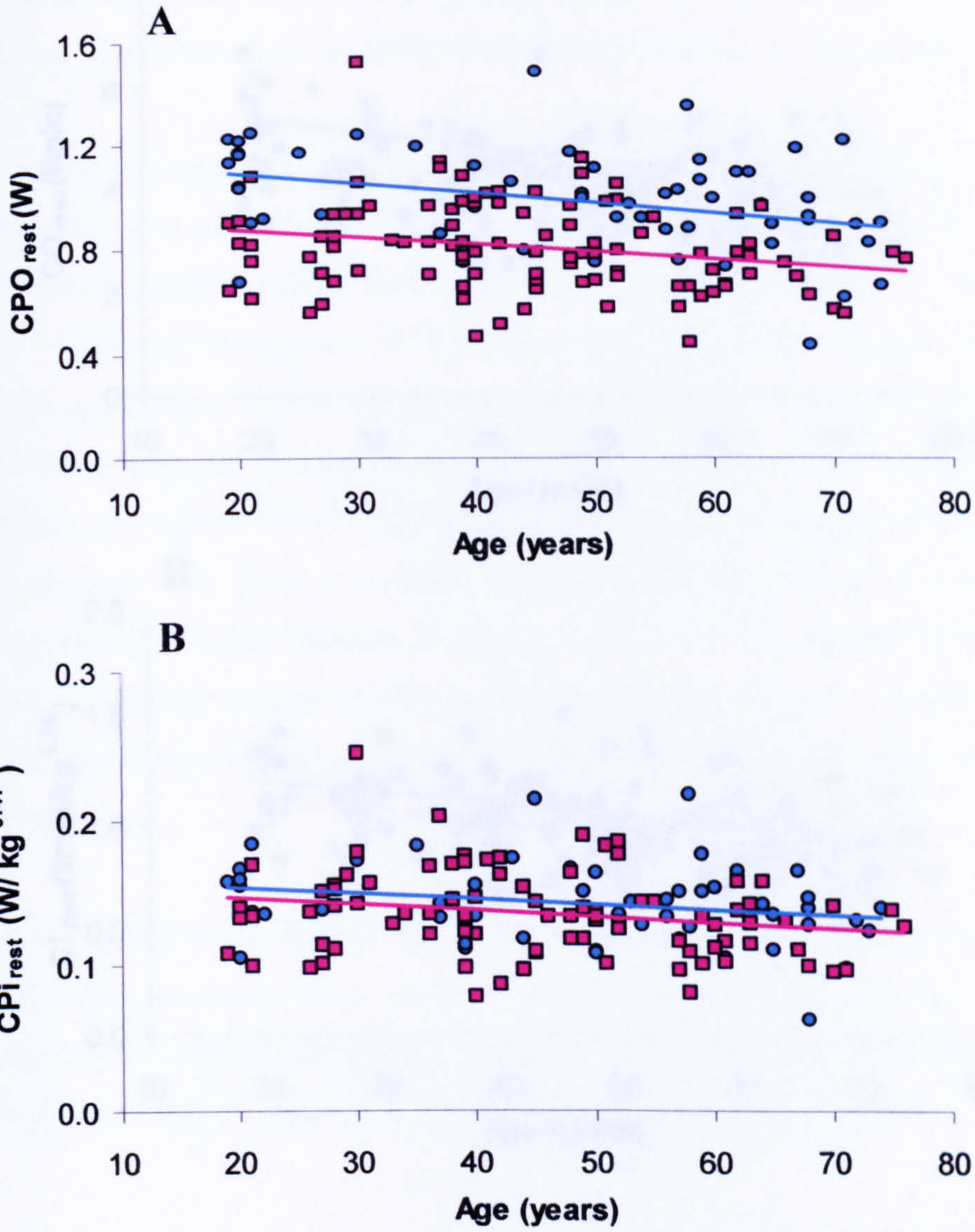


Figure 3.11. The relationships between age, sex and resting cardiac power.

Cardiac power output (A) and cardiac power index (B) are shown for sedentary men (●) and women (■). The lines of best fit for men (——) and women (——) are shown.

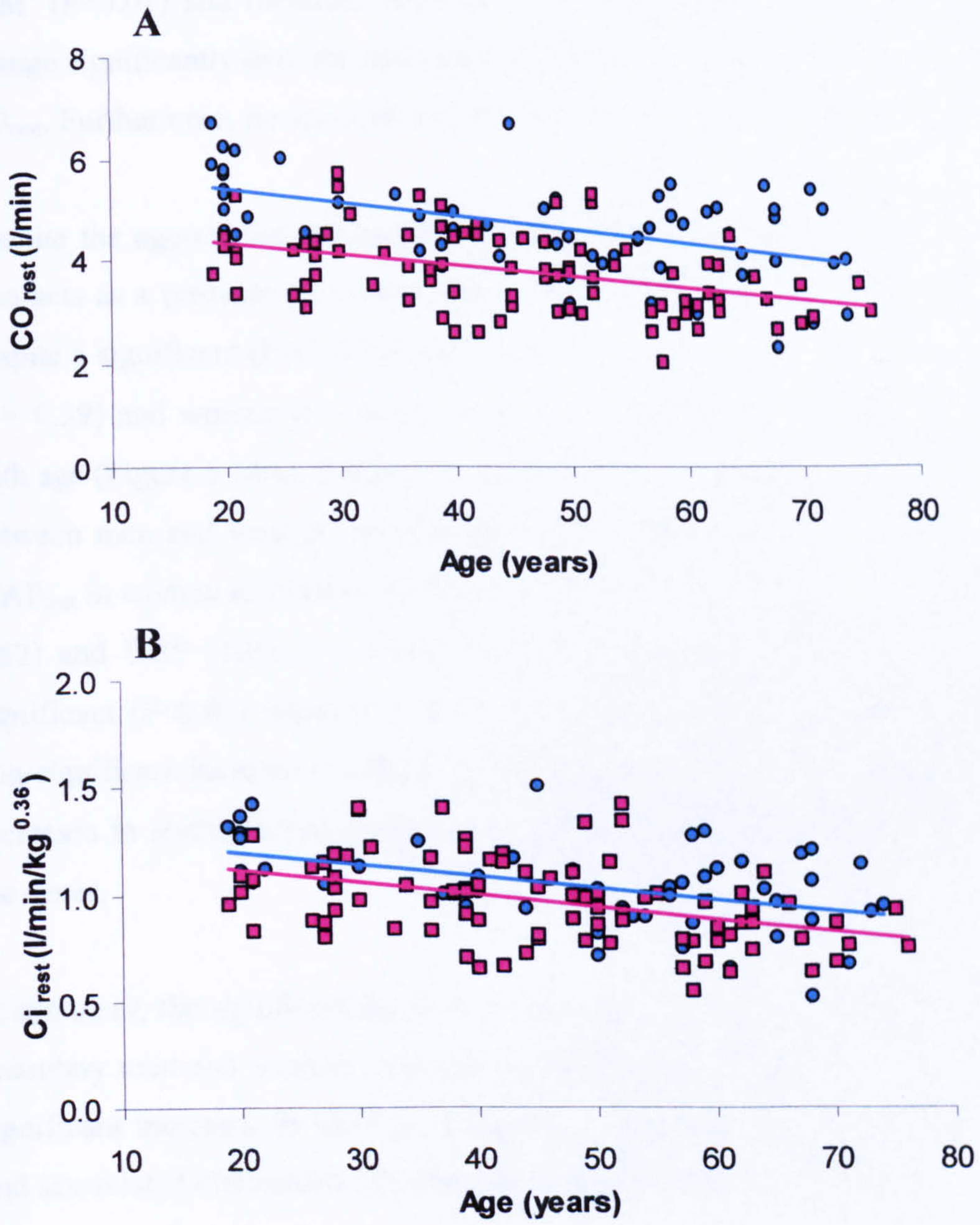


Figure 3.12. The relationship between age and resting cardiac output.

The physiological variables are cardiac output (A) and cardiac index (B) for sedentary men (●) and women (■). Superimposed on these data are the lines of best fit for men (——) and women (——).

in men than women (Figure 3.13A). However, once scaled to FFM^b this sex-difference was lost (Figure 3.13B). The age-related decline in CO_{rest} was due to a significant ($P<0.001$) decline in SV_{rest} in both men (24%; $r = -0.44$) and women (22%; $r = -0.28$) (Figure 3.13A). This age-related decline was also evident when SV_{rest} was scaled for FFM^b ($P<0.01$) and therefore contributed to the decline in Ci_{rest}. Resting HR did not change significantly over the age-range and therefore did not contribute to the decline in CO_{rest}. Furthermore, no sex-related differences in HR_{rest} were measured (Figure 3.13C).

Despite the age-related decline in the heart's ability to generate blood flow, the heart also acts as a pressure generator. The observed age-related decline in CPO_{rest} occurred despite a significant ($P<0.01$) increase in MAP_{rest} (Figure 3.14A) in both sedentary men ($r = 0.39$) and women ($r = 0.51$). Both sexes had similar increases (16%) in pressure with age (Figure 3.14A). Indeed, the changes in MAP_{rest} were not significantly different between men and women. When analysed in more detail, the age-related increases in MAP_{rest} in women resulted from significant ($P<0.01$) increases in resting SBP (22%; $r = 0.62$) and DBP (10%; $r = 0.36$) (Figures 3.14B and 3.14C). In contrast, in men a significant ($P<0.01$) increase in SBP_{rest} (13%; $r = 0.46$) together with a smaller (7%) non-significant increase in DBP_{rest} contributed to the increase in MAP_{rest}. Despite these increases in resting blood pressure, no significant differences were measured between the sexes.

In summary, the significant age-related decreases in resting cardiac function (CPO_{rest}) in sedentary men and women were due to significant declines in CO_{rest}. This was despite significant increases in MAP_{rest}. However, when CPO was adjusted to FFM^b the age- and sex-related differences in resting cardiac function were removed.

(C) Changes in resting systemic vascular resistance (SVR) with age and the differences between men and women.

Systemic vascular resistance, a surrogate of pump afterload, has an important role in influencing the performance of the heart. Age for age, the sedentary men had significantly ($P<0.001$) lower (~18%) resting SVR values compared to the women (Figure 3.15A). Both sexes experienced significant ($P<0.01$) increases in SVR_{rest} with

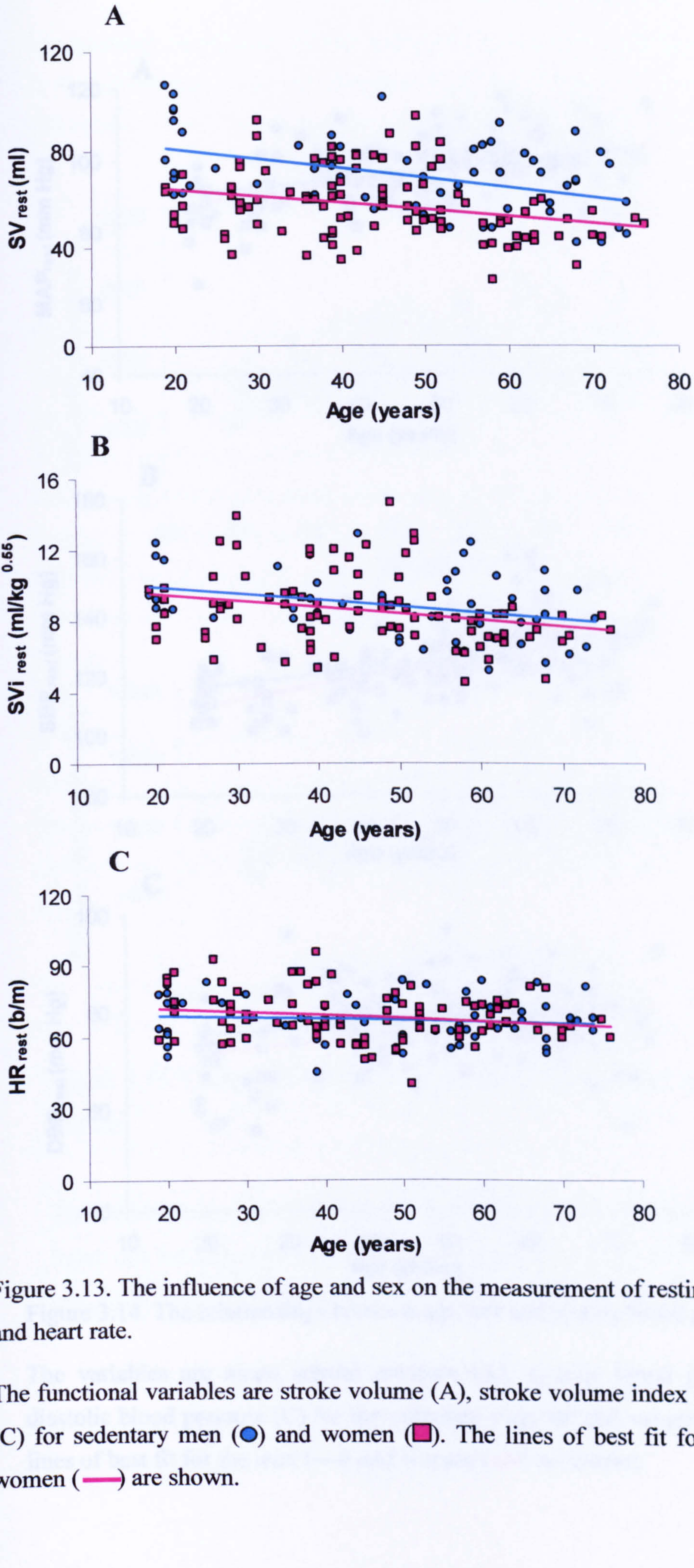


Figure 3.13. The influence of age and sex on the measurement of resting stroke volume and heart rate.

The functional variables are stroke volume (A), stroke volume index (B), and heart rate (C) for sedentary men (●) and women (■). The lines of best fit for men (——) and women (——) are shown.

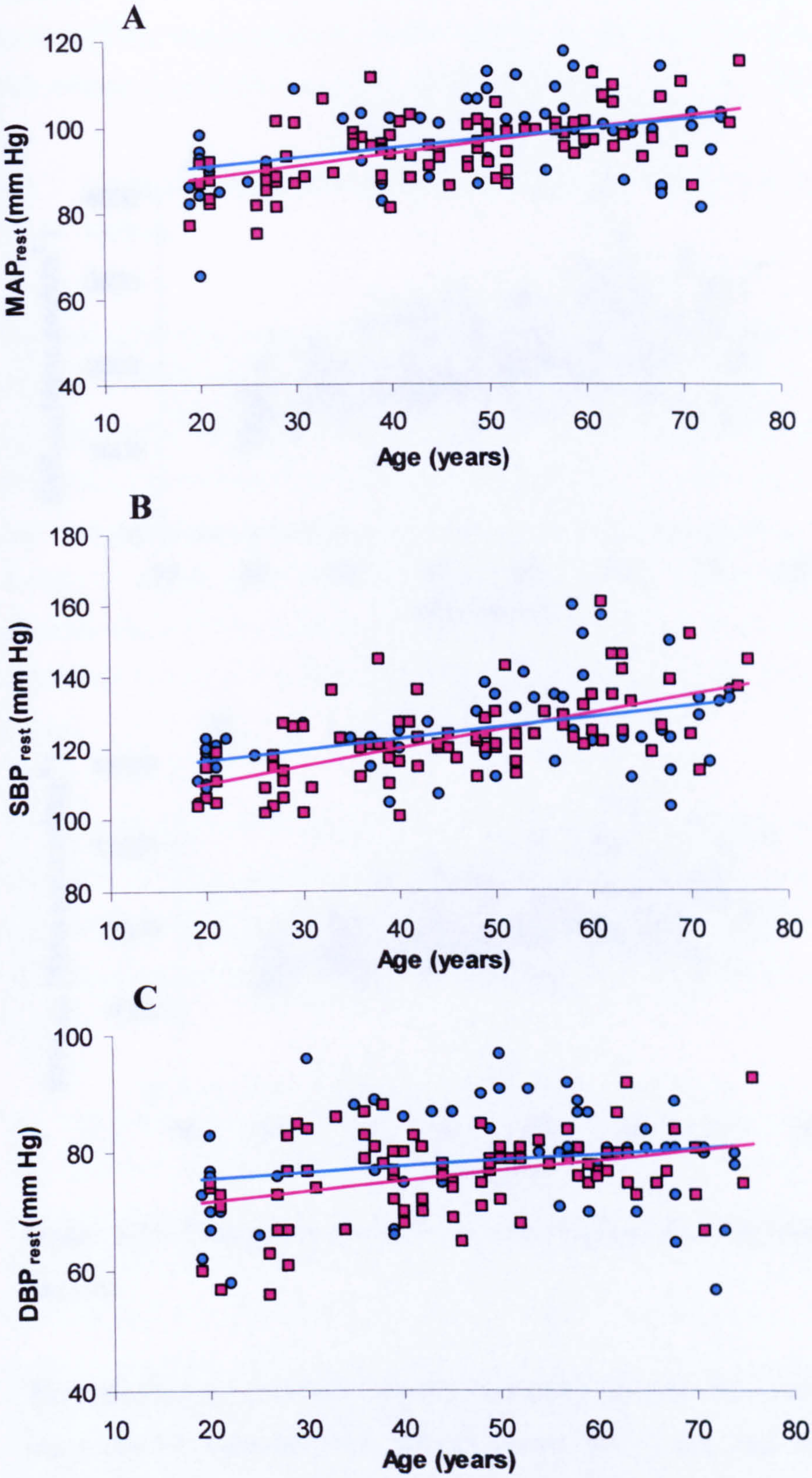


Figure 3.14. The relationships between age, sex and resting blood pressure.

The variables are mean arterial pressure (A), systolic blood pressure (B) and diastolic blood pressure (C) for the sedentary men (●) and women (■) at rest. The lines of best fit for the men (—) and women (—) are shown.

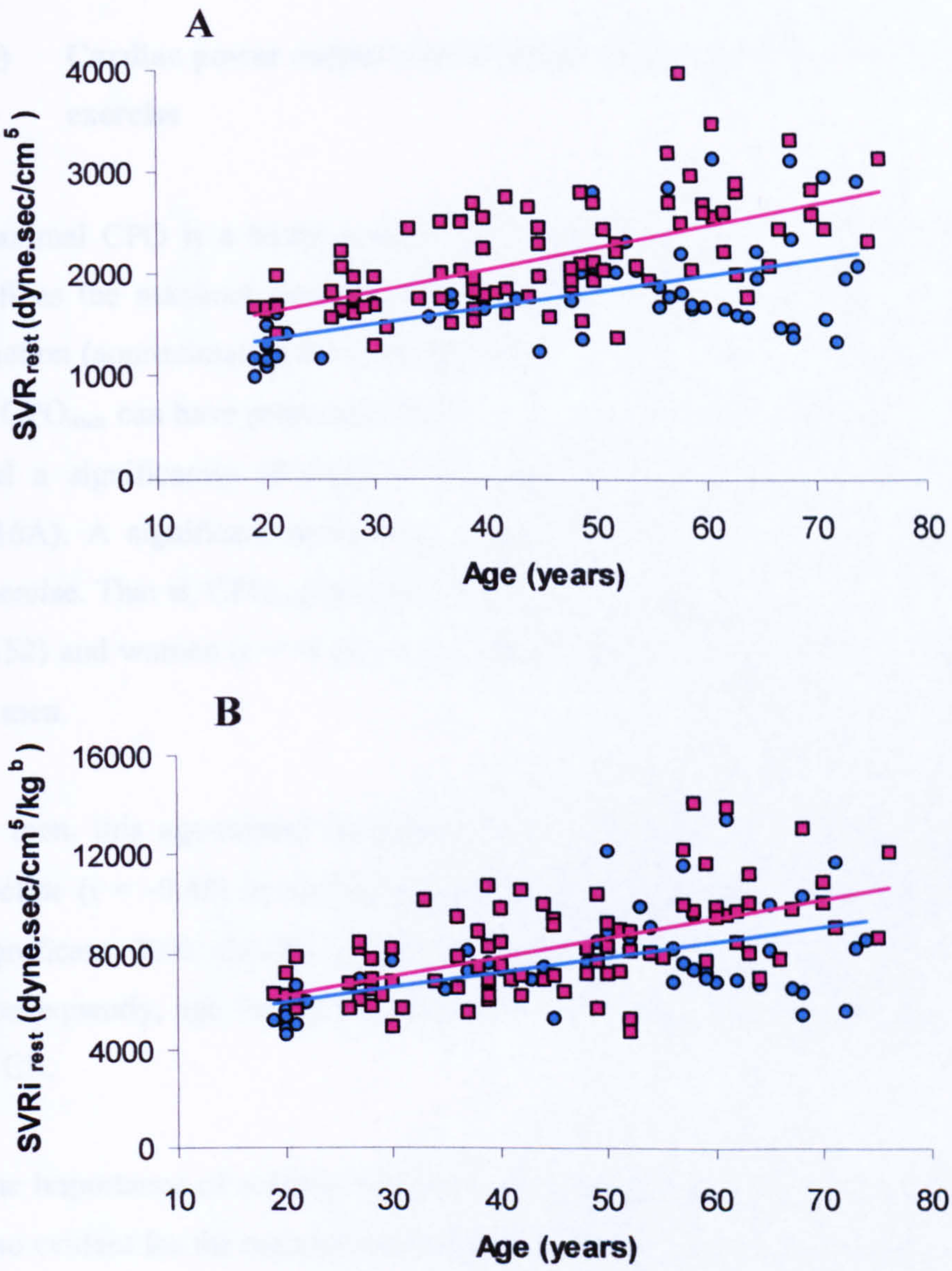


Figure 3.15. Changes in systemic vascular resistance at maximal exercise with age and sex.

The variables are systemic vascular resistance (A) and systemic vascular resistance index (B) for sedentary men (●) and women (■) at maximal exercise. The lines of best fit for men (—) and women (—) are superimposed on these data.

age, however the sedentary women expressed a greater rate of change (65%) compared to men (57%). Once expressed relative to FFM^b the differences between the sexes were still evident, as were the age-related increases in $SVRi_{rest}$ (Figure 3.15B).

(D) Cardiac power output and its component parts when measured at maximal exercise

Maximal CPO is a better measure of maximal functional capacity than $\dot{V}O_{2max}$ as it defines the maximal pumping capacity of the heart. Also, CPO_{rest} only represents a fraction (approximately 20%) of the total capacity of the heart. Any changes that occur in CPO_{max} can have pronounced affects on daily living. Age for age, the sedentary men had a significantly ($P<0.001$) ~23% greater CPO_{max} compared to women (Figure 3.16A). A significant decline in cardiac function was also evident during maximal exercise. That is, CPO_{max} declined by 18% and 12% between 20 to 75 years in men ($r = -0.52$) and women ($r = -0.23$), respectively. The age-related rate of decline was greater in men.

In men, this age-related decline in CPO_{max} resulted in a significant ($P<0.001$) 18% decline ($r = -0.45$) in cardiac reserve (CR). This was smaller in women, with a non-significant 10% decline ($r = -0.17$) measured in CR with age (Figure 3.17A). Consequently, age for age significant ($P<0.001$) sex-related differences were observed in CR.

The importance of scaling for FFM^b, as demonstrated in resting cardiac function, was also evident for the measurements made at maximal exercise. The significant ($P<0.001$) age-related decreases in CPO_{max} and CR were still evident once expressed relative to FFM^b in the male subjects. That is, from 20 to 75 years of age the sedentary men demonstrated a 15% decline in both CPi_{max} ($r = -0.44$) and CRi ($r = -0.35$). In contrast, despite a decrease of 8% in CPi_{max} in the sedentary women with age, no significant differences were found. In addition, no age-related decline in CRi was found for women. Normalisation of CPO_{max} and CR for FFM^b removed the significant sex-related differences (Figure 3.16B and 3.17B).

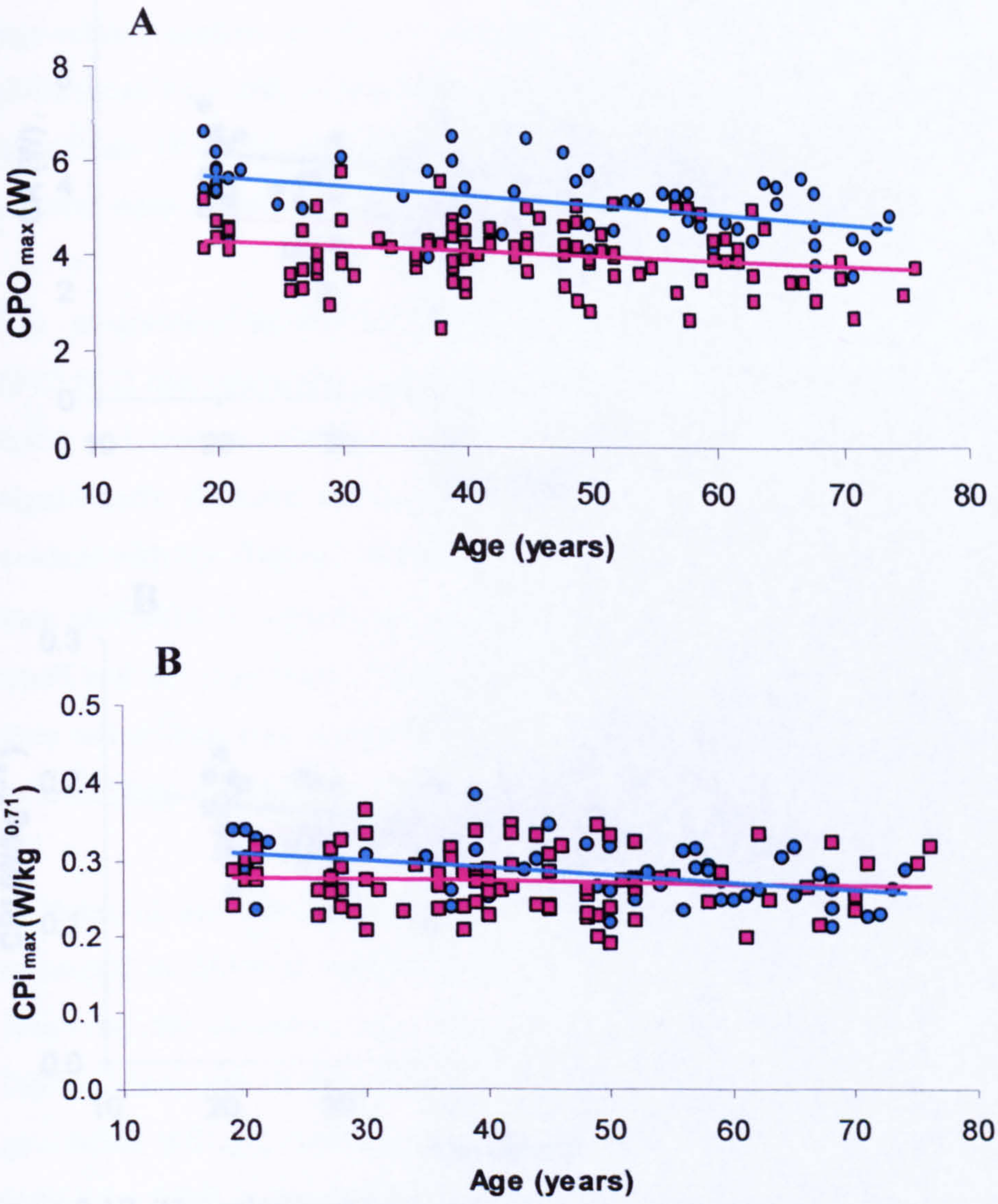
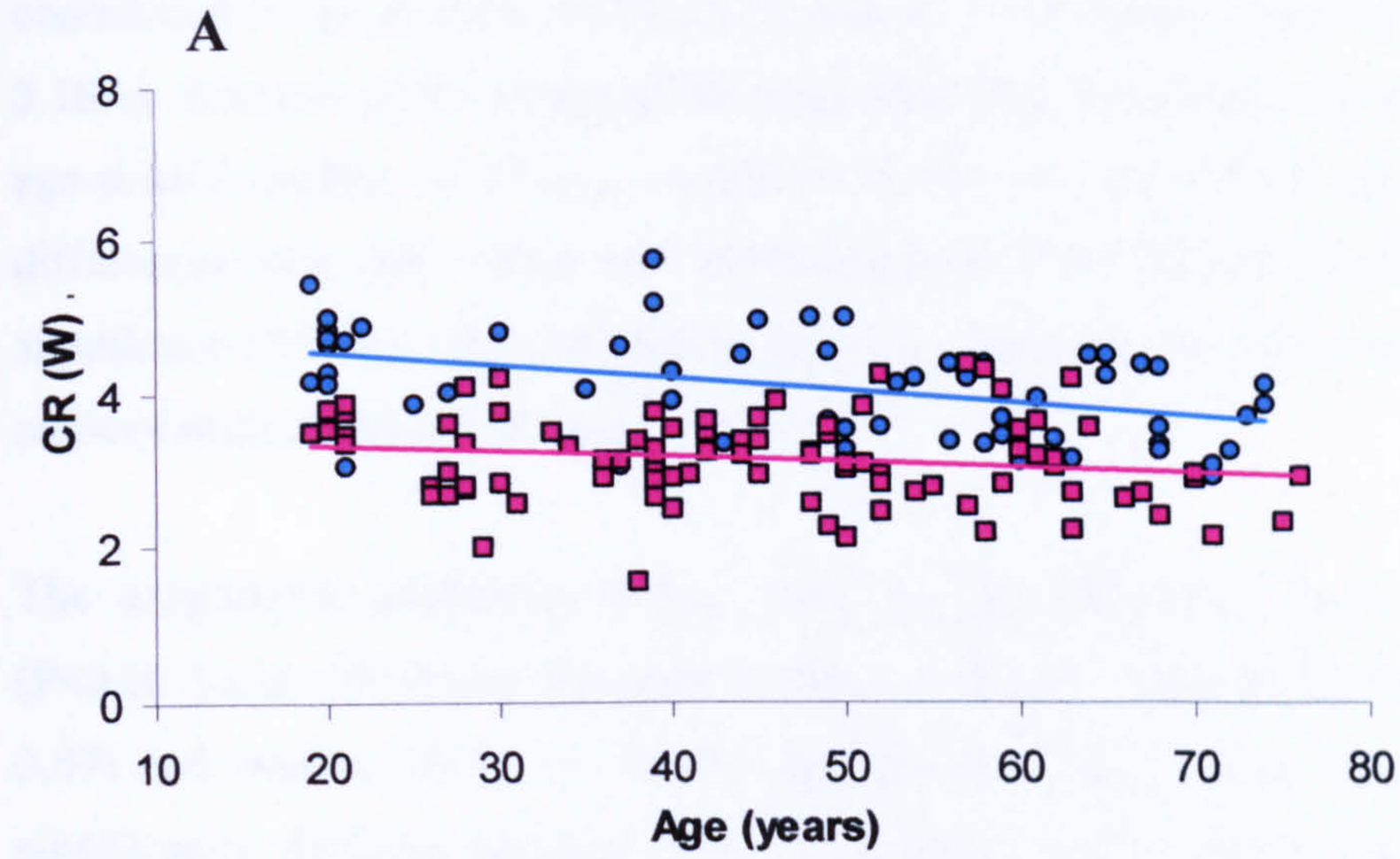


Figure 3.16. The relationships between maximal cardiac power, age and sex.

The physiological variables analysed were cardiac power output (A), and cardiac power index (B) for sedentary men (●) and women (■). The lines of best fit for men (——) and women (——) are illustrated above.



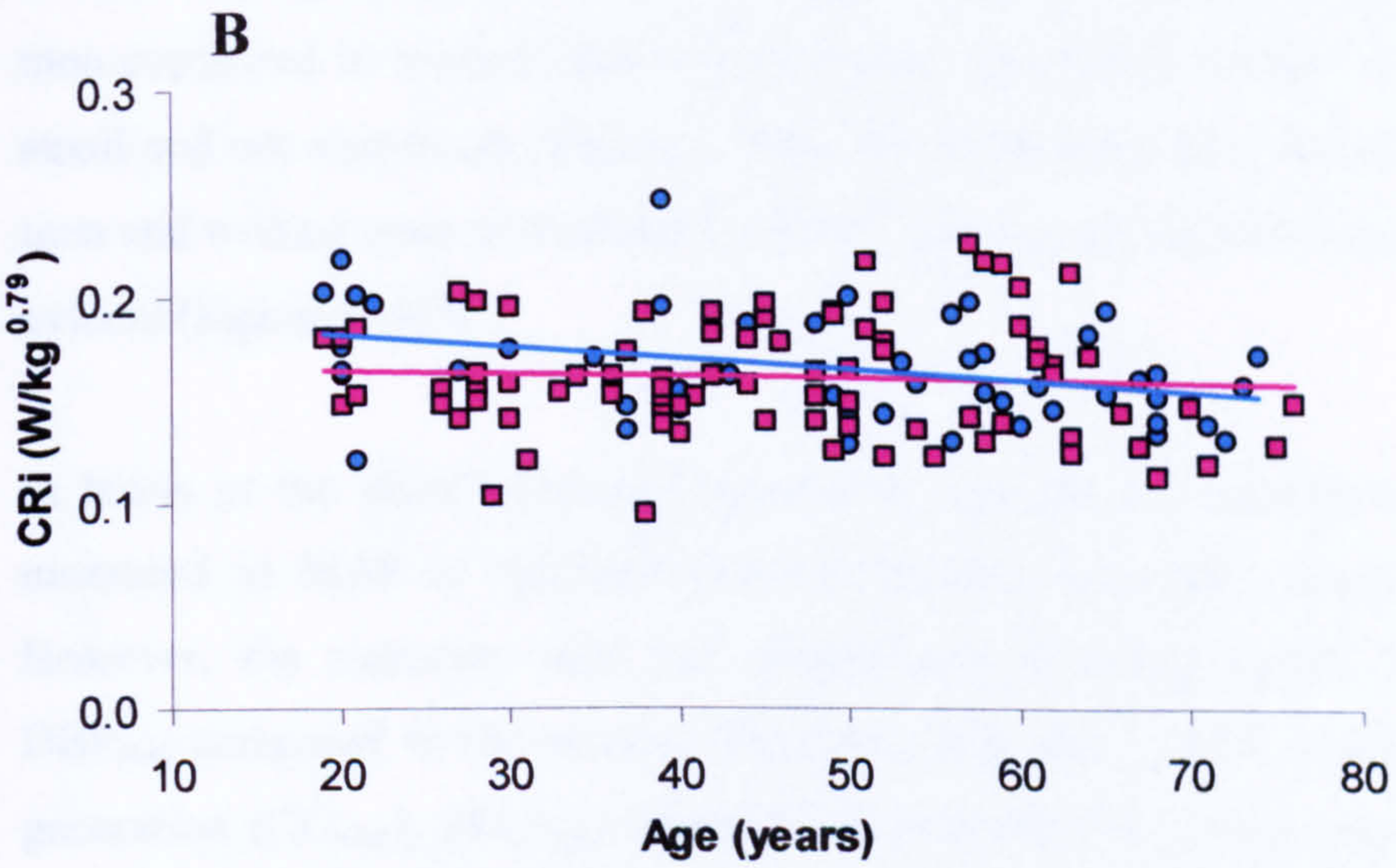


Figure 3.17. The relationships between the reserve capacity of the heart, age and sex.

The variables of cardiac functional reserve (A), and cardiac reserve index (B) for sedentary men (●) and women (■), were calculated by subtracting values of CPO_{rest} (Figure 3.11) from CPO_{max} (Figure 3.16). The lines of best fit for men (——) and women (——) are illustrated above.

These changes in CPO_{max} were explained by examining the age-related changes in CO and MAP. Age for age, sedentary men had a significantly ($P<0.001$) 22% greater CO_{max}, compared to women. Significant ($P<0.001$) age-related decrease (25%) in CO_{max} contributed to the decline in CPO_{max} in men ($r = -0.65$) and women ($r = -0.58$; Figure 3.18A). Analysis of the slopes of the regression lines identified that men had a steeper age-related decline in CO_{max}, compared to the women. These sex-and age-related differences were still evident once normalised for FFM^b (Figure 3.18B). But while still significant ($P<0.05$), the differences in CO_{max} between the sexes were dramatically reduced once expressed as Ci_{max}.

The progressive decline in CO_{max} with age was attributed in part to significant ($P<0.001$) and substantial decreases in HR_{max} (Figure 3.19A) for both men (21%; $r = -0.87$) and women (19%; $r = -0.64$). Age for age, HR_{max} were very similar and not significantly different between men and women, and a similar rate of decline was evident with age (Figure 3.19A). In contrast, SV_{max} was significantly ($P<0.05$) greater in men compared to women, but in both sexes, age-related changes in SV_{max} were only small and not significant (Figure 3.19B). No differences were found in SV_{max} between men and women once normalised for FFM^b, and no age-related changes in SVi_{max} were evident (Figure 3.19C).

In terms of the heart's pressure generating capacity, no significant differences were measured in MAP at maximal exercise between men and women (Figure 3.20A). However, the sedentary men had significantly ($P<0.05$) greater SBP_{max} and lower DBP_{max} compared to the women (Figures 3.20B and 3.20C). Unlike the fall in flow generation (CO_{max}), MAP_{max} significantly ($P<0.001$) increased with age in both men (19%; $r = 0.39$) and women (18%; $r = 0.45$). Analysis of the slopes of the regression lines indicated that both sexes increased their MAP_{max} at similar rates with age (Figure 3.20A). Significant ($P<0.01$) 36% and 56% increases in DBP_{max} contributed to the increases in MAP_{max}, in both men ($r = 0.58$) and women ($r = 0.66$) respectively, while SBP_{max} remained relatively constant with age (Figure 3.20B).

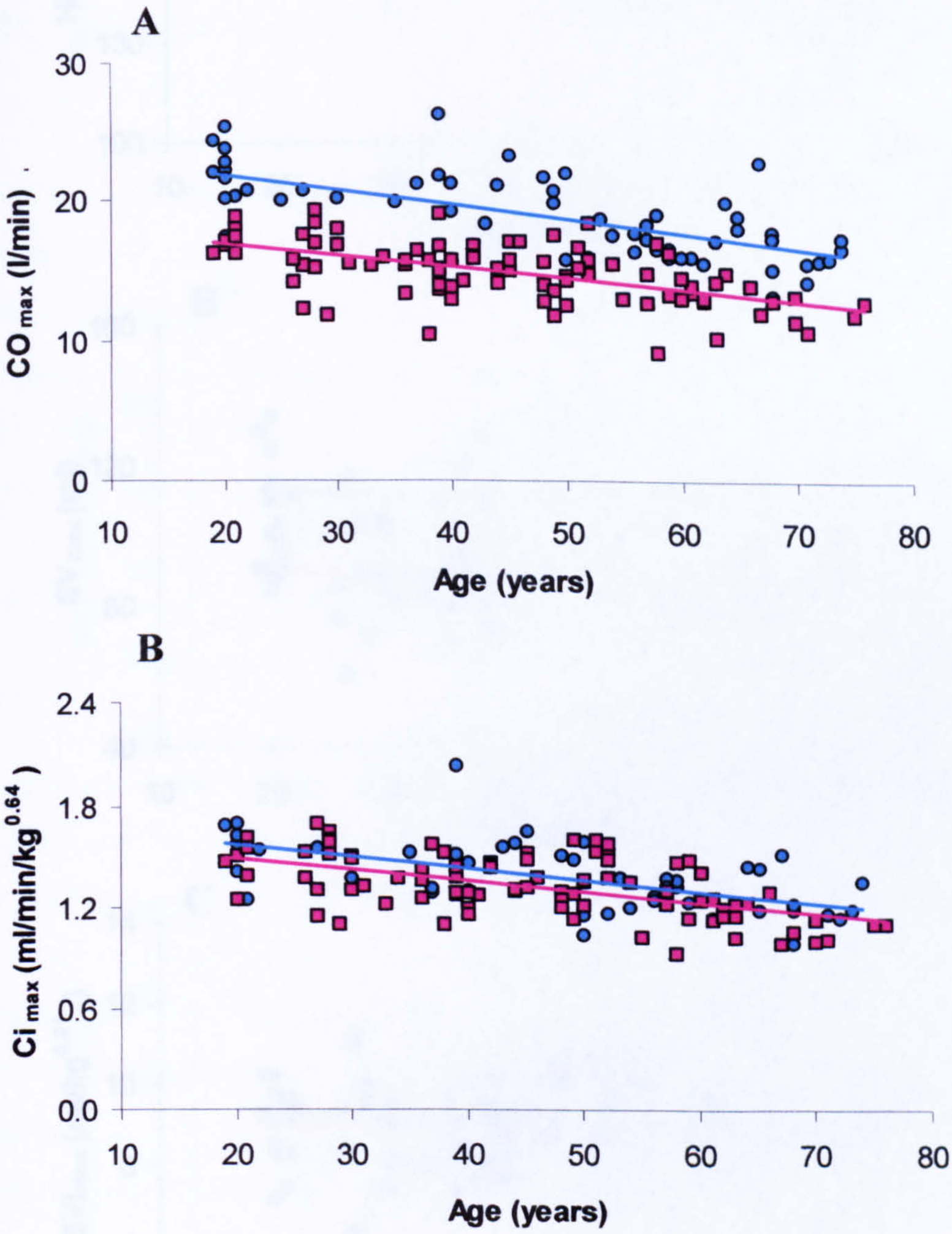


Figure 3.18. The relationships between maximal cardiac output, age and sex.

The variables are cardiac output (A) and cardiac index (B) for sedentary men (●) and women (■). The lines of best fit for men (——) and women (——) are illustrated.

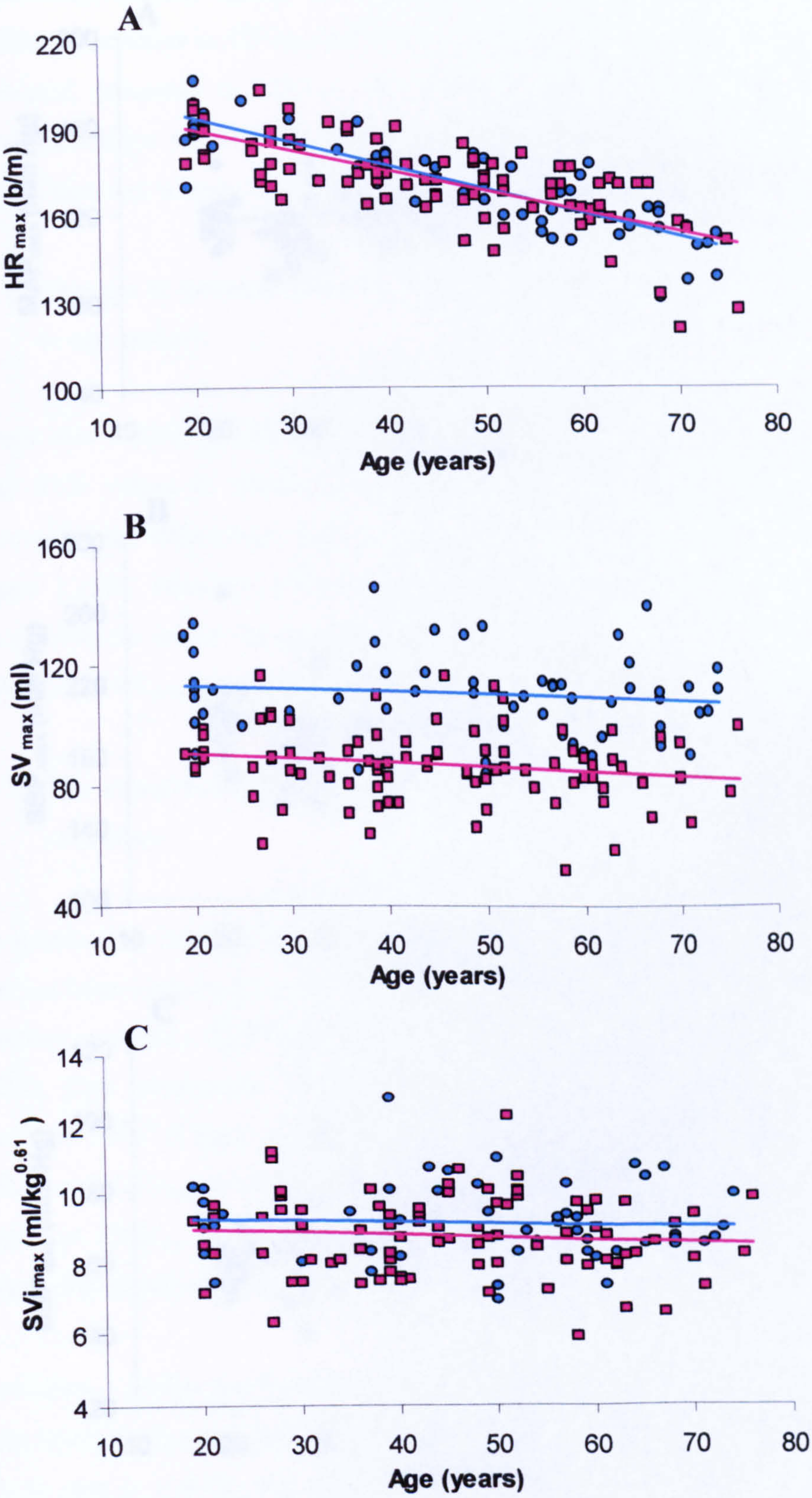


Figure 3.19. The changes in maximal heart rate and stroke volume with age and sex.

The variables are heart rate (A), stroke volume (B), and stroke volume index (C) for sedentary men (●) and women (■). The lines of best fit for men (——) and women (——) are shown.

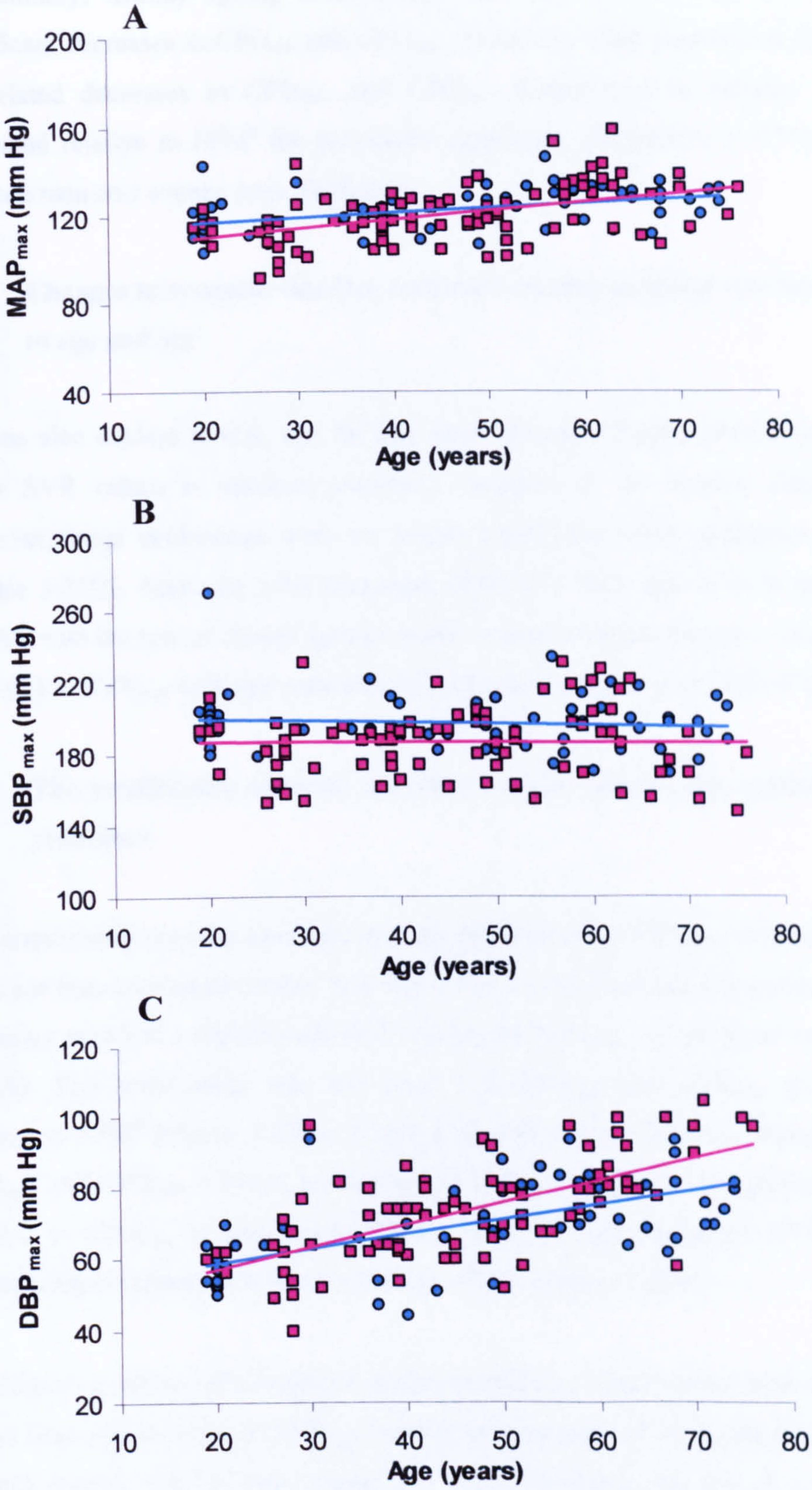


Figure 3.20. The relationships between age, sex and maximal blood pressure.

The variables are mean arterial pressure (A), systolic blood pressure (B) and diastolic blood pressure (C) for the sedentary men (●) and women (■). The lines of best fit for the men (—) and women (—) are shown.

In summary, healthy ageing in sedentary men and women were associated with significant decreases in CPO_{rest} and CPO_{max}. However, when normalised for FFM^b the age-related decreases in CPO_{rest}, and CPO_{max} disappeared in women. Also, once expressed relative to FFM^b the previously significant differences in CPO_{max} and CR between men and women were abolished.

(E) Changes in systemic vascular resistance during maximal exercise in relation to age and sex

As was also evident at rest, age for age, men had significantly ($P<0.001$) 16 to 23% lower SVR values at maximal exercise, compared to the women (Figure 3.21A). However, these differences were no longer significant when expressed as $SVRi_{max}$ (Figure 3.21B). Maximal SVR increased ($P<0.001$) with age in both sexes (Figure 3.21A), with the rate of change greater in the women compared to men. These increases ($P<0.01$) in SVR_{max} with age were still evident when expressed as SVRi (Figure 3.21B).

(F) The relationship between maximal cardiac power and systemic vascular resistance

The relationship between systemic vascular resistance and CPO_{max}, in men and women have not been examined before. It is interesting to note that for any given SVR_{max}, the sedentary men had a significantly ($P<0.05$) greater CPO_{max} compared to women (Figure 3.22A). This relationship was lost once both CPO_{max} and SVR_{max} were expressed relative to FFM^b (Figure 3.22B). A strong inverse relationship was identified between SVR_{max} and CPO_{max}. That is, an increase in SVR_{max} resulted in a significant ($P<0.001$) decline in CPO_{max} in both sexes (Figure 3.22A). This significant ($P<0.05$) inverse relationship remained even when scaled for FFM^b (Figure 3.22B).

In addition, a similar relationship was also identified of the pressure generating capacity of the heart. An increase in SVR_{max} resulted in significant ($P<0.01$) increases in MAP_{max} in both men ($r = 0.73$) and women ($r = 0.75$). However, for any given SVR_{max}, the sedentary men had a significantly ($P<0.01$) greater MAP_{max} than women (Figure 3.23A). Although reduced, this relationship was still evident even when SVR_{max} was expressed as $SVRi_{max}$ (Figure 3.23B).

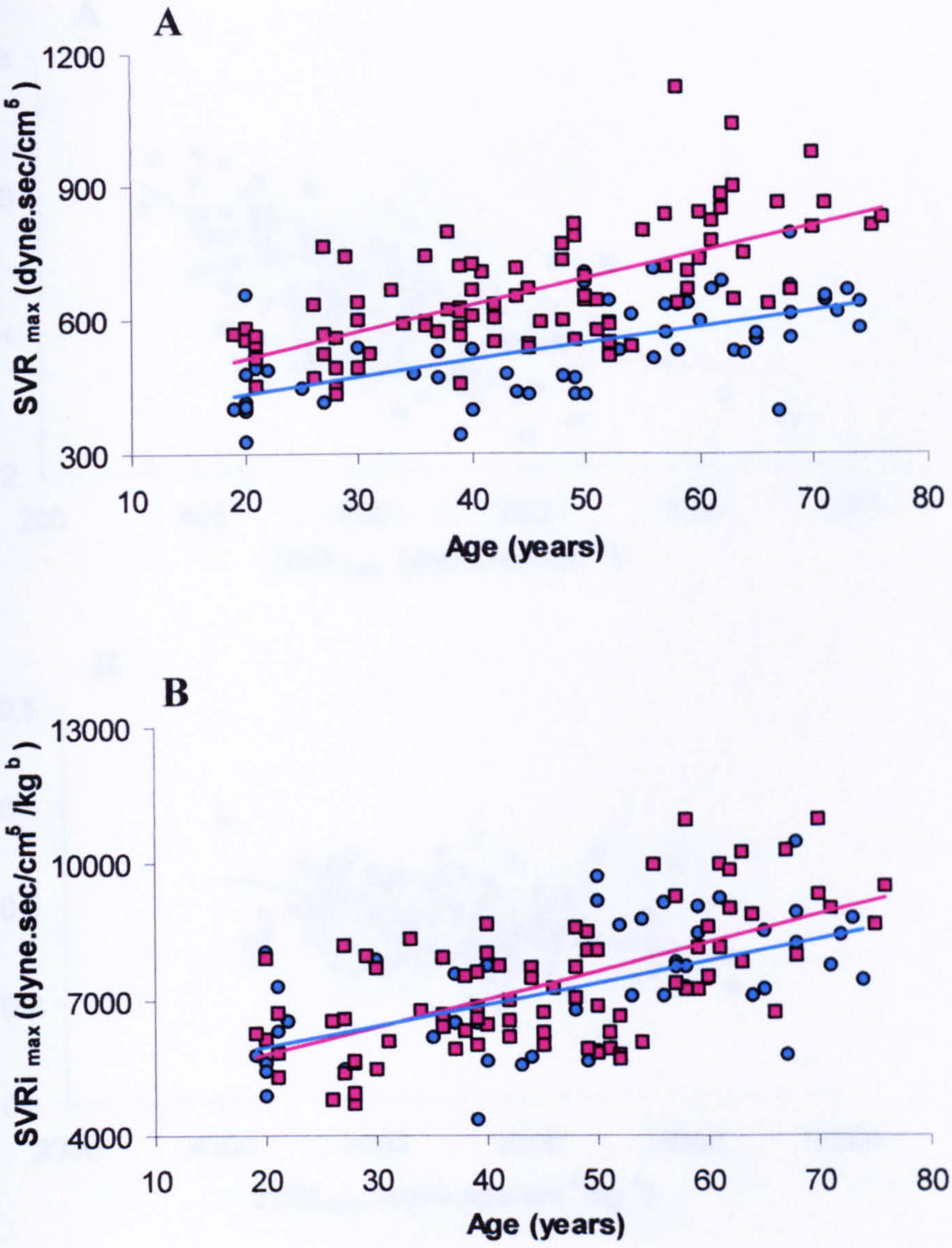
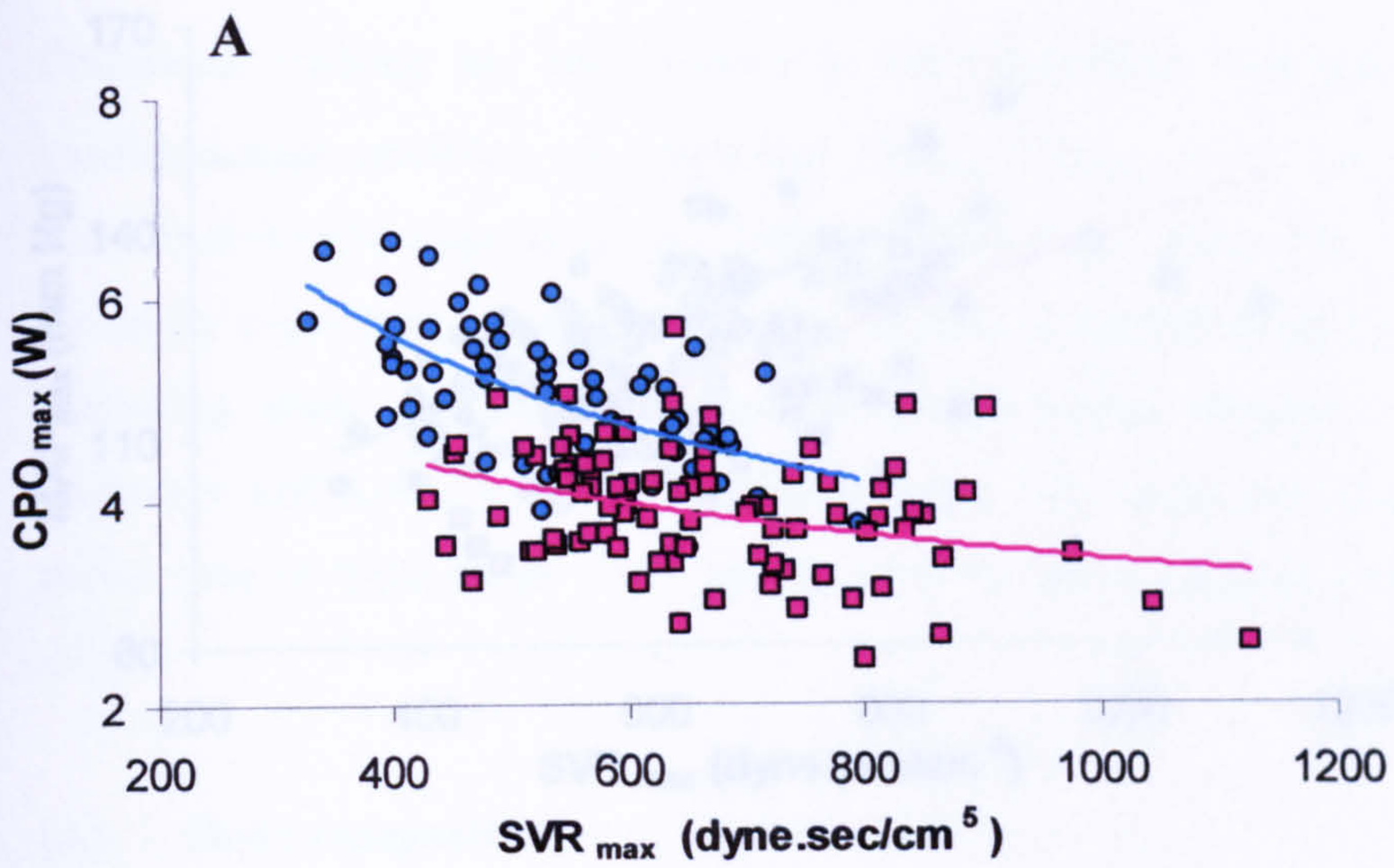


Figure 3.21. Changes in systemic vascular resistance at maximal exercise with age and sex.

The variables are systemic vascular resistance (A) and systemic vascular resistance index (B) for sedentary men (●) and women (■) at maximal exercise. The lines of best fit for men (—) and women (—) are superimposed on these data.



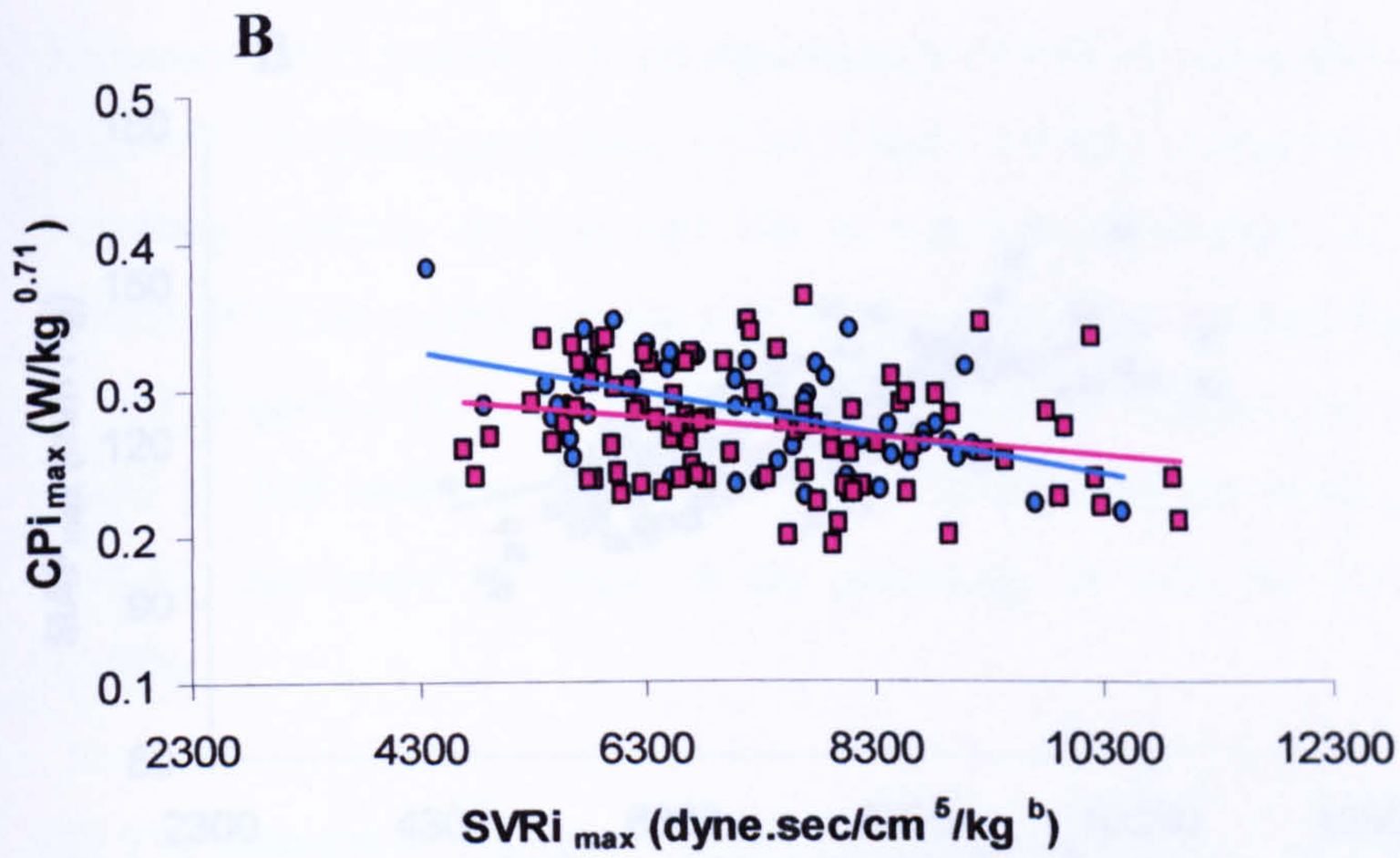
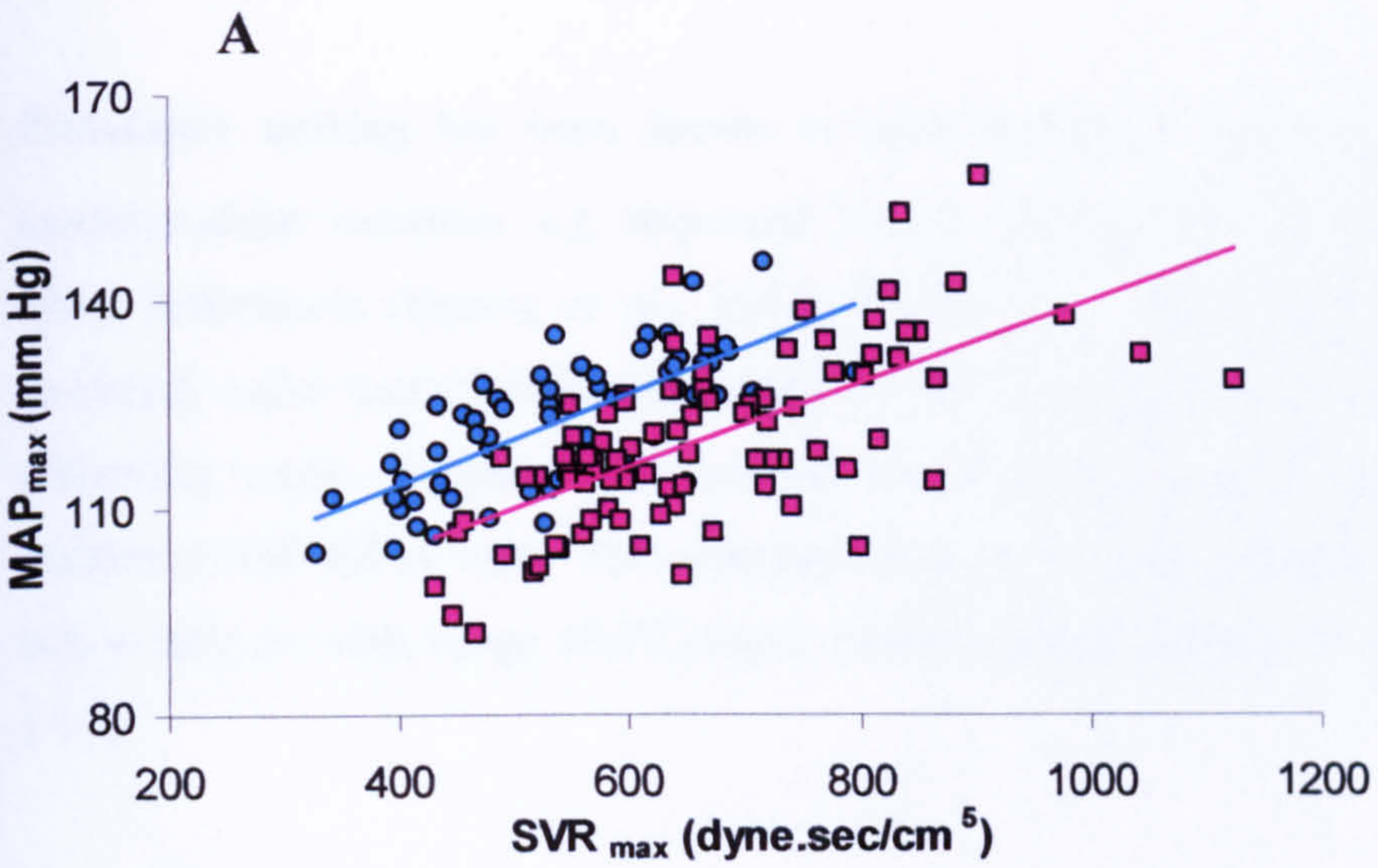


Figure 3.22. The relationship between maximal systemic vascular resistance and cardiac power output.

(A) cardiac power output and (B) cardiac power index are plotted for sedentary men (●) and women (■) and the lines of best fit for men (—) and women (—) are superimposed on these data.



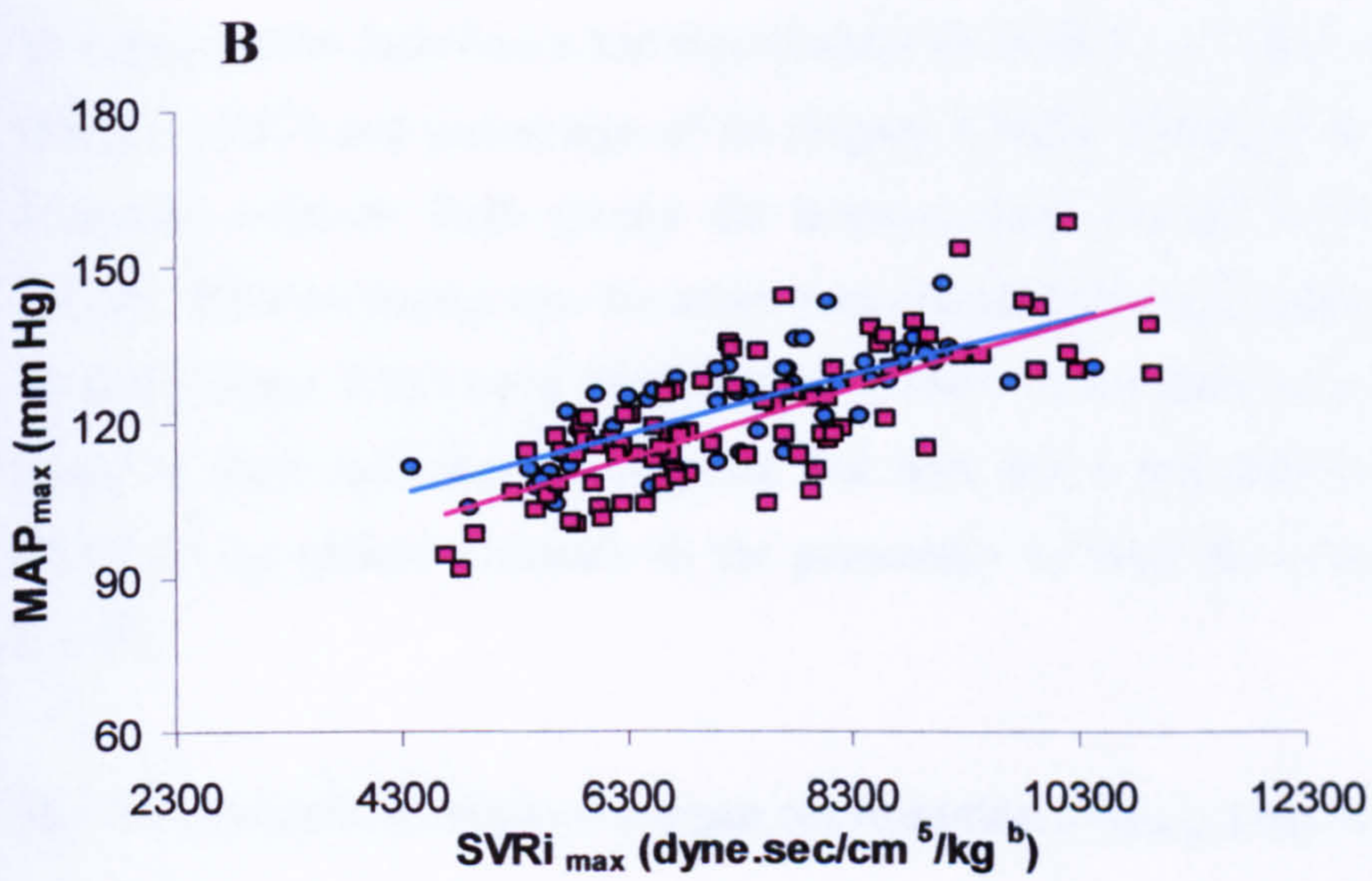


Figure 3.23. The relationships between systemic vascular resistance and mean arterial pressure at maximal exercise.

Systemic vascular resistance in absolute terms (A) and relative to FFM^b (B) were plotted against maximal mean arterial pressure for sedentary men (●) and women (■). The lines of best fit for men (—) and women (—) are shown above.

3.3.2. The effects of training status on the measurement of cardiac function in men

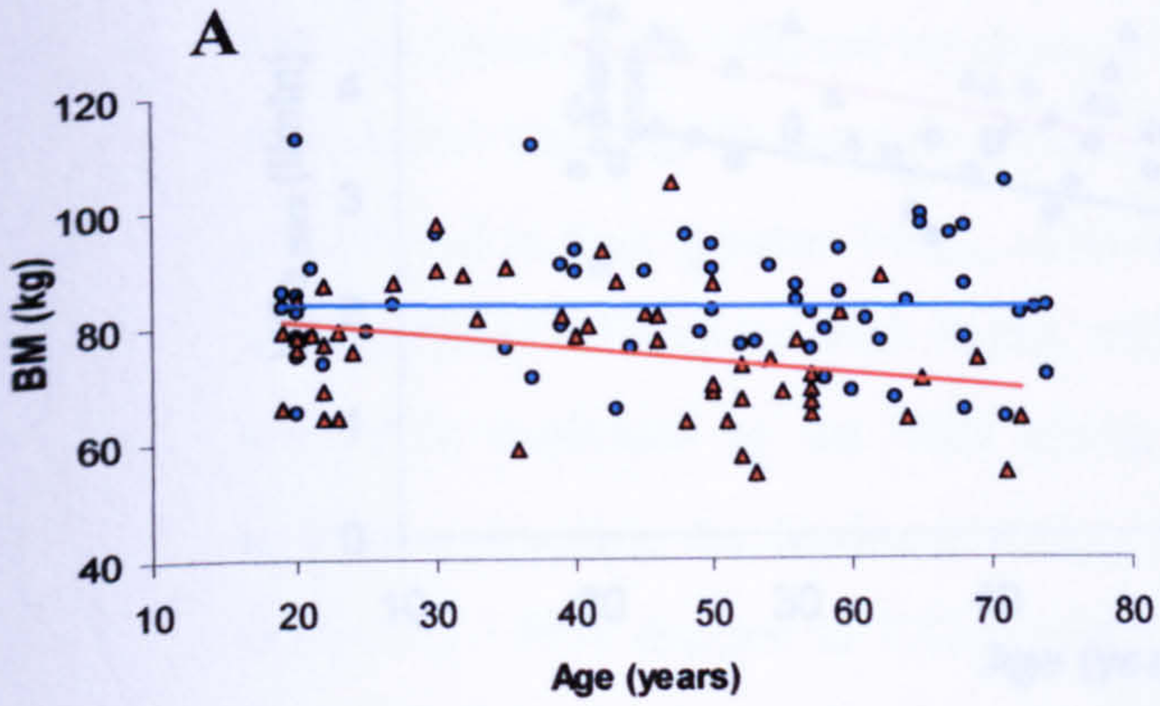
Endurance training has been shown to have beneficial responses on a number of cardiovascular variables, e.g. improved $\dot{V}O_{2max}$, CO_{max}, SV_{max} etc, in both young and older individuals (Ogawa *et al.,* 1992). Furthermore, those who are physical active generally enjoy better health and quality of life, compared to inactive individuals. The following study compares the age-and fitness-related changes in CPO in healthy sedentary and active men. The sedentary men, who acted as control subjects for the active men (n = 60; range 19-72 years), were the same subjects as described in section 3.3.1.

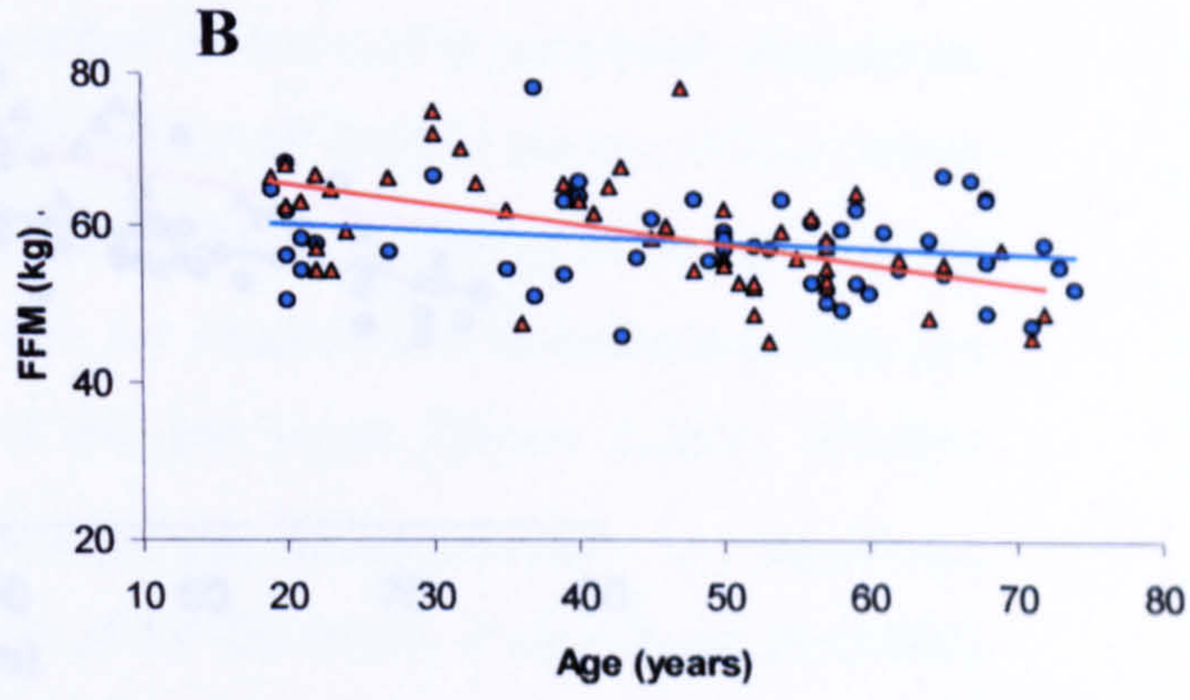
(A) Body composition

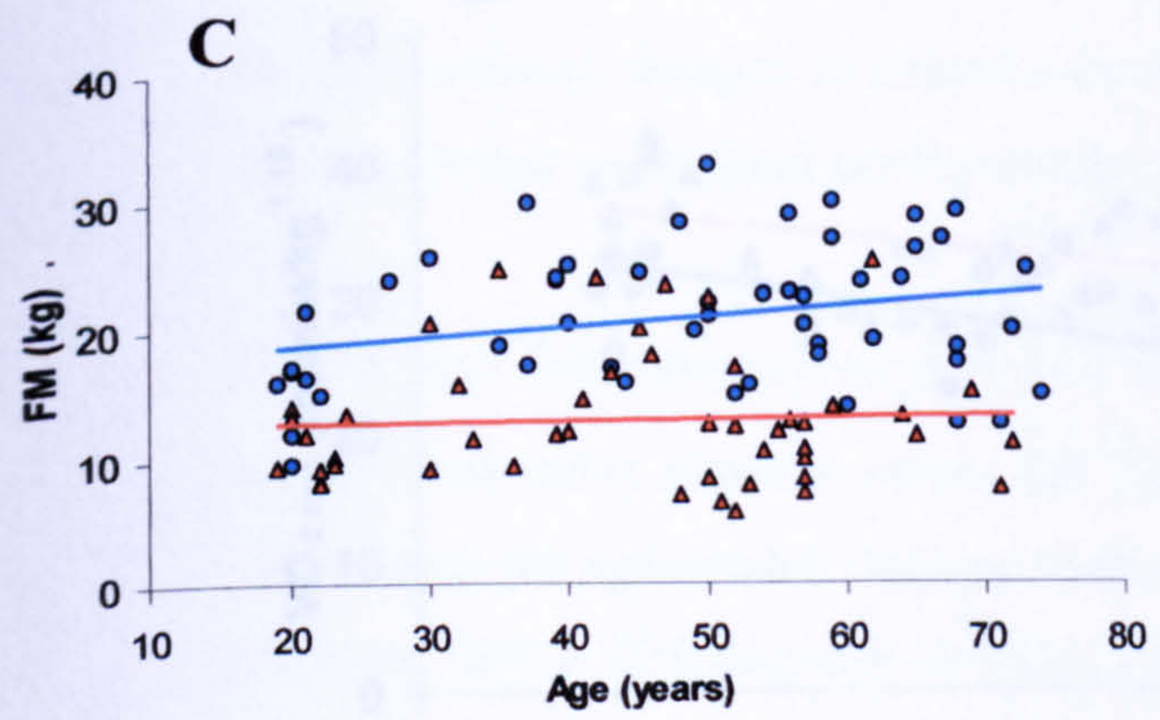
The more active individuals had significantly ($P<0.001$) lower BM (Figure 3.24A), FM (Figure 3.24C) and percentage of fat (Figure 3.24D), compared to their age-matched sedentary controls. Both groups did however have similar values of FFM (Figure 3.24B). With increasing age, the active men demonstrated a significant ($P<0.05$) decline in BM (Figure 3.24A) and FFM (Figure 3.24B). In contrast, no such decreases were found in their sedentary counterparts. For both active and sedentary men significant ($P<0.01$) age-related increases in the percentage of body fat were measured (Figure 3.24D).

(B) The changes in maximal oxygen consumption ($\dot{V}O_{2max}$) due to fitness and age

Maximal oxygen consumption is often used as a marker of the functional capacity of the cardiovascular system and as such has been used as an indirect indicator of cardiac function (Tan *et al.,* 1997). Furthermore, values of $\dot{V}O_{2max}$ are often used to identify how physically fit individuals are. It is clear to see that, age for age, the active men had significantly ($P<0.001$) greater $\dot{V}O_{2max}$ values than their sedentary counterparts (Figures 3.25A and 3.25B), both in absolute terms (19 to 26%) and relative to FFM^b (12 to 36%). Therefore, it is conceivable that these fitter individuals would have a better cardiac function than their sedentary counterparts.







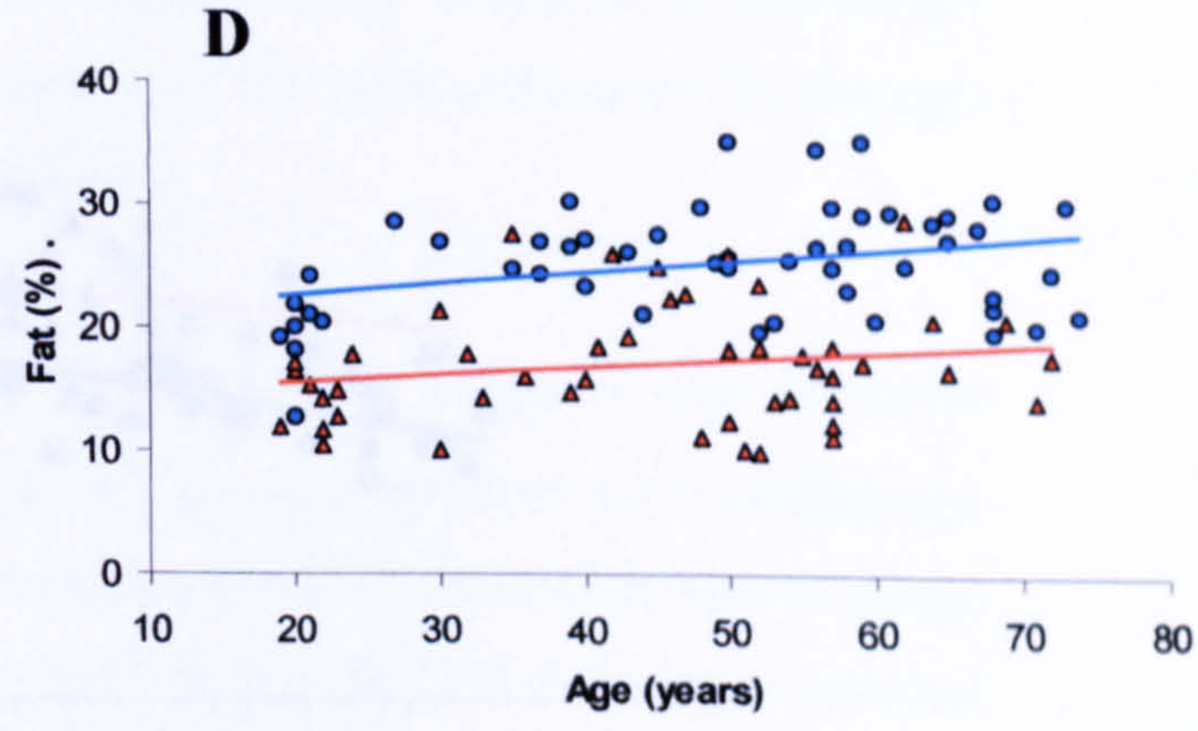
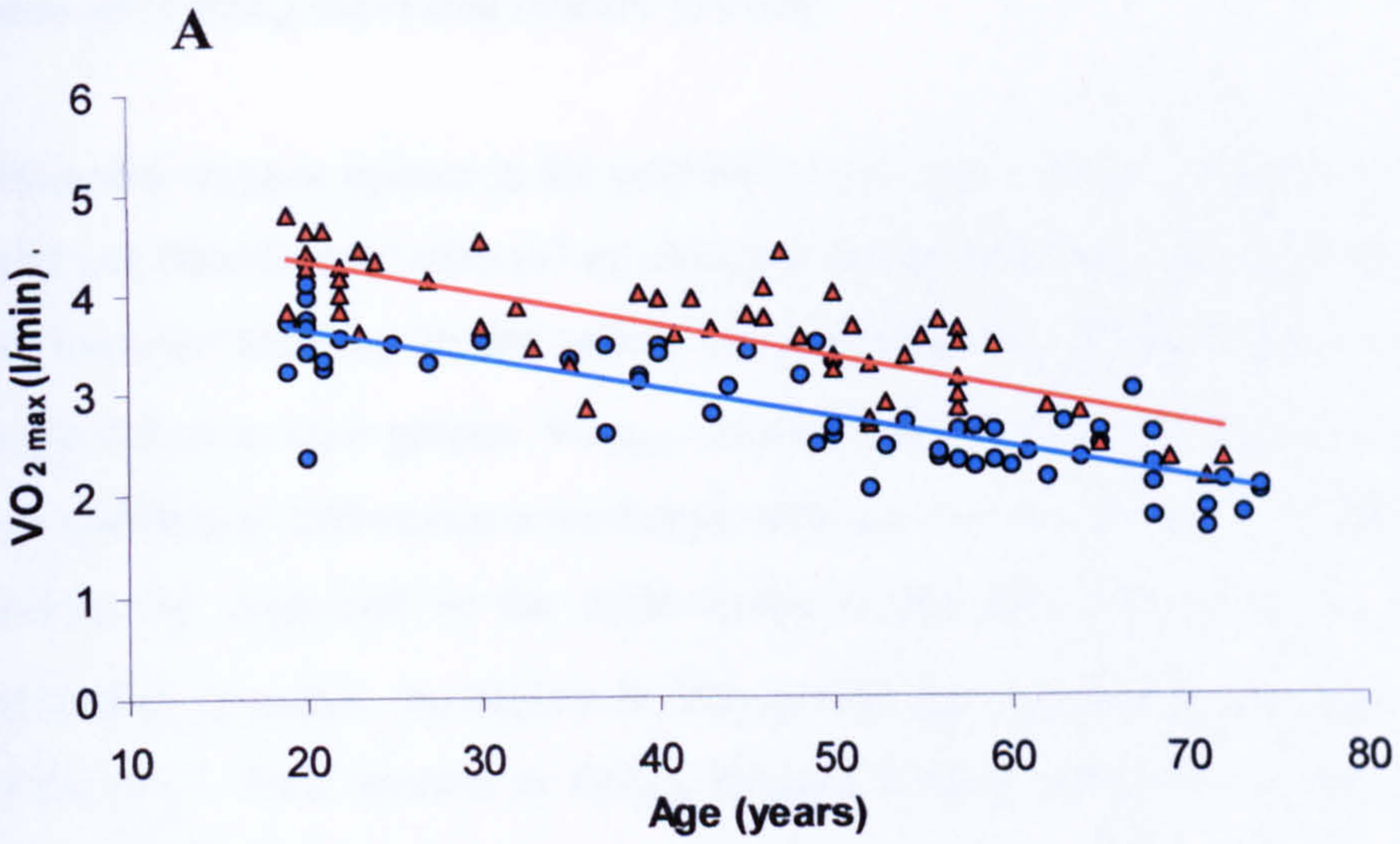


Figure 3.24. The relationships between body composition, age and fitness.

Body mass (A), fat free mass (B), fat mass (C) and percentage of fat are shown for sedentary (●) and active (▲) men. The lines of best fit for sedentary (—) and active (—) men are shown. The sedentary men were the same subjects as studied in section 3.2.1.



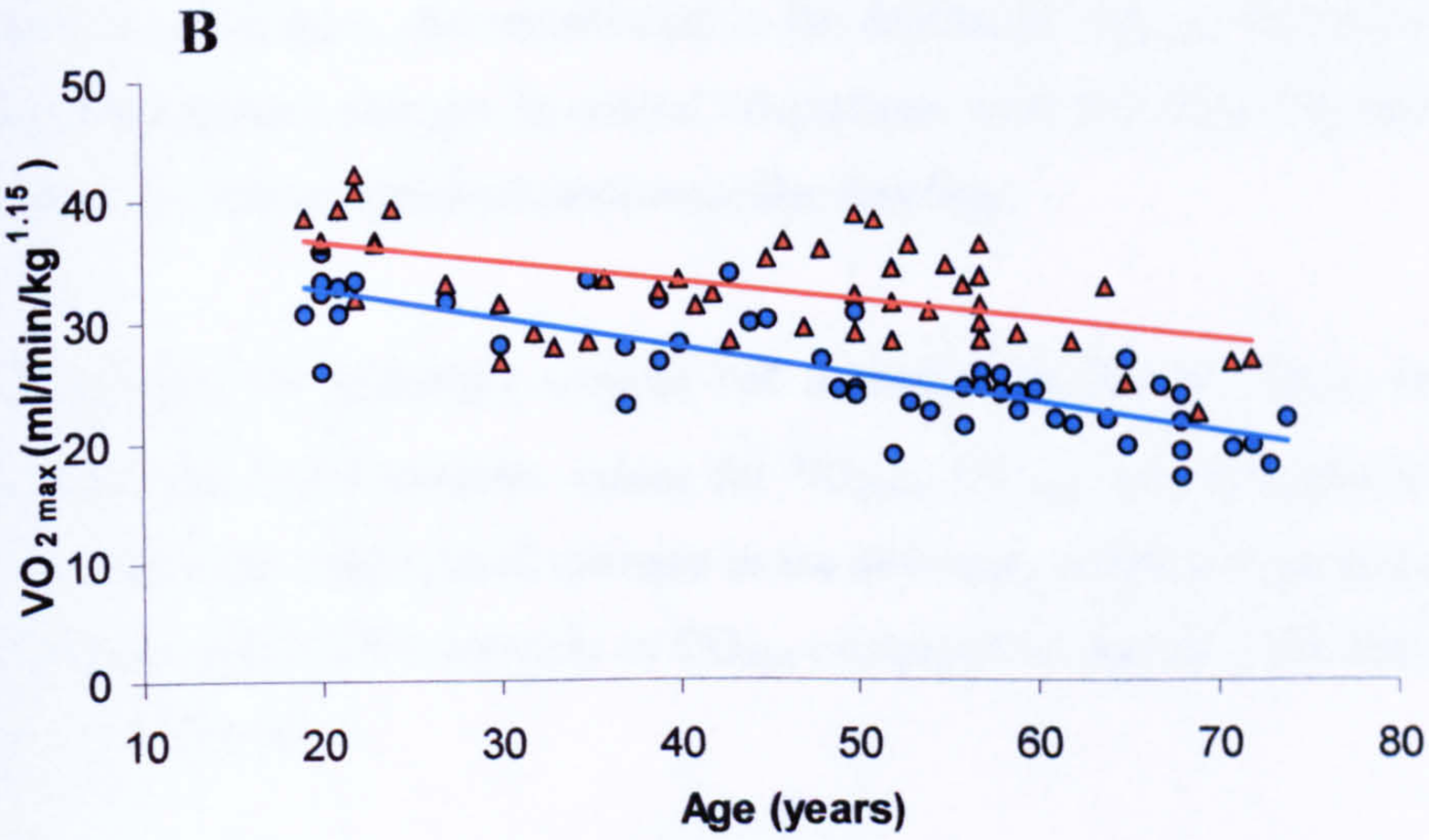


Figure 3.25. Changes in maximal oxygen consumption with age and fitness.

The functional variables are maximal oxygen consumption in absolute terms (A) and relative to FFM^b (B) for sedentary (●) and active (▲) men. Lines of best fit are for sedentary (——) and active (——) men.

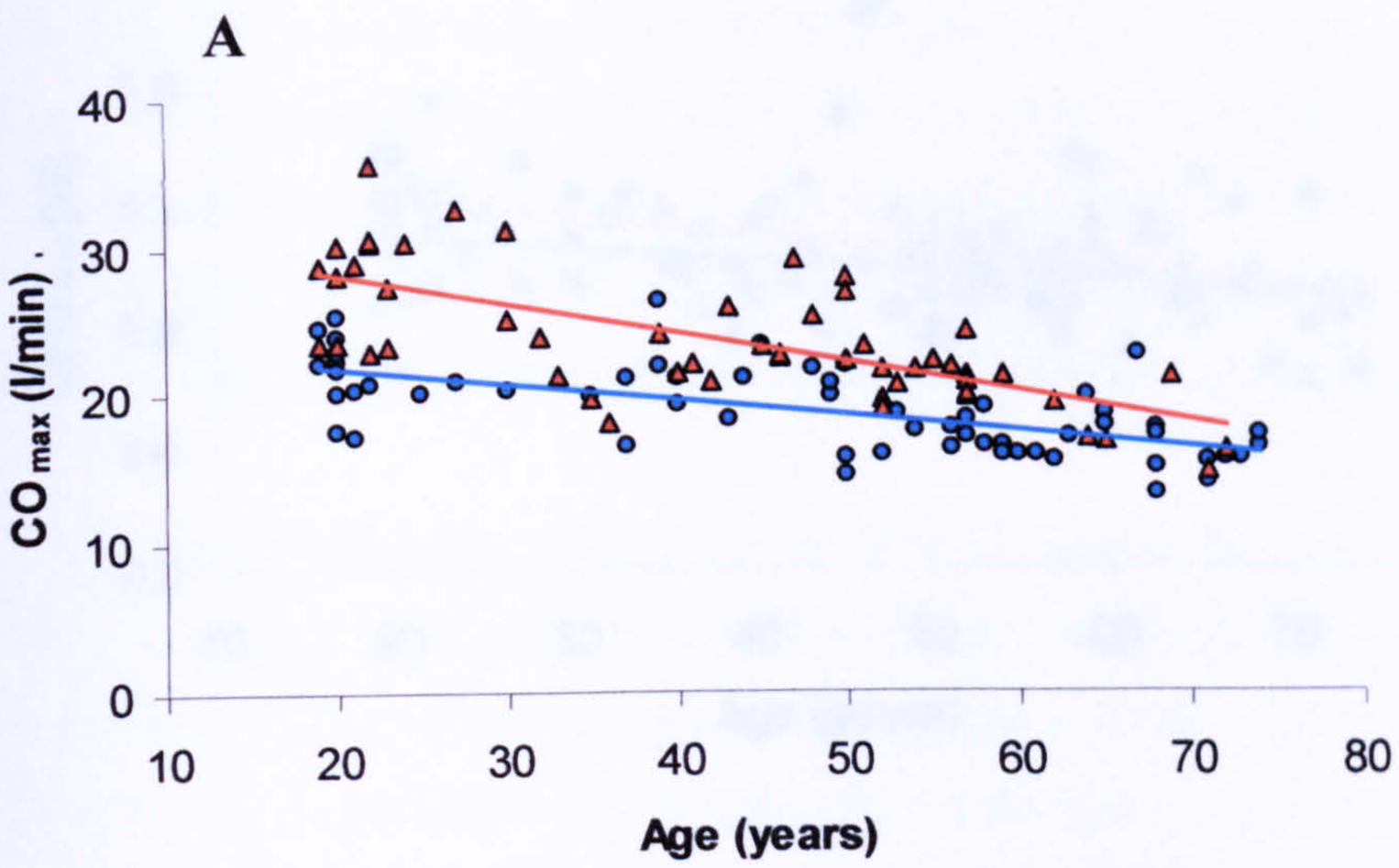
Irrespective of the levels of fitness, the sedentary and active men experienced similar rates of decline in $\dot{V}O_{2max}$ with age, with values of 38 and 41%, respectively. When $\dot{V}O_{2max}$ values were adjusted for FFM^b, the age-related decreases in $\dot{V}O_{2max}$ values were still evident (Figure 3.25B). However the rate of decline was greater in the sedentary men after being expressed relative to FFM^b.

Maximal oxygen uptake is the product of maximal CO and maximal a-v O_2 difference and can therefore be affected by changes in either central and/or peripheral adaptations to exercise training. In the active men, significantly ($P<0.001$) greater CO_{max} values contributed to their greater $\dot{V}O_{2max}$ values (Figure 3.26A). However, in the active group no significant differences were found, with age, for maximal a-v O_2 difference. This can mainly be explained by the wide scatter of the data points (Figure 3.26B). Whether sedentary or active, the decline in $\dot{V}O_{2max}$ with age was mainly attributed to a significant ($P<0.001$) ~30% decline in CO_{max} (Figure 3.26A). However, a significant ($P<0.001$) age-related decline in maximal a-v O_2 difference in the sedentary men (22%; $r = -0.69$) but not active men, also contributed to the decline in $\dot{V}O_{2max}$. Therefore, in both groups the predominant changes in central adaptations were the main explanation for the age-related decline in maximal cardiovascular function.

Of interest, the sedentary women had a similar decline in $\dot{V}O_{2max}$ to men. However women had lower absolute values for $\dot{V}O_{2max}$, CO_{max}, and maximal a-v O_2 difference. Once again the age-related changes in the sedentary women were mainly due to central changes, with a 25% decrease in CO_{max} compared to only an 11% decrease in maximal a-v O_2 difference.

(C) Lifestyle effects on resting cardiac power output and its component parts

No significant differences in resting cardiac function were found between the sedentary or active men, whether expressed in absolute terms (CPO_{rest}; Figure 3.27A) or relative to FFM^b (CPi_{rest}; Figure 3.27B). As already indicated CPO_{rest} decreased with age in both sedentary and active men ($r = -0.40$). By testing the regression lines for parallelism, it was found that while the slopes of the changes in CPO_{rest} (± adjusted for FFM) with age



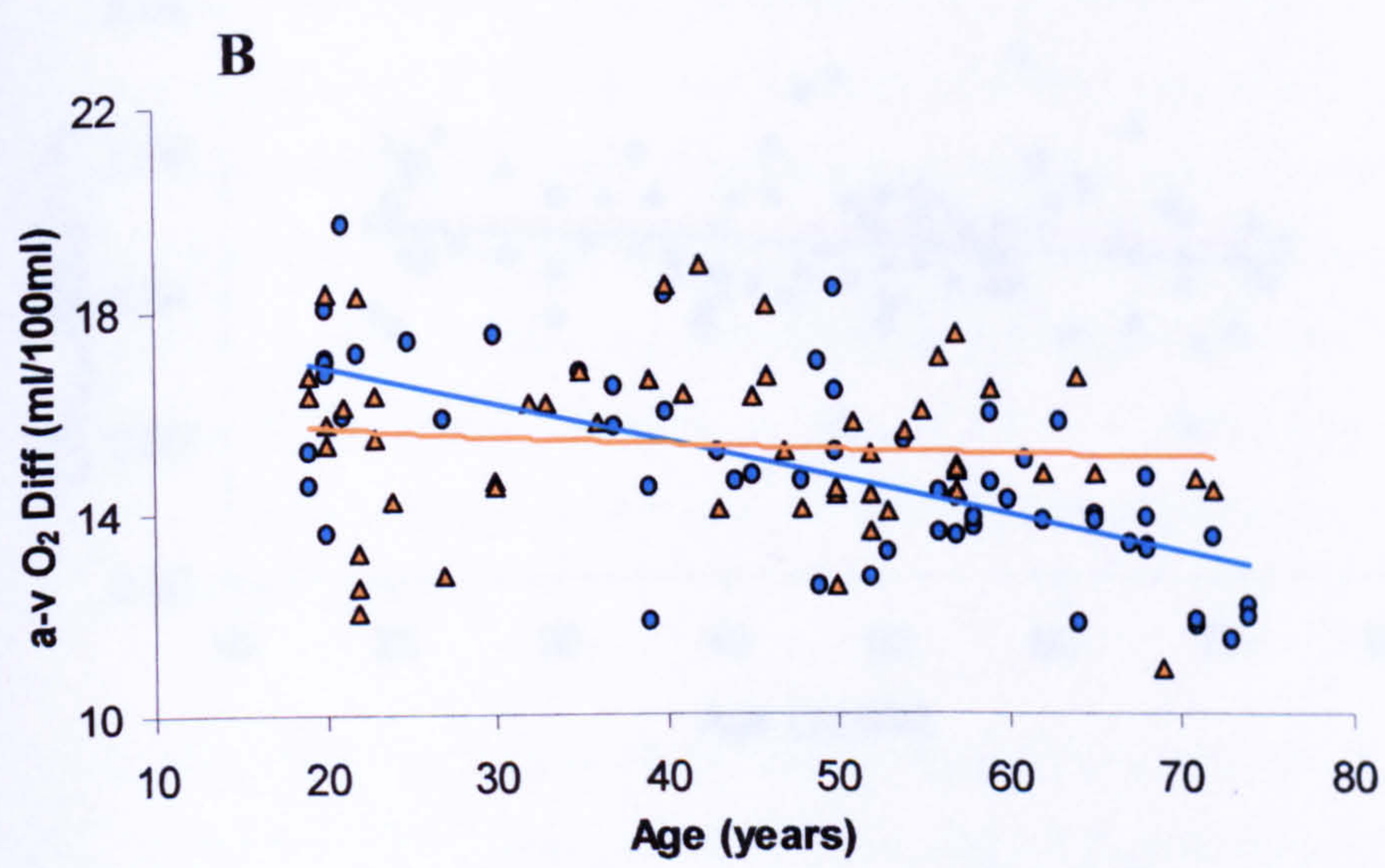


Figure 3.26. Changes in maximal cardiac output and arteriovenous oxygen differences with age and fitness levels.

The variables measured at maximal exercise are (A) cardiac output and (B) arteriovenous oxygen difference (a-v O_2 Diff) for sedentary (●) and active (▲) men. Plotted on these data are lines of best fit for the sedentary (——) and active (——) men.

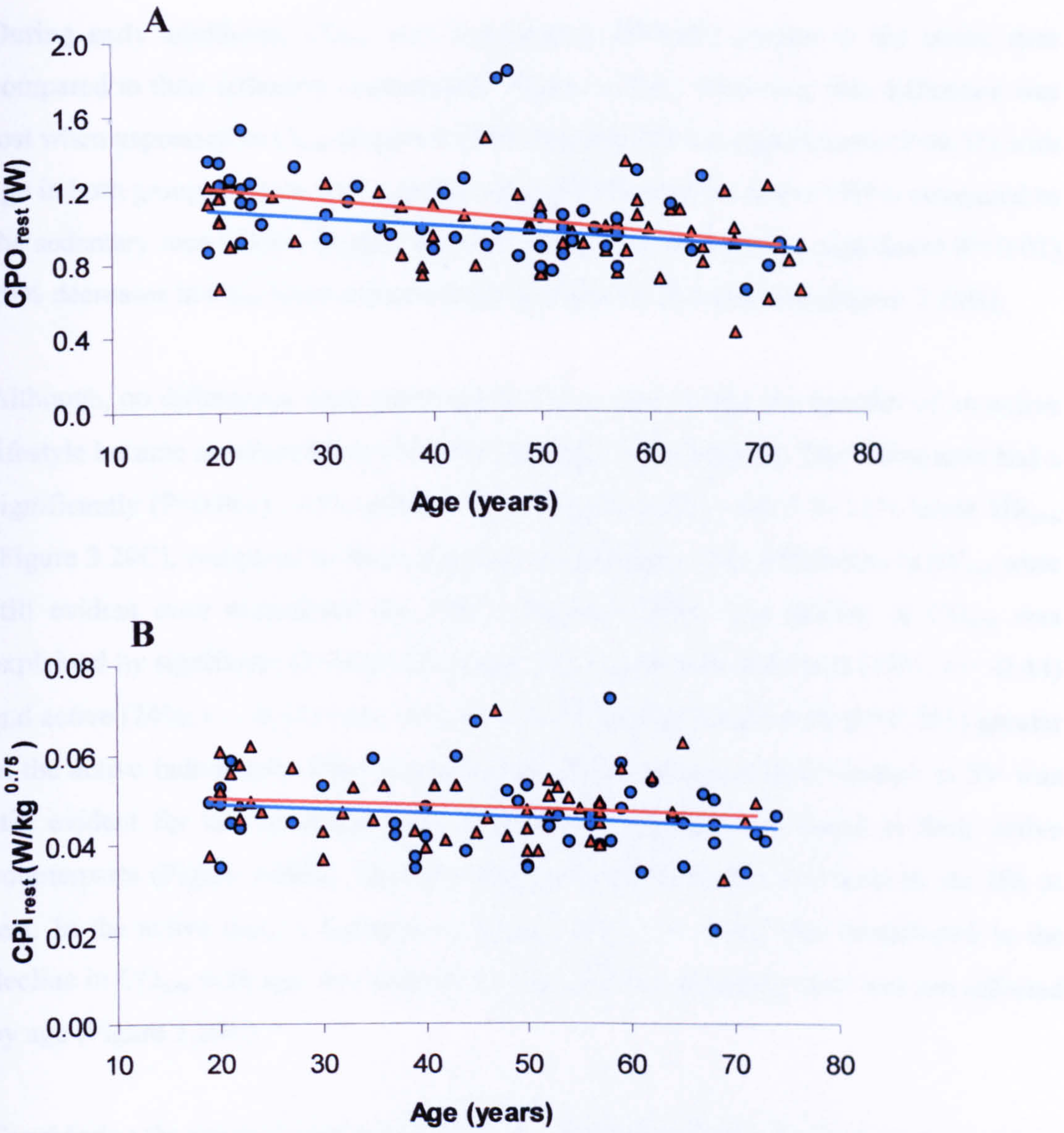


Figure 3.27. Age and fitness in relation to measurement of resting cardiac power.

The functional variables are cardiac power output (A) and cardiac power index (B), for sedentary (●) and active (▲) men. The lines of best fit for the sedentary (—) and active (—) men are illustrated.

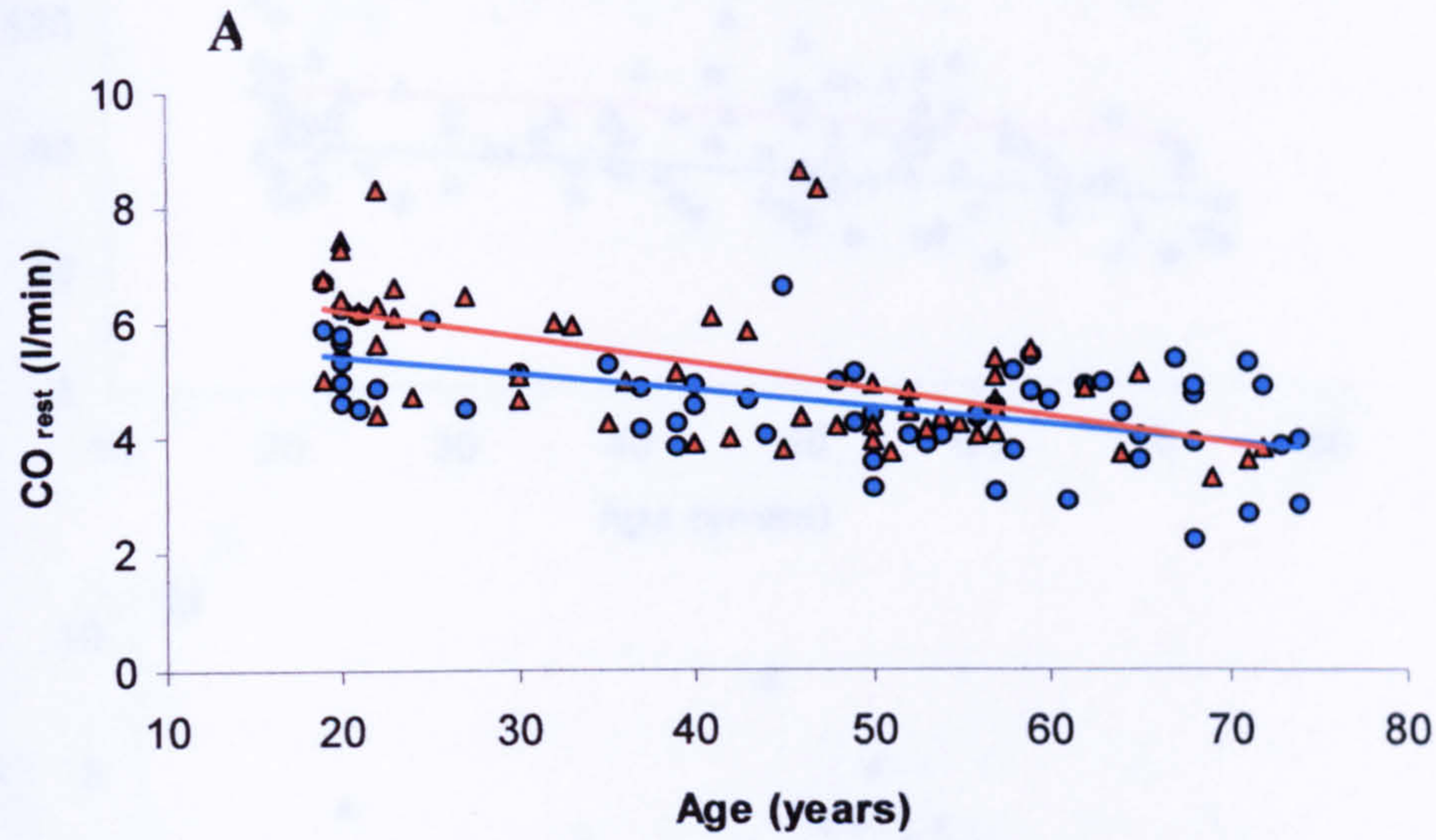
were slightly greater in the active men, no significant differences were obtained (Figure 3.27B).

During early adulthood, CO_{rest} was significantly ($P<0.05$) greater in the active men compared to their sedentary counterparts (Figure 3.28A). However, this difference was lost when expressed as Ci_{rest} (Figure 3.28B). Resting CO fell significantly ($P<0.01$) with age in both groups of men with a greater rate of decline in the active (37%) compared to the sedentary men (26%). Despite the lack of distinction in CPi_{rest}, significant ($P<0.01$) 20% decreases in Ci_{rest} were expressed, irrespective of fitness levels (Figure 3.28B).

Although, no differences were measured in CO_{rest} later in life, the benefits of an active lifestyle became apparent when viewed as changes in SV and HR. The active men had a significantly ($P<0.001$) ~21% greater SV_{rest} (Figure 3.29A) and 3 to 21% lower HR_{rest} (Figure 3.29C), compared to their sedentary counterparts. The differences in SV_{rest} were still evident once normalised for FFM^b (Figure 3.29B). The decline in CO_{rest} was explained by significant ($P<0.05$) decreases in SV_{rest} in both sedentary (18%; $r = -0.44$) and active (24%; $r = -0.31$) men, with the rate of decline significantly ($P<0.001$) greater in the active individuals. When expressed as SVi_{rest} the age-related decline in SV was still evident for the sedentary men. However no change was found in their active counterparts (Figure 3.29B). An interesting area of difference was seen in the HR at rest. In the active men, a decrease in HR_{rest} (21%; $r = -0.42$) also contributed to the decline in CO_{rest} with age. In contrast, the HR_{rest} of the sedentary men was not affected by age (Figure 3.29C).

Considering the pressure generating capacity of the heart, near identical absolute values, and increases in MAP (Figure 3.30A), SBP (Figure 3.30B) and DBP (Figure 3.30C) were measured in both groups of men.

In summary, similar age-related decreases in CPO_{rest} were found in sedentary and active men. In both cases this was explained by age-related decreases in CO_{rest}, despite increases in MAP_{rest}. After being normalised for FFM^b these decreases in Ci_{rest} remained similar with age.



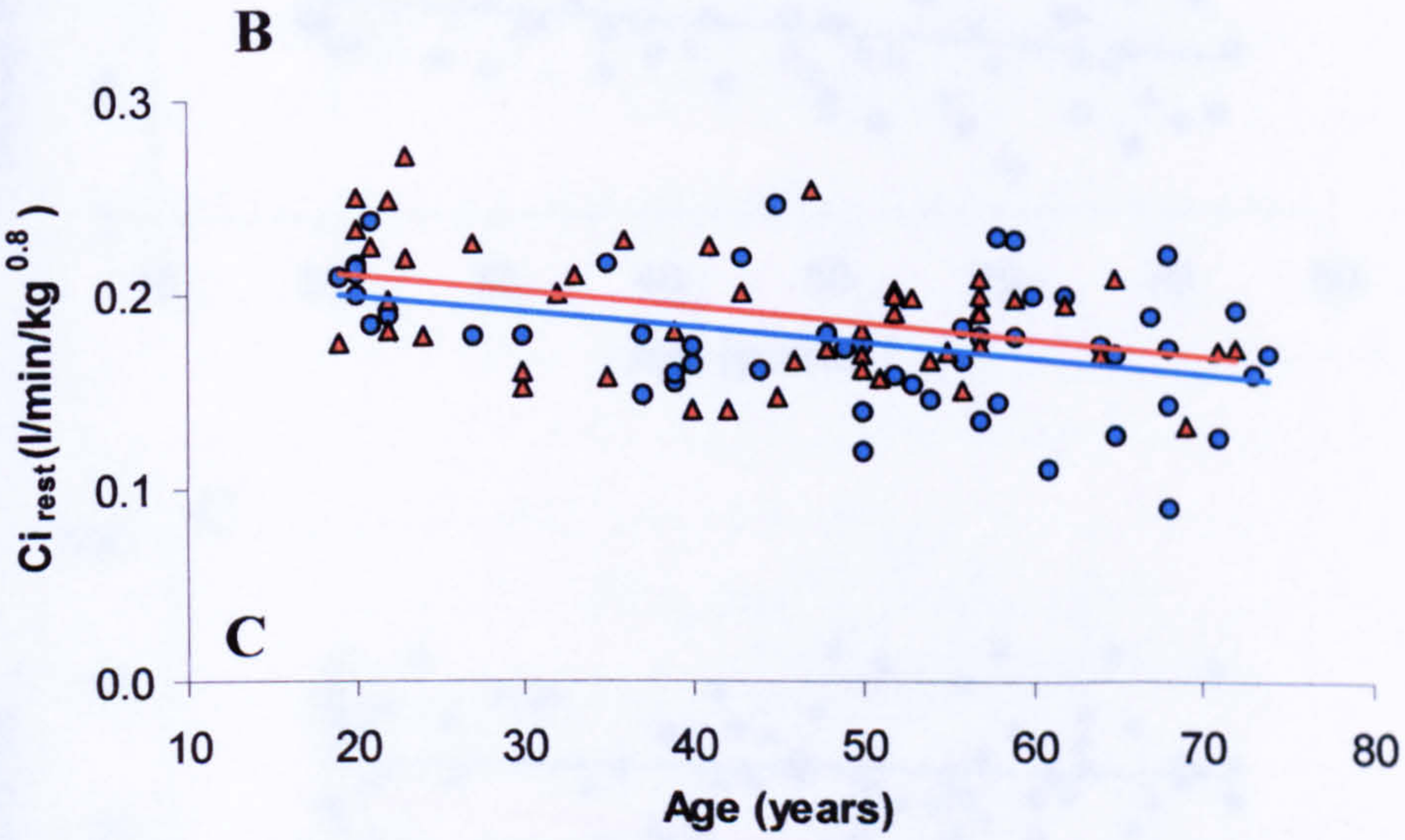


Figure 3.28. The relationship between age and fitness in the measurement of resting blood flow.

The physiological variables are cardiac output (A) and cardiac index (B), for sedentary (●) and active (▲) men. The lines of best fit for the sedentary (—) and active (—) men are shown.

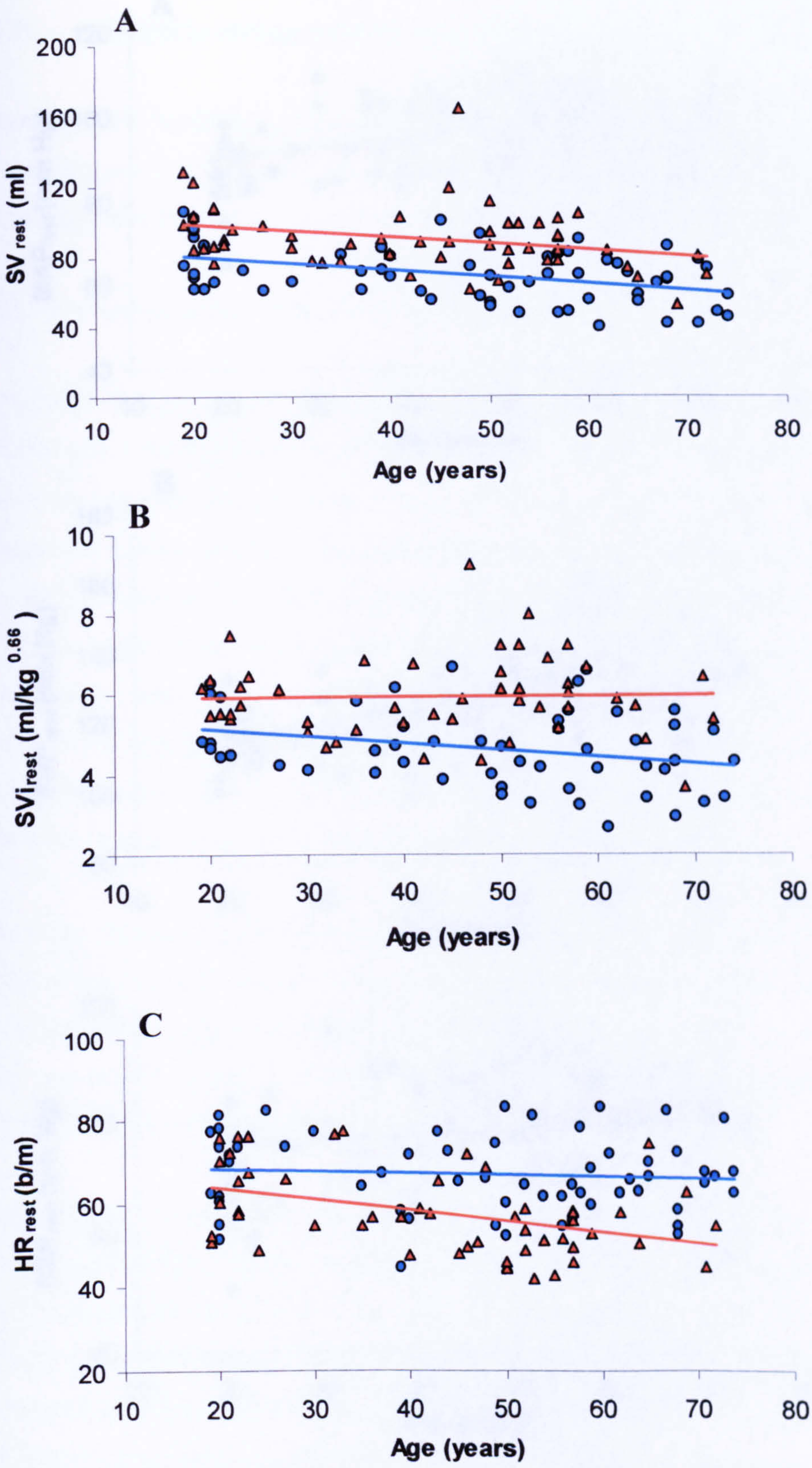


Figure 3.29. The relationships between age and fitness in the measurements of resting stoke volume and heart rate.

Stroke volume (A), stroke volume index (B), and heart rate (C) are plotted against age for sedentary (●) and active (▲) men, with the lines of best fit for sedentary (—) and active (—) men.

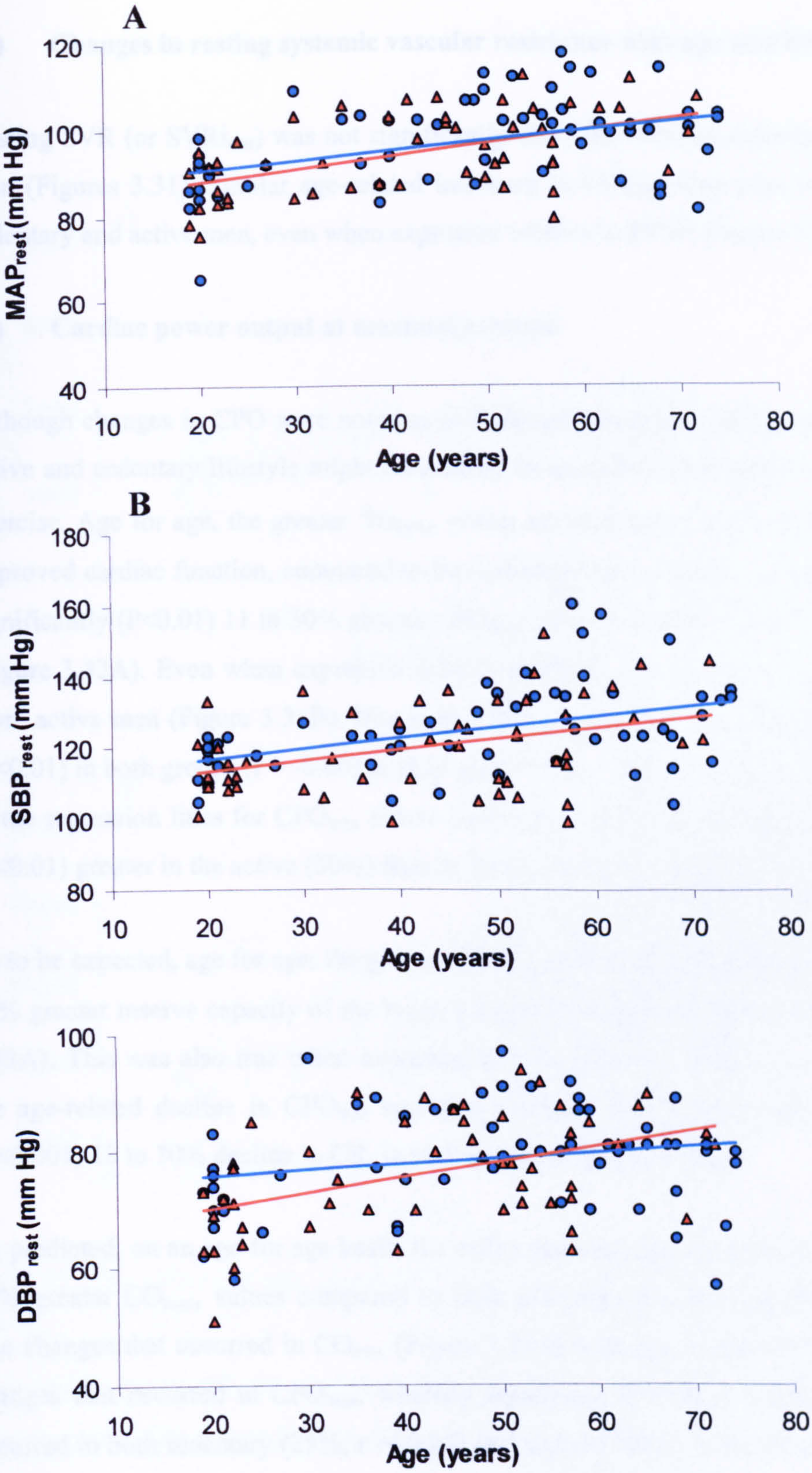


Figure 3.30. The relationships between age and fitness on the measurements of resting blood pressure.

Mean arterial pressure (A), systolic pressure (B) and diastolic pressure (C) for sedentary (●) and active (▲) men, along with the lines of best fit plotted against age for sedentary (—) and active (—) men are shown.

(D) Changes in resting systemic vascular resistance with age and fitness

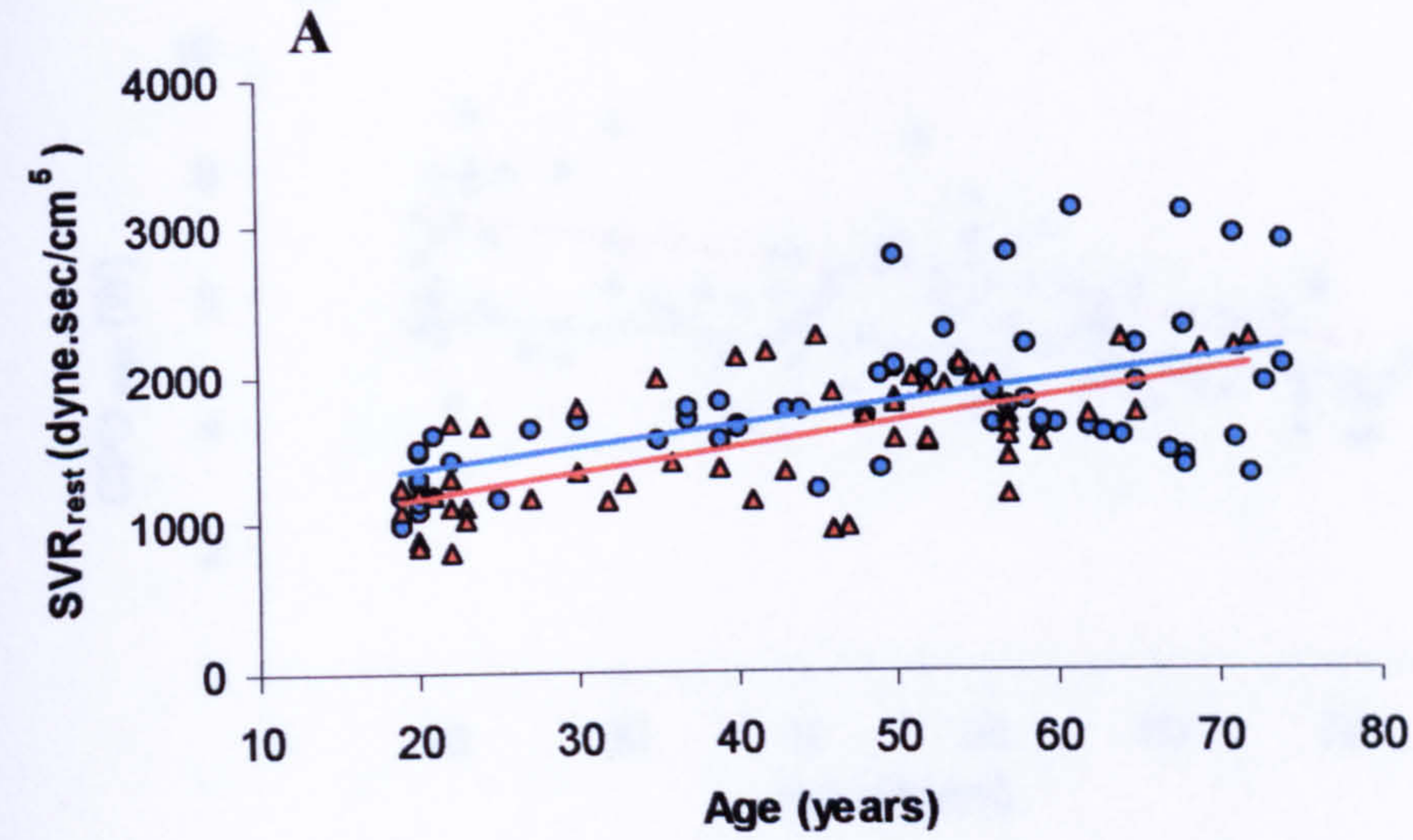
Resting SVR (or $SVRi_{rest}$) was not significantly different between sedentary and active men (Figures 3.31). Similar age-related increases in SVR_{rest} were also evident in the sedentary and active men, even when expressed relative to FFM^b (Figure 3.31B).

(E) Cardiac power output at maximal exercise

Although changes in CPO were noted at rest, the most dramatic difference between an active and sedentary lifestyle might reasonably be expected when performing maximal exercise. Age for age, the greater $\dot{V}O_{2max}$ values attained in the active men suggests an improved cardiac function, compared to the sedentary men. Indeed, the active men had significantly ($P<0.01$) 11 to 30% greater CPO_{max} values compared to the sedentary men (Figure 3.32A). Even when expressed relative to FFM^b, CPi_{max} was still greater in the more active men (Figure 3.31B). However, CPO_{max} (or CPi_{max}) decreased significantly ($P<0.01$) in both groups ($r = -0.60$) as they aged (Figure 3.32). By testing for parallelism of the regression lines for CPO_{max} it was determined that the decline was significantly ($P<0.01$) greater in the active (30%) than in the sedentary (18%) men.

As to be expected, age for age, the greater CPO_{max} in the active men resulted in an 18 to 30% greater reserve capacity of the heart, compared to their sedentary controls (Figure 3.33A). This was also true when expressed as CRi (Figure 3.33B). A consequence of the age-related decline in CPO_{max} was also reflected in a corresponding, significant ($P<0.001$) 18 to 30% decline in CR, in both groups (Figure 3.33A).

As predicted, on an age for age basis, the active men had significantly ($P<0.001$) 10 to 23% greater CO_{max}, values compared to their sedentary counterparts (Figure 3.34A). The changes that occurred in CO_{max} (Figure 3.34A) with age essentially mimicked the changes that occurred in CPO_{max}, whereby significant ($P<0.001$) decreases in CO_{max} occurred in both sedentary (25%; $r = -0.65$) and active (35%; $r = -0.70$) men. However, the active men had a greater rate of decline than their sedentary counterparts. The adjustment of CO_{max} for FFM^b did not change the interpretation of these data; maximal CO remained greater in the active men and the decreases in CO_{max} with age were still evident for both groups when expressed as Ci_{max}.



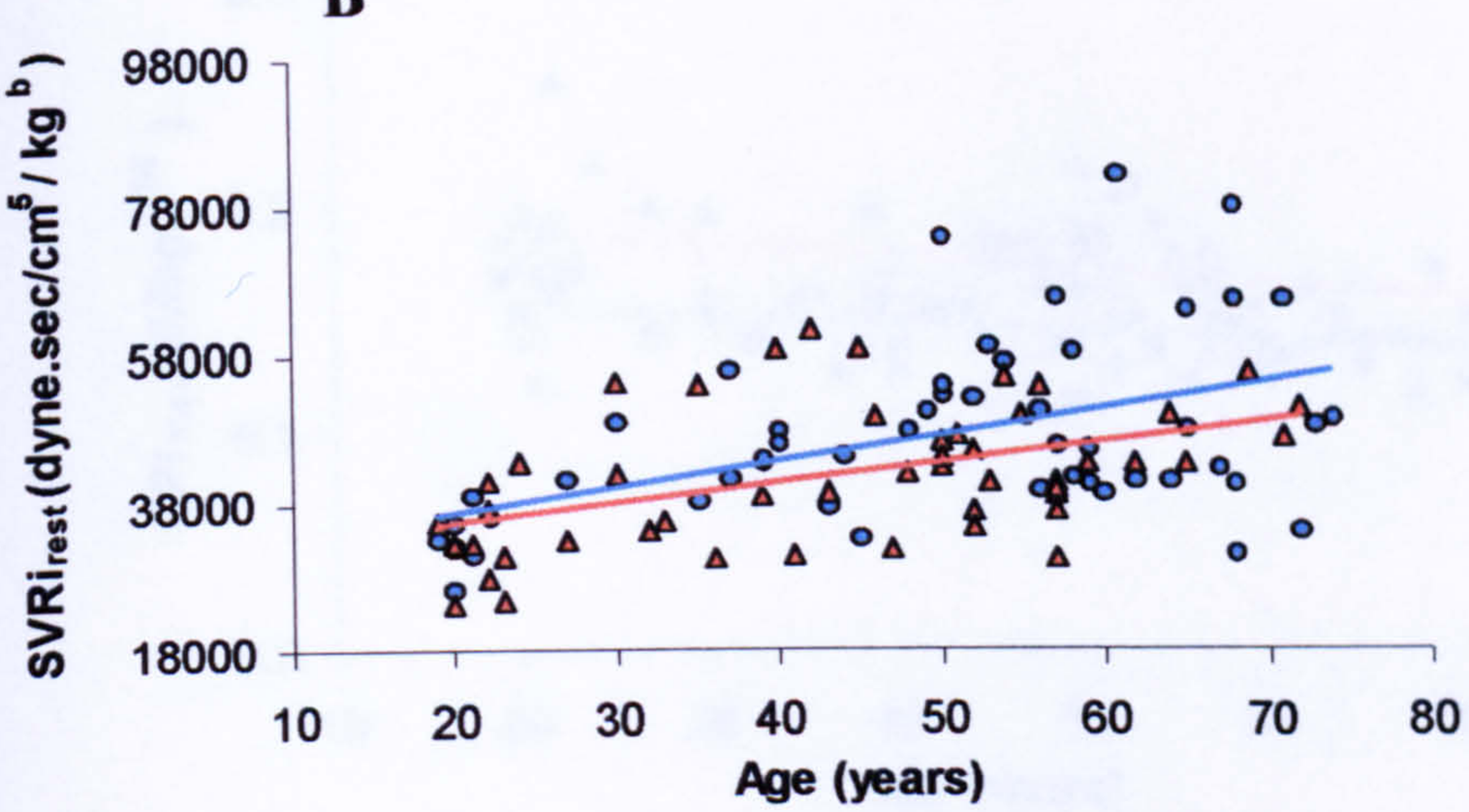


Figure 3.31. The effects of age, physical fitness on resting systemic vascular resistance.

The variables presented are systemic vascular resistance (A) and systemic vascular resistance index (B) for sedentary (●) and active (▲) men with the lines of best fit superimposed on the data for sedentary (——) and active (——) men.

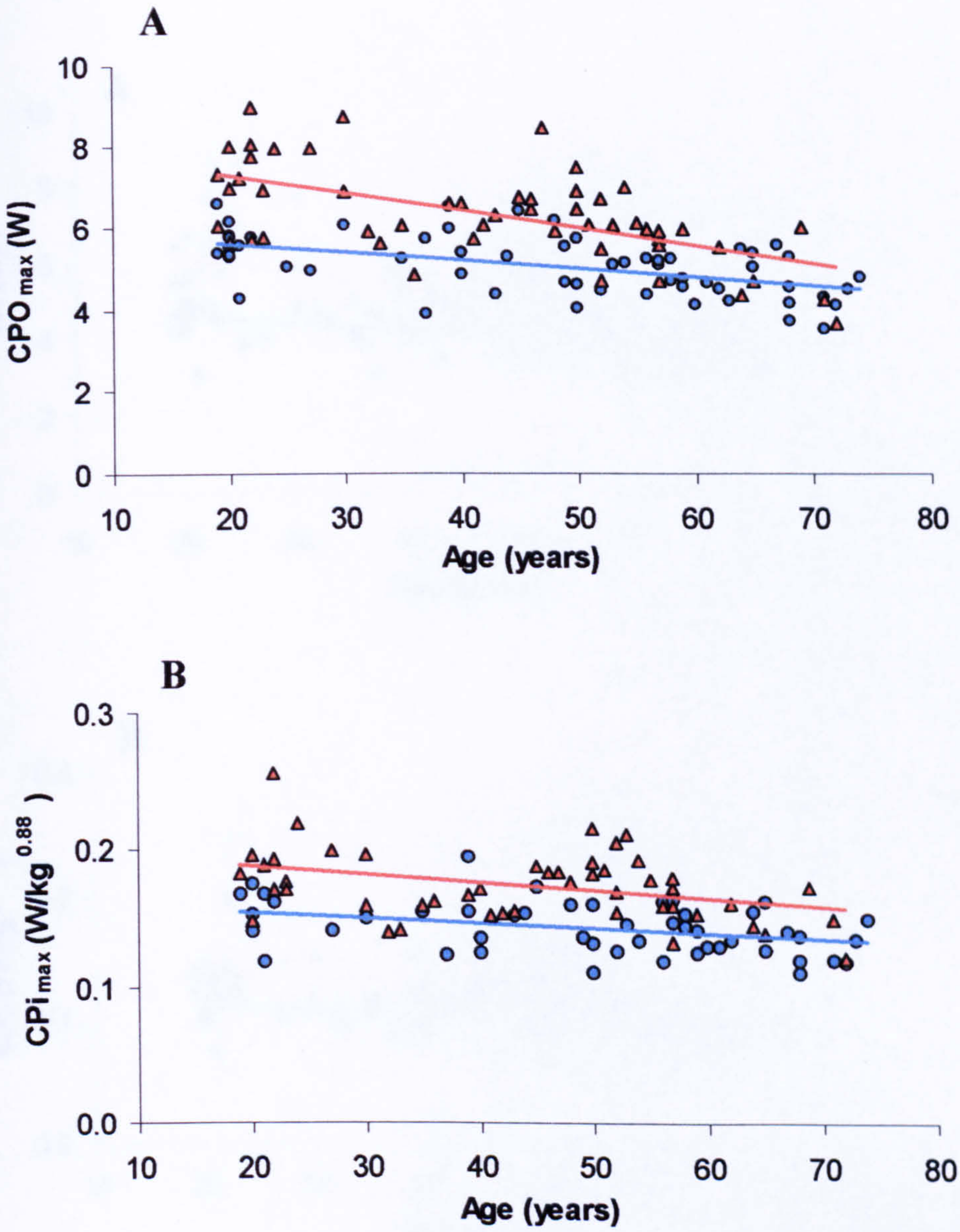


Figure 3.32. Age, fitness and measurements of maximal cardiac power. The variables are cardiac power output (A) and cardiac power index (B), for sedentary (●) and active (▲) men. Superimposed on the figures are the lines of best fit for sedentary (——) and active (——) men.

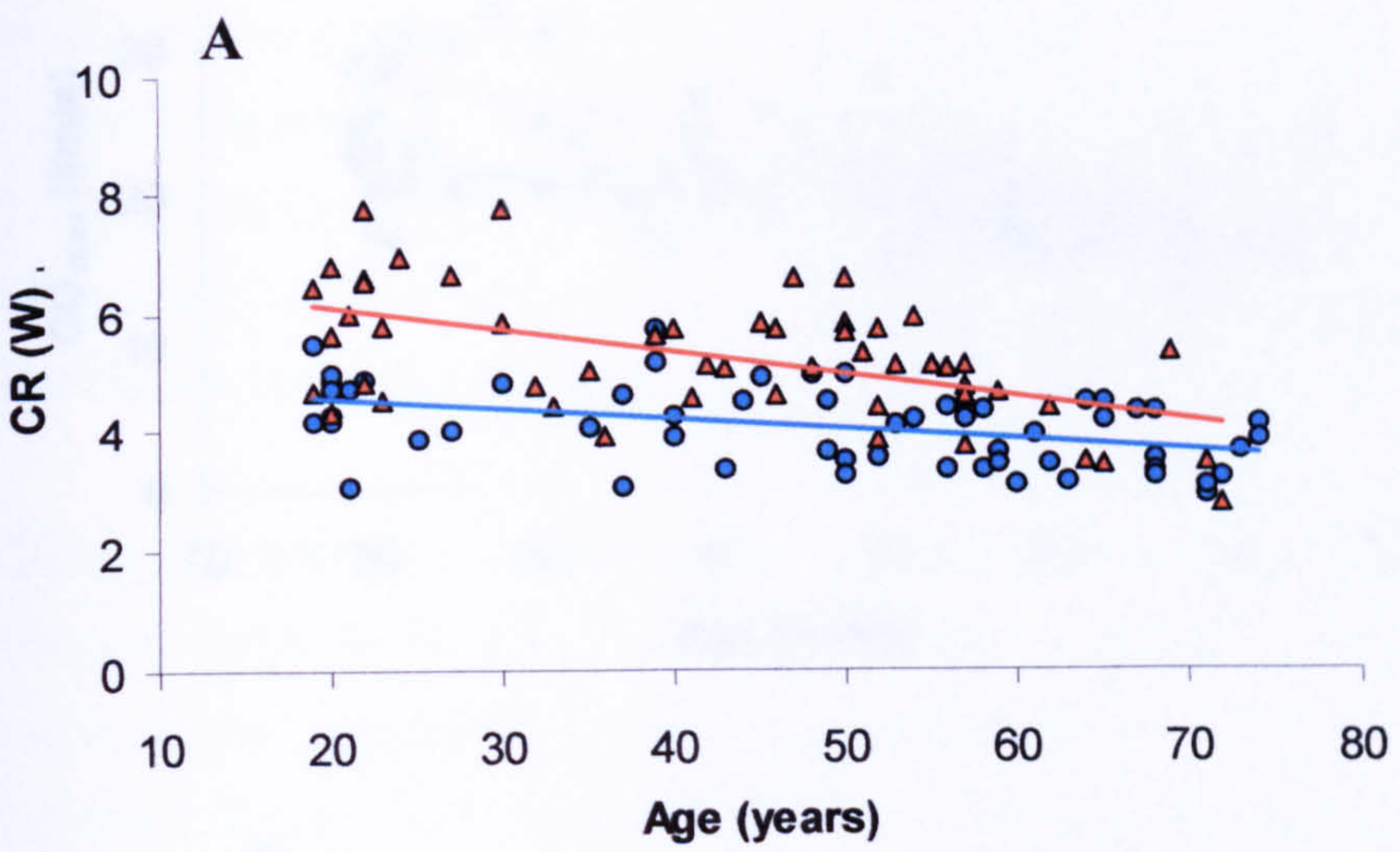


Figure 3.33. Age and fitness in relation to measurements of the reserve capacity of the heart.

The variables are cardiac reserve (A) and cardiac reserve index (B) for sedentary (●) and active (▲) men, with the lines of best fit for the sedentary (—) and active (—) men.

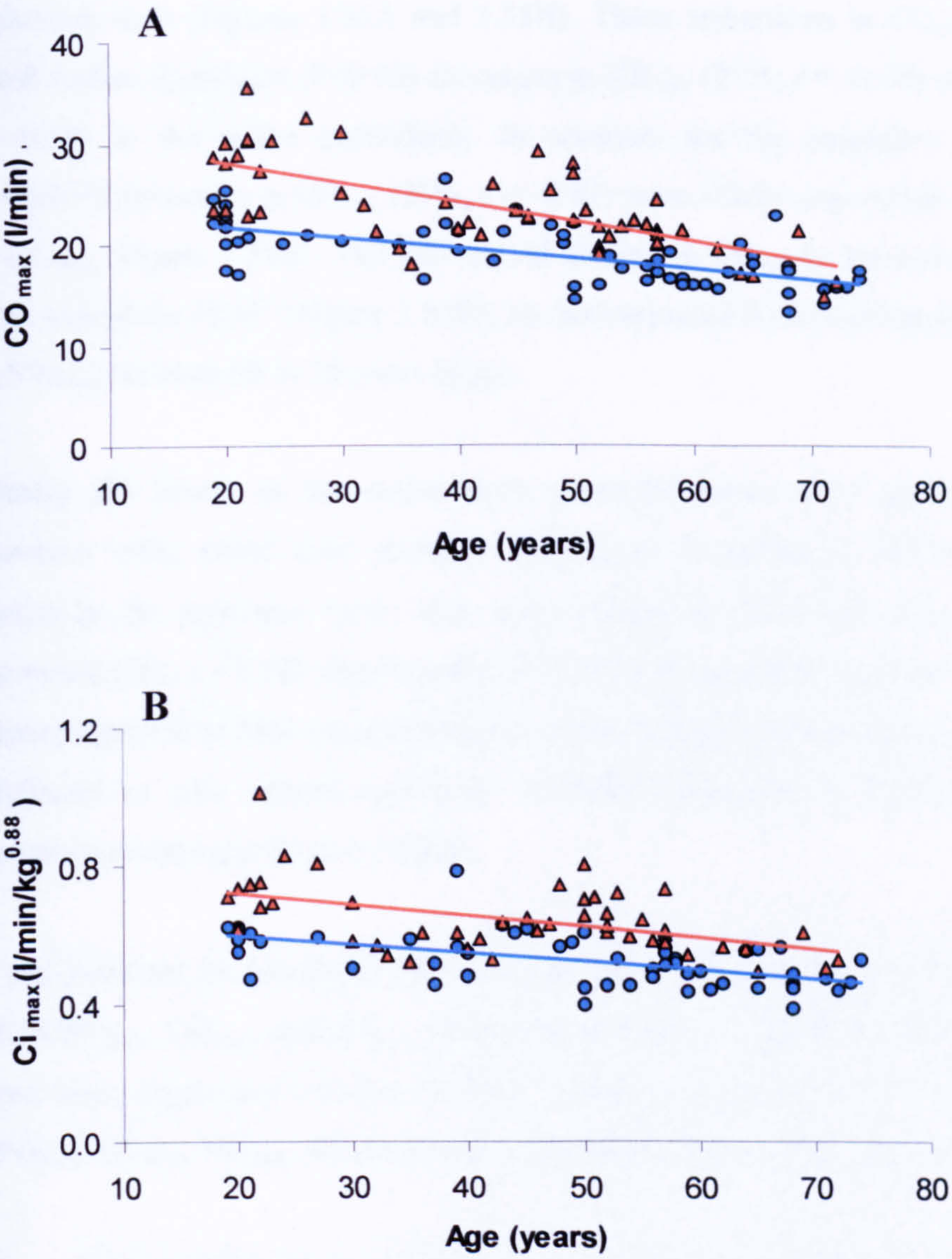


Figure 3.34. The relationship between age and fitness and the measurement of maximal cardiac output.

The variables are cardiac output (A) and cardiac index (B), for sedentary (●) and active (▲) men. Superimposed on the figures are the lines of best fit for sedentary (—) and active (—) men.

In keeping with their larger CO_{max}, (or Ci_{max}) age for age, the active men possessed significantly ($P<0.01$) 12 to 24% greater SV_{max} (or SVi_{max}) values, compared to the sedentary men (Figures 3.35A and 3.35B). These reductions in CO_{max} with age were attributed to significant ($P<0.05$) decreases in HR_{max} (21%; $r = -0.79$) and SV_{max} (18%; $r = -0.39$) in the active individuals. In contrast, for the sedentary men, significant ($P<0.001$) decreases in HR_{max} (21%; $r = -0.87$) were solely responsible for the decreases in CO_{max} (Figure 3.35A). The age-related decline in SV_{max} in the active group was lost once scaled for FFM^b (Figure 3.35B), as demonstrated by a non-significant 7% decline in SVi_{max} between 20 to 75 years of age.

Clearly the hearts of the active men possessed better flow generating capacities. However what about their pressure generation? Increases in MAP_{max}, as identified earlier in the sedentary men, were also evident in the active men. Maximal MAP increased (8%; $r = 0.29$) significantly ($P<0.05$) with age. The increases in MAP_{max} were almost identical in both groups (Figure 3.36A). In all men the increases in MAP_{max} were attributed to very similar significant ($P<0.001$) increases in DBP_{max}, while SBP_{max} remained unchanged (Figure 3.36B).

It can therefore be concluded that the more active men had greater absolute values for CR, CPO_{max}, CO_{max}, and SV_{max}, compared to their age-matched sedentary counterparts even when expressed relative to FFM^b. However, irrespective of fitness levels, CR, CPO_{max}, CO_{max}, HR_{max}, all decreased, while MAP_{max} increased with age.

(F) Maximal changes in systemic vascular resistance with age and fitness

Age for age, maximal pump afterload (SVR_{max}) was significantly ($P<0.01$) 13 to 22% lower in the active men, compared to their sedentary counterparts (Figure 3.37A). As previously noted, the significant ($P<0.001$) increases in SVR_{max} with age in the sedentary men were also evident in the active men (Figure 3.37A). This age-related relationship remained evident even when expressed as $SVRi_{max}$ (Figure 3.37B), as did the differences ($P<0.01$) between sedentary and active men (Figure 3.37B).

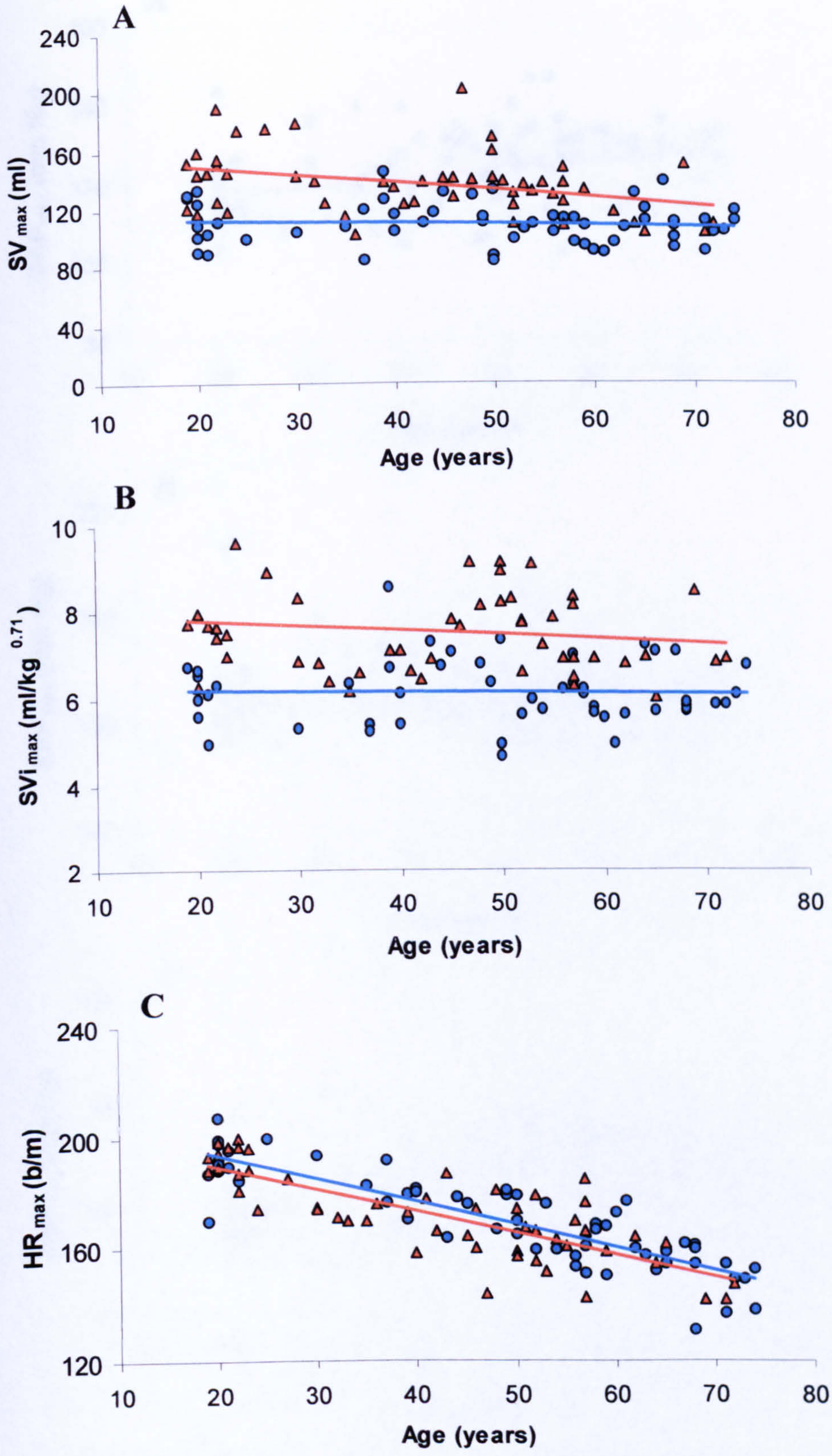


Figure 3.35. The effects of age and fitness on maximal stoke volume and heart rate.

Stroke volume (A), stroke volume index (B), and heart rate (C) are plotted for sedentary (●) and active (▲) men, with the lines of best fit provided for sedentary (—) and active (—) men.

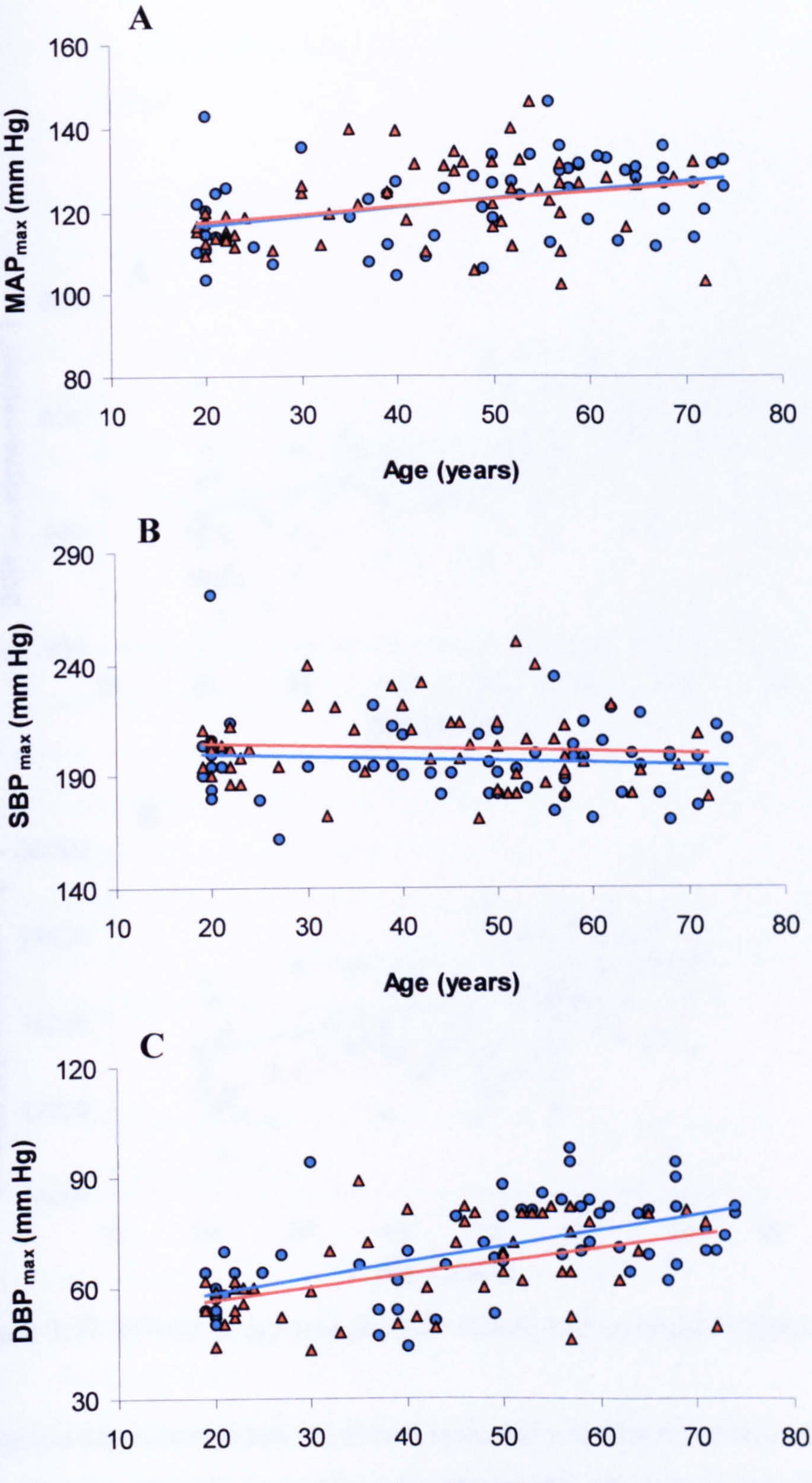


Figure 3.36. Effects of age and physical fitness on maximal blood pressure.

Mean arterial pressure (A), systolic blood pressure (B), and diastolic blood pressure (C) are presented for sedentary (●) and active (▲) men, along with the lines of best fit for sedentary (——) and active (——) men.

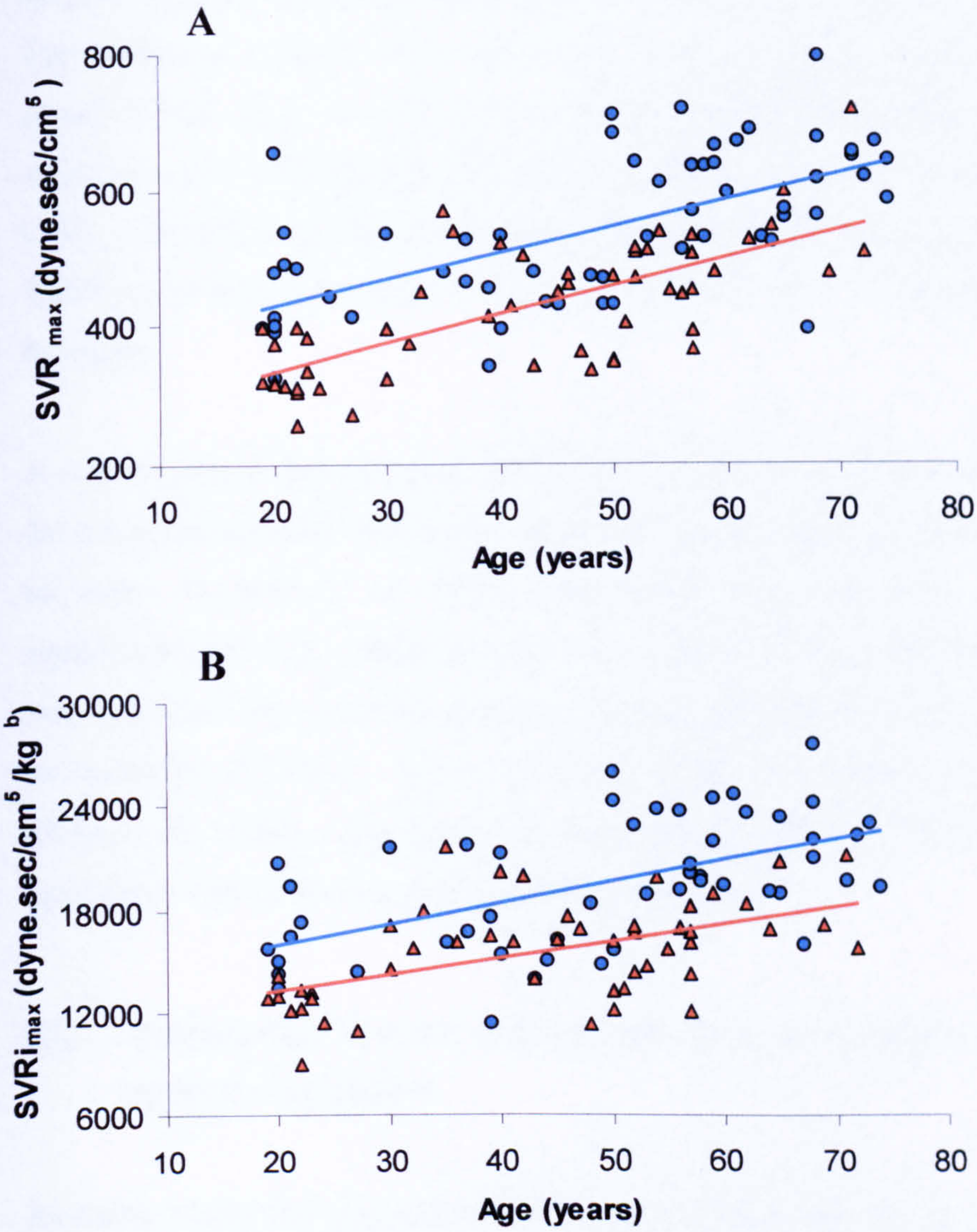


Figure 3.37. Effects of age and physical fitness and maximal systemic vascular resistance. Systemic vascular resistance (A) and systemic vascular resistance index (B) are presented for sedentary (●) and active (▲) men, along with the lines of best fit for sedentary (—) and active (—) men.

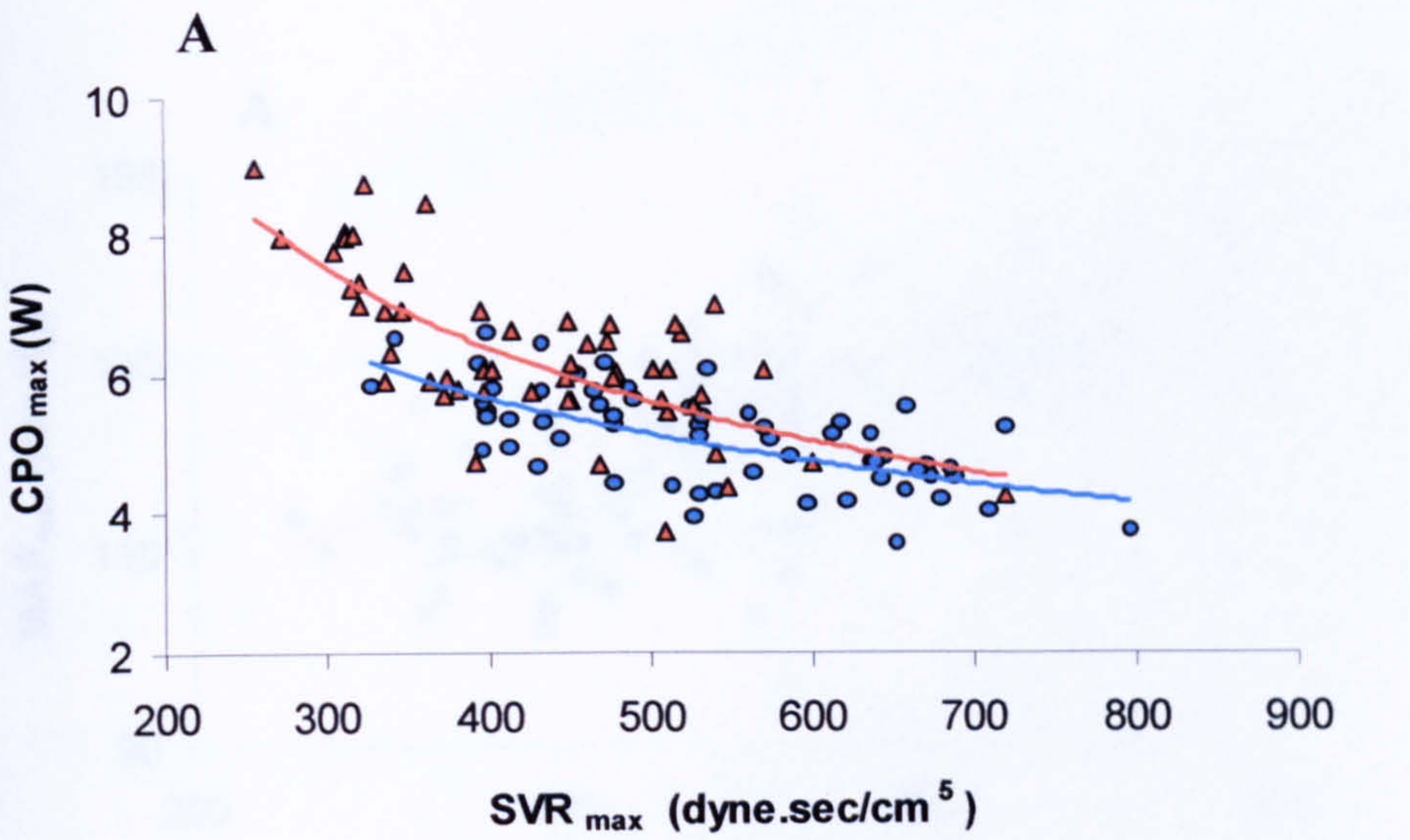
(G) The relationship between maximal cardiac power and systemic vascular resistance

When comparing the maximal pumping performance of the heart (CPO_{max}) and the maximal pump afterload (SVR_{max}) between the sedentary and active men an interesting relationship was found. That is, for a given SVR_{max}, CPO_{max} was significantly ($P<0.05$) greater in the active men (Figure 3.38A). However, both fitness groups expressed a significant ($P<0.001$) decline in CPO_{max} as SVR_{max} increased. Scaling of SVR_{max} and CPO_{max} for FFM^b, did not change the interpretation of these data for active men (Figure 3.38B). But now, no change in CPi_{max} was found in the sedentary men as $SVRi_{max}$ increased.

A similar relationship was also identified between the pressure generating capacity of the heart and vascular resistance at maximal exercise. Both groups of men experienced increases in MAP_{max} as SVR_{max} increased. However active men possessed a significantly ($P<0.01$) greater MAP_{max} for any given SVR_{max}, compared to the sedentary men (Figure 3.39A), indicating that the pressure generating capacity was at least in part independent of SVR_{max}. When scaled for FFM^b, the positive relationships between $SVRi_{max}$ and MAP_{max} remained significant (Figure 3.39B), but with the active men still presenting with greater pressure generating capacities.

(H) Relationship between maximal pumping performance of the heart and oxygen consumption

Research examining the relationship between CO_{max} and $\dot{V}O_{2max}$ has reported strong positive correlations between the two variables (Cooke *et al.,* 1998). This relationship was confirmed in the current study. That is, when the sedentary and active male data were pooled together a Pearson's correlation of 0.86 was obtained for relationship between CO_{max} (l/min) and $\dot{V}O_{2max}$ (l/min; Figure 3.40A). This relationship was also evident in women ($r = 0.80$). Strong significantly ($P<0.001$) positive relationships between $\dot{V}O_{2\,max}$ (l/min) and CPO_{max} were also evident (Figure 3.40C), in men ($r = 0.80$) and women ($r = 0.58$), despite significant ($P<0.01$) negative correlations between $\dot{V}O_{2max}$ (l/min) and MAP_{max} in men ($r = -0.31$) and women ($r = -0.25$) (Figure 3.40B).



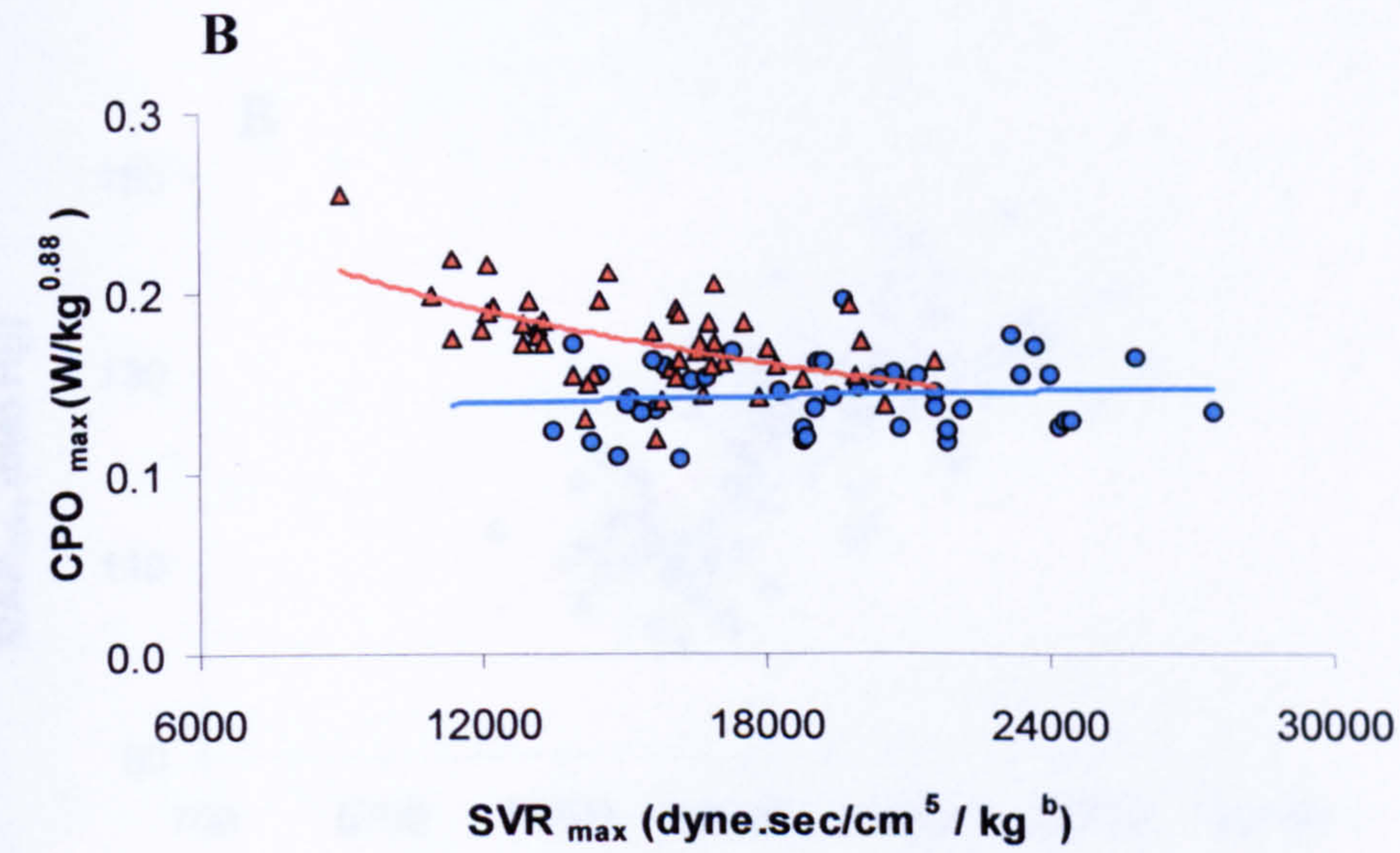
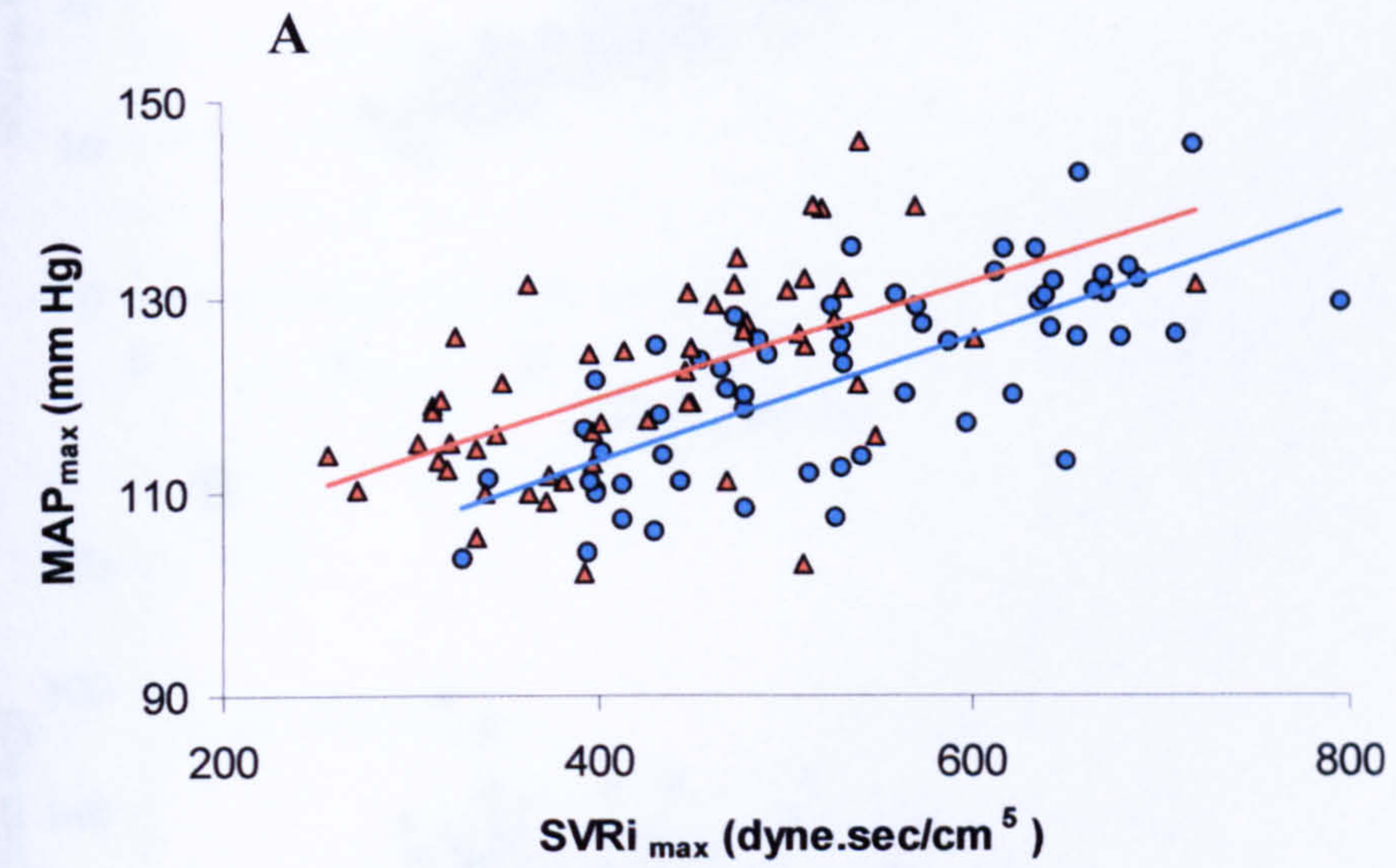


Figure 3.38. The relationship between maximal systemic vascular resistance and maximal cardiac power output in sedentary and active men.

The variables presented are maximal systemic vascular resistance compared to maximal cardiac power (A), and systemic vascular resistance index compared to maximal cardiac power index (B) for sedentary (●) and active (▲) men. The lines of best fit for the sedentary (—) and active men (—) are shown.



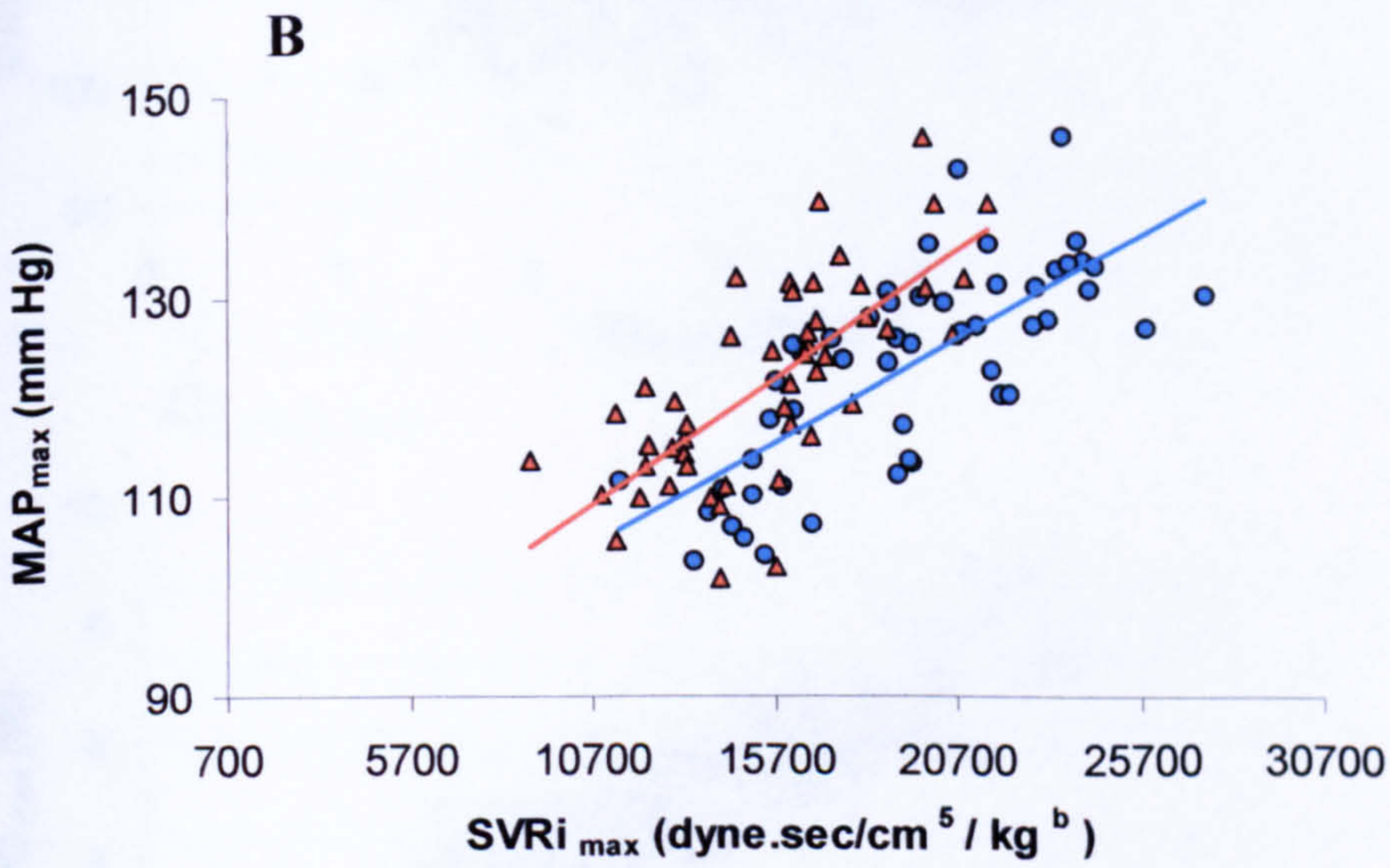


Figure 3.39. Maximal systemic vascular resistance relative to maximal mean arterial pressure in sedentary and active men.

The variables plotted are for maximal systemic vascular resistance (A) and maximal systemic vascular resistance index (B), compared against maximal mean arterial pressure as measured in sedentary (●) and active (▲) men. Lines of best fit for the sedentary (—) and active men (—) are shown.

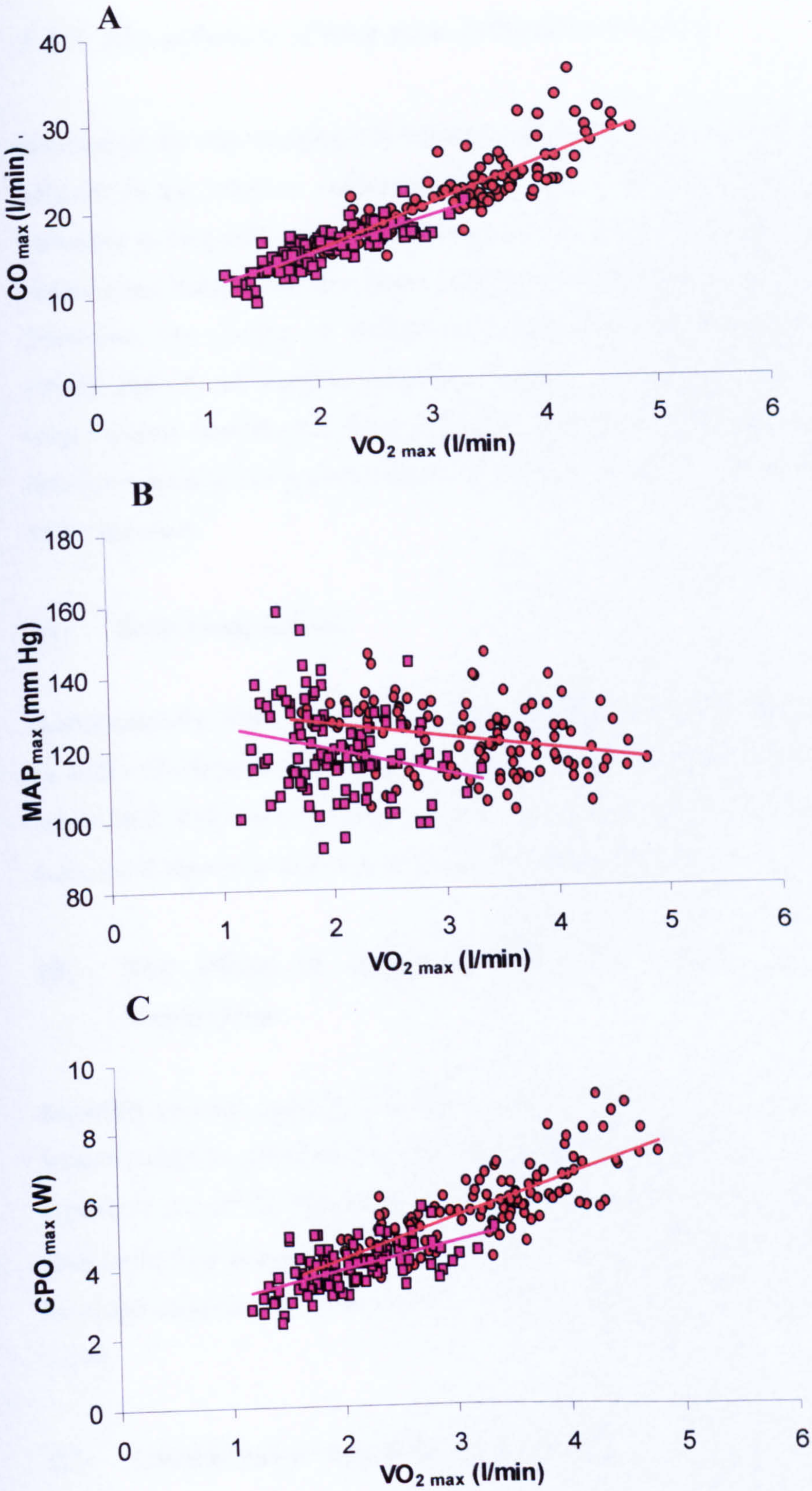


Figure 3.40. Changes in maximal cardiac output, mean arterial pressure and cardiac power output relative to maximal oxygen uptake.

The variables shown are (A) cardiac output, (B) mean arterial pressure, and (C) cardiac power output for active and sedentary men (●) and women (■). The lines of best fit are shown for men (——) and women (——). Data corresponds to all fitness levels for men and women, n = 222.

3.3.3. The influence of long-term endurance training

Because of the wide ranging and heterogeneous sample of ages and fitness levels of the subjects in the previous section (section 3.3.2), a more in-depth examination of the influence of long-term endurance training on CPO was undertaken. The purpose was to obtain more insight into the effects of high level of physical activity on ageing per se. Therefore, two groups of veteran endurance-trained, male subjects were examined strictly against age-matched sedentary controls. The veteran athletes consisted of 20 long distance runners, and 1 long distance swimmer. On average the veteran athletes had been training for approximately 18 years with an average training distance of 32 miles per week.

(A) Body Composition

Anthropometric data describing the effects of fitness on body composition are presented in Table 3.9. Veteran athletes (mean ages of 50 and 58 years) had significantly ($P<0.05$) lower BM, FM and percentage of body fat, compared to the age-matched sedentary men. No differences were found for FFM between the groups.

(B) The effects of long-term endurance training on maximal oxygen consumption

Maximal aerobic capacity has been shown to be significantly higher in endurance trained subjects, compared to their sedentary counterparts (Tanaka and Seals, 2003; Ogawa *et al.*, 1992). This study confirms these reports. The 50 and 58 year-old veteran athletes had on average 34 to 44% greater ($P<0.001$) $\dot{V}O_{2max}$ values, whether expressed in either absolute terms or relative to FFM^b, compared to the sedentary men (Table 3.10).

(C) Cardiac power output measured at rest

No significant differences were found in any of the resting values, i.e. CPO_{rest}, CO_{rest}, or MAP_{rest} between the veteran athletes and their age-matched controls (Table 3.11 and Figure 3.41A). Although, SVR_{rest} was lower at 50 (10%) and 58 (16%) years, compared

Table 3.9. Anthropometric characteristics of veteran endurance trained athletes and sedentary men.

	Ages of men (years)				
	Veteran Athletes		Sedentary		
	50 ± 0.8	58 ± 0.7	21 ± 0.5	50 ± 0.8	60 ± 0.8
Height (cm)	171.7 ± 2.3	172.8 ± 1.8	177.5 ± 2.5	175.9 ± 2.2	171.9 ± 1.4
Body mass (kg)	73.2 ± 4.1*	72.9 ± 2.6*	82.3 ± 3.3	85.0 ± 2.3	80.7 ± 2.3
Body surface area (m^2)	1.8 ± 0.03	1.9 ± 0.04	2.0 ± 0.05	2.0 ± 0.03	1.9 ± 0.03
Fat free mass (kg)	57.2 ± 2.5	57.4 ± 1.3	59.3 ± 1.8	59.7 ± 0.9	57.0 ± 1.4
Fat mass (kg)	13.3 ± 1.8**	12.6 ± 1.8**	15.4 ± 1.1	22.5 ± 1.8^{++}	22.7 ± 1.2^{++}
Fat (%)	17.4 ± 1.5*	16.8 ± 1.7**	19.4 ± 1.0	25.9 ± 1.5^{+}	27.7 ± 1.1^{+}

Table 3.10. Changes in maximal oxygen consumption and arterial-venous oxygen difference with age and fitness.

	Ages of men (years)				
	Veteran Athletes		Sedentary		
	50 ± 0.8	58 ± 0.7	21 ± 0.5	50 ± 0.8	60 ± 0.8
$\dot{V}O_{2\,max}$ (l/min)	3.5 ± 0.1**	3.3 ± 0.1**	3.6 ± 0.1	2.8 ± 0.2^{++}	2.4 ± 0.1^{++}
$\dot{V}O_{2\,max}$ (ml/min/kg)	48.9 ± 1.8**	45.6 ± 2.1**	43.7 ± 1.7	33.2 ± 1.8^{++}	30.1 ± 1.0^{++}
$\dot{V}O_{2\,max}$ (ml/min/$kg^{1.15}$)	32.5 ± 0.8**	28.7 ± 1.4**	31.7 ± 1.2	22.6 ± 1.3^{++}	21.1 ± 0.8^{++}
a-v O_2 diff (ml/100ml)	15.0 ± 0.4	15.6 ± 0.4	16.4 ± 0.4	15.0 ± 0.6	14.2 ± 0.3

Data are presented as means ± SEM, n = minimum of 9 per group (range = 9 – 14). Significant differences at *P<0.05 and **P<0.001 compared to age-matched controls, and $^{+}$P<0.05 and $^{++}$P<0.001 compared to sedentary 21 year-old men.

Table 3.11. Haemodynamic values at rest in relation to long-term endurance training and age.

	Ages of men (years)				
	Veteran Athletes		Sedentary		
	50 ± 0.8	58 ± 0.7	21 ± 0.5	50 ± 0.8	60 ± 0.8
HR (b/m)	51 ± 1.5**	53 ± 1.9**	70 ± 3.0	67 ± 3.3	66 ± 2.1
SV (ml)	92.3 ± 7.5*	90.2 ± 3.4*	81.1 ± 4.8	67.5 ± 5.6	67.5 ± 4.2
SVi (ml/kg $^{0.66}$)	6.4 ± 0.4**	6.2 ± 0.2*	5.1 ± 0.2	4.3 ± 0.3	4.7 ± 0.3
CO (l/min)	4.6 ± 0.4	4.7 ± 0.2	5.5 ± 0.2	4.4 ± 0.3^{+}	4.4 ± 0.2^{+}
Ci (l/min/kg $^{0.8}$)	0.2 ± 0.01	0.2 ± 0.01	0.2 ± 0.01	0.2 ± 0.01	0.2 ± 0.01
SBP (mm Hg)	121 ± 3.6	123 ± 5.6	116 ± 1.7	129.4 ± 3.0	133.0 ± 4.0^{+}
DBP (mm Hg)	80 ± 2.0^{+}	76 ± 2.9	71 ± 2.0	86 ± 2.1^{++}	80.8 ± 1.8^{+}
MAP (mm Hg)	97 ± 2.3^{+}	95 ± 3.1	87 ± 2.4	103 ± 2.6^{++}	102 ± 2.3^{++}

Data are presented as means ± SEM, for the same subjects used in Table 3.9. Significant differences *P<0.05 and **P<0.001 are compared to age-matched controls, and at $^{+}$P<0.05 and $^{++}$P<0.001 compared to sedentary 21 year-old men.

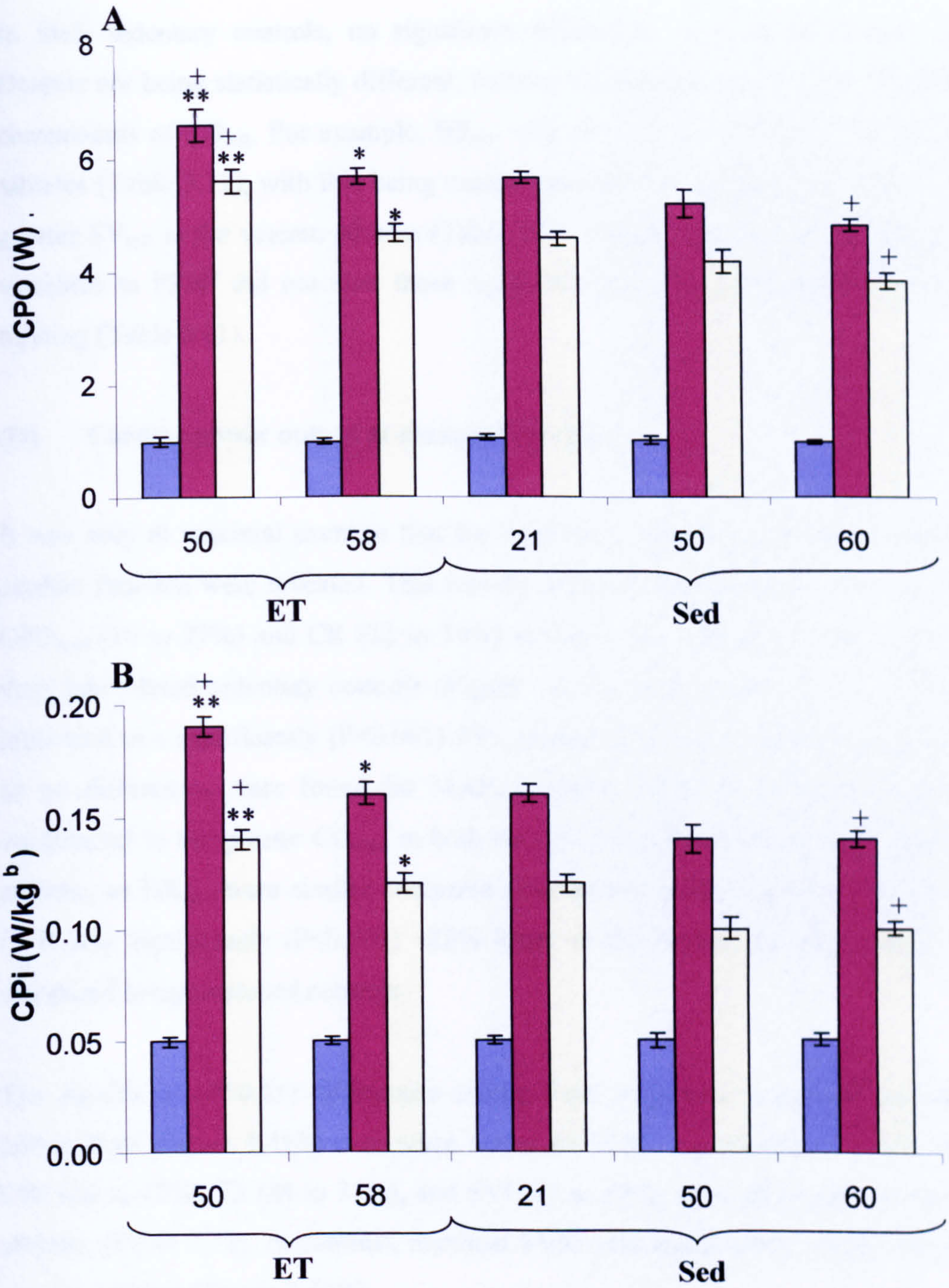


Figure 3.41. Effects of long-term endurance training and ageing on cardiac power output.

The variables are cardiac power output (A) and cardiac power index (B) for endurance trained (ET) and sedentary (Sed) men. Resting measures are presented in the blue (■), maximal measures in the purple (■) and cardiac reserve in the cream (□) bars. Data are presented as Means ± SEM, n = 9 - 14. Significant differences at *P<0.05 and **P<0.001 are compared to age-matched controls, and at $^{+}$P<0.05 and $^{+}$P<0.001 compared to sedentary 21 year-old men.

to their sedentary controls, no significant differences were found (Figure 3.42A). Despite not being statistically different, training-related differences were evident in the components of CO_{rest}. For example, HR_{rest} was ~22% lower ($P<0.001$), in the veteran athletes (Table 3.11), with this being compensated for by significantly ($P<0.01$) ~35% greater SV_{rest} in the veteran athletes (Table 3.11). Normalisation of the haemodynamic variables to FFM^b did not alter these significant differences produced by endurance training (Table 3.11).

(D) Cardiac power output at maximal exercise

It was only at maximal exercise that the benefits of long-term endurance training on cardiac function were revealed. This was illustrated by significantly ($P<0.001$) greater CPO_{max} (18 to 27%) and CR (22 to 34%) values in the veteran athletes, compared to their age-related sedentary controls (Figure 3.41A). The greater CPO_{max} values were attributed to a significantly ($P<0.001$) 25% greater CO_{max} value in the veteran athletes, as no differences were found for MAP_{max} (Table 3.12). In turn, the larger SV_{max} contributed to the greater CO_{max} in both the 50 (32%) and 58 (21%) year-old veteran athletes, as HR_{max} were similar compared to sedentary controls (Table 3.12). Maximal SVR was significantly ($P<0.001$) ~22% lower in the veteran athletes (Figure 3.42A) compared to age matched controls.

The significant ($P<0.01$) differences arising from long-term endurance training were still evident (Figure 3.41B) even when scaled for FFM^b, i.e. maximal CPi (16 to 34%), CRi (20 to 42%), Ci (24 to 31%), and SVi (21 to 37%) were all greater in the veteran athletes (Table 3.12). In contrast, maximal SVRi was significantly lower (24%) in the veteran athletes (Figure 3.42B).

Not only were the benefits of long-term endurance training apparent on measuring maximal cardiac function in relation to men of the same age, but interesting differences arose when comparing active older men to sedentary 21 year-old men. That is, CPO_{max} and CR values were significantly ($P<0.01$) higher in the 50 year-old veteran athletes, by as much as 17% and 22%, respectively (Figure 3.41A). These findings indicate that maximal cardiac function had been more than fully preserved against the

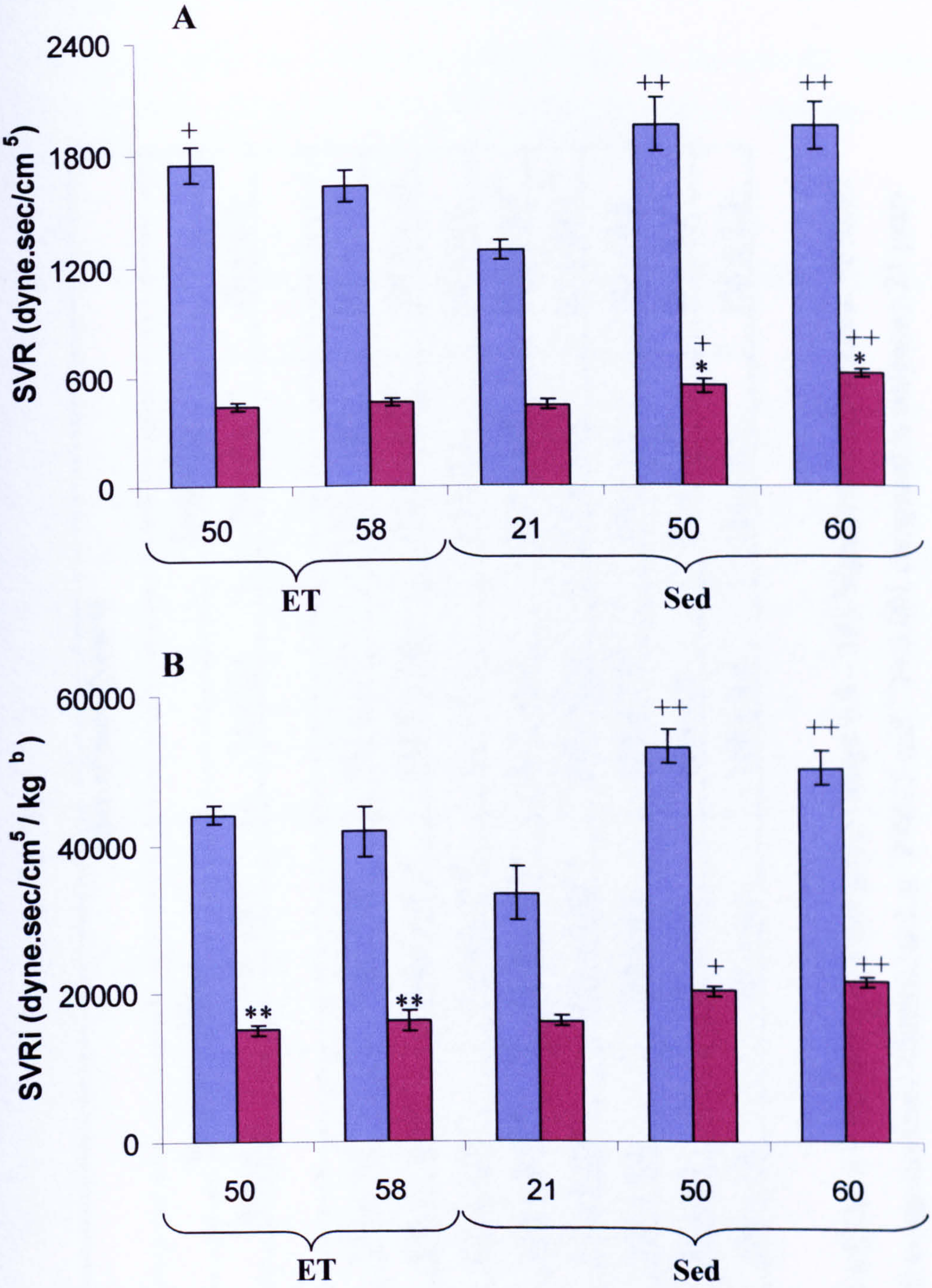


Figure 3.42. The relationships between long-term endurance training, age and systemic vascular resistance.

Systemic vascular resistance (A) and systemic vascular resistance index (B) are given for endurance trained (ET) and sedentary (Sed) men, with resting measures in blue (■) and maximal measures in the purple (■) bars. Data are presented as Means ± SEM, n = 9 - 14. Significant differences at *P<0.05 and **P<0.001 are compared to age-matched controls, and at $^{+}$P<0.05 and $^{++}$P<0.001 compared to sedentary 21 year-old men.

Table 3.12 Haemodynamic values at maximal exercise relative to long-term endurance training and age.

	Ages of men (years)				
	Veteran Athletes		Sedentary		
	50 ± 0.8	58 ± 0.7	21 ± 0.5	50 ± 0.8	60 ± 0.8
HR (b/m)	162 ± 2.4^{++}	166 ± 3.9^{++}	192 ± 2.7^{++}	171 ± 2.6^{++}	161 ± 2.3^{++}
SV (ml)	146.0 ± 6.5**$^{+}$	128.4 ± 4.1*	113.6 ± 4.0	110.3 ± 5.5	105.9 ± 3.0
SVi (ml/kg $^{0.71}$)	8.3 ± 0.2**$^{+}$	7.2 ± 0.2**$^{+}$	6.3 ± 0.1	6.0 ± 0.3	6.0 ± 0.2
CO (l/min)	23.6 ± 0.9**	21.2 ± 0.6**	21.7 ± 0.6	18.9 ± 1.0^{+}	17.0 ± 0.4^{++}
Ci (l/min/kg $^{0.88}$)	0.7 ± 0.02**	0.6 ± 0.02**	0.6 ± 0.01	0.5 ± 0.03^{+}	0.5 ± 0.01^{++}
SBP (mm Hg)	205 ± 6.4	198 ± 4.3	202 ± 7.0	194 ± 3.2	197 ± 4.8
DBP (mm Hg)	71 ± 2.1	67 ± 4.3	59 ± 1.8	75 ± 3.3^{++}	79 ± 2.5^{++}
MAP (mm Hg)	126 ± 3.0	121 ± 3.2	118 ± 3.0	124 ± 2.5	128 ± 2.4

Data are presented as means ± SEM. n = minimum of 9 per group (range = 9 – 14). Significant differences at *P<0.05 and **P<0.001 are compared to age-matched controls, and at $^{+}$P<0.05 and $^{++}$P<0.001 compared to sedentary 21 year-old men.

process of ageing by endurance training. Even, the 58 year-old veteran athletes presented with similar CPO_{max} and CR values compared to sedentary men 38 years younger.

(E) Changes in cardiac structure due to long-term endurance training and age

Long-term endurance training and ageing have been shown to affect certain structural features of the heart, which may account for the observed differences in maximal cardiac function. Therefore, echocardiographic data obtained on groups of sedentary men between 20 and 70 years were examined to show any age-and fitness-related changes in cardiac structures. Although not statistically significant, age-related decreases in posterior wall thickness (PWT), left ventricular internal diameter in diastole (LVIDd) and systole (LVIDs), left ventricular end diastolic volume (LVEDV), left ventricular volume (LVV) and left ventricular mass (LVM) were apparent over the 50 year age span (Figure 3.43). These trends were either prevented or delayed by long-term endurance training.

In summary, long-term endurance training appears to preserve cardiac structures and overall performance when viewed against healthy ageing and a sedentary lifestyle.

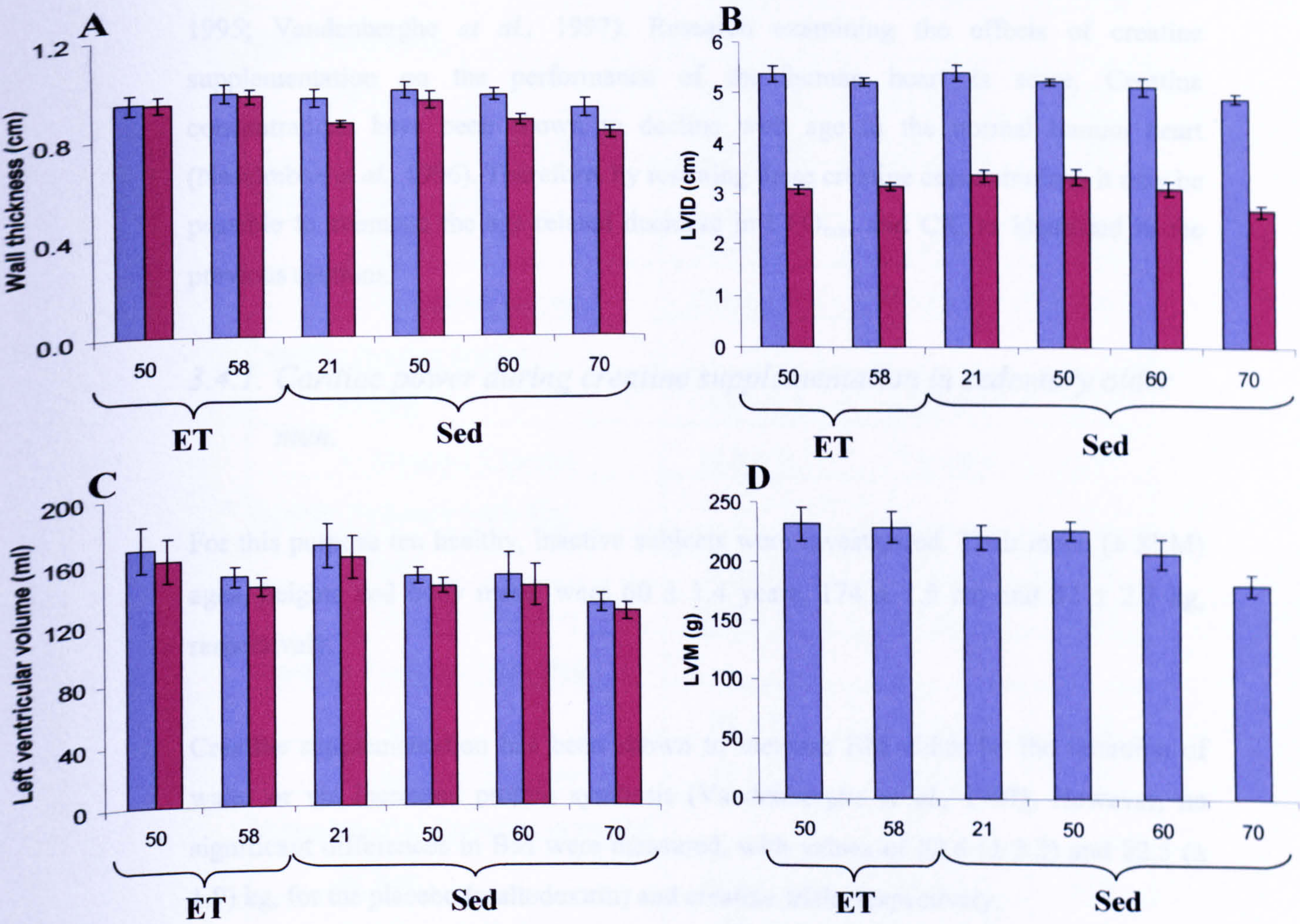


Figure 3.43. The relationship between age, fitness and structural dimensions of the heart

The structure variables measured are [A] septal wall (■) and posterior wall (■) thickness; [B] left ventricular internal diameter during diastole (■) and systole (■); [C] left ventricular volume (■) and left ventricular end diastolic volume (■); [D] left ventricular mass. Data are expressed as means ± SEM, n = 9 - 14. No significant differences were found.

3.4. The effects of creatine supplementation on measurements of cardiac power output in older sedentary and trained men.

Dietary creatine supplementation has been shown to have positive ergogenic effects in improving skeletal muscle performance in both young and older men (Balsom *et al.*, 1995; Vandenberghe *et al.*, 1997). Research examining the effects of creatine supplementation on the performance of the human heart is scare. Creatine concentrations have been shown to decline with age in the normal human heart (Nascimben *et al.*, 1996). Therefore, by restoring these creatine concentrations it may be possible to attenuate the age-related decrease in CPO_{max} and CR, as identified in the previous sections.

3.4.1. Cardiac power during creatine supplementation in sedentary older men.

For this purpose ten healthy, inactive subjects were investigated. Their mean (± SEM) ages, heights and body mass' were 60 ± 1.4 years, 174 ± 1.9 cm and 82 ± 2.2 kg, respectively.

Creatine supplementation has been shown to increase BM either by the retention of water or via increased protein synthesis (Vandenberghe *et al.*, 1997). However, no significant differences in BM were measured, with values of 82.6 (± 2.2) and 82.5 (± 1.9) kg, for the placebo (maltodextrin) and creatine trials, respectively.

Examination of resting cardiac function revealed no significant differences in CPO_{rest}, when comparing 5 days of either creatine or placebo supplementation (Table 3.12). Furthermore, no significant differences were measured in either of the component parts used to that determine CPO that is, MAP_{rest} and CO_{rest} (Table 3.13). Other basal haemodynamic variables such as resting HR, SV, SBP, and DBP were also unchanged by creatine ingestion.

Therefore, all of these measurements made at rest were very similar regardless of whether creatine or maltodextrin (drinks) was ingested.

Table 3.13. Resting and maximal measures of cardiac function in response to either placebo or creatine supplementation.

	Supplementation		
	Placebo	Creatine	P-Value
Heart Rate (b/m)			
At Rest	65 ± 2.2	67 ± 2.3	0.43
At Maximal Exercise	160 ± 2.6	158 ± 3.6	0.20
Stroke Volume (ml)			
At Rest	65.4 ± 3.9	64.5 ± 2.6	0.82
At Maximal Exercise	115.5 ± 5.5	114.4 ± 6.4	0.76
Cardiac Output (l/min)			
At Rest	4.2 ± 0.2	4.3 ± 0.1	0.59
At Maximal Exercise	18.4 ± 0.7	17.9 ± 0.6	0.37
Systolic Pressure (mm Hg)			
At Rest	132 ± 5.0	122 ± 2.7	0.07
At Maximal Exercise	206 ± 5.5	201 ± 4.3	0.25
Diastolic Pressure (mm Hg)			
At Rest	81 ± 2.7	76 ± 3.4	0.40
At Maximal Exercise	82 ± 2.4	80 ± 2.6	0.47
Mean Arterial Pressure (mm Hg)			
At Rest	102 ± 3.4	96 ± 3.0	0.06
At Maximal Exercise	137 ± 2.8	133 ± 3.7	0.43
Cardiac Power Output (Watts)			
At Rest	1.0 ± 0.0	0.9 ± 0.0	0.42
At Maximal Exercise	5.6 ± 0.2	5.3 ± 0.2	0.16
Cardiac Reserve (Watts)	4.6 ± 0.3	4.3 ± 0.2	0.26

Data presented as mean ± SEM, n = 10.

A similar story was also observed at maximal exercise. No significant differences were measured in CPO_{max}, CO or MAP, or in their component parts, i.e. HR, SV, SBP and DBP (Table 3.12). Inevitably, the lack of effect of creatine supplementation on either resting or maximal CPO values, resulted in no significant differences when CR was determined (Table 3.13).

To confirm that the lack of disenable changes were not a result of averaging responses as mean values, each subject's individual responses were examined (Figures 3.44 to 3.46). No consistent trends were seen with the ten individual subjects.

Further supporting the lack of change in cardiac function, no significant differences were measured in the subjects' maximal aerobic capacity with creatine supplementation. Mean values of 30.2 ± 1.4 (range 23.7 to 38.2 ml/kg/min) and 27.5 ± 1.3 (range 22.2 to 34.8) were recorded for the placebo and creatine trials, respectively.

In summary, creatine supplementation at 20 grams/day over five days failed to exert any ergogenic effect on the hearts of older sedentary men.

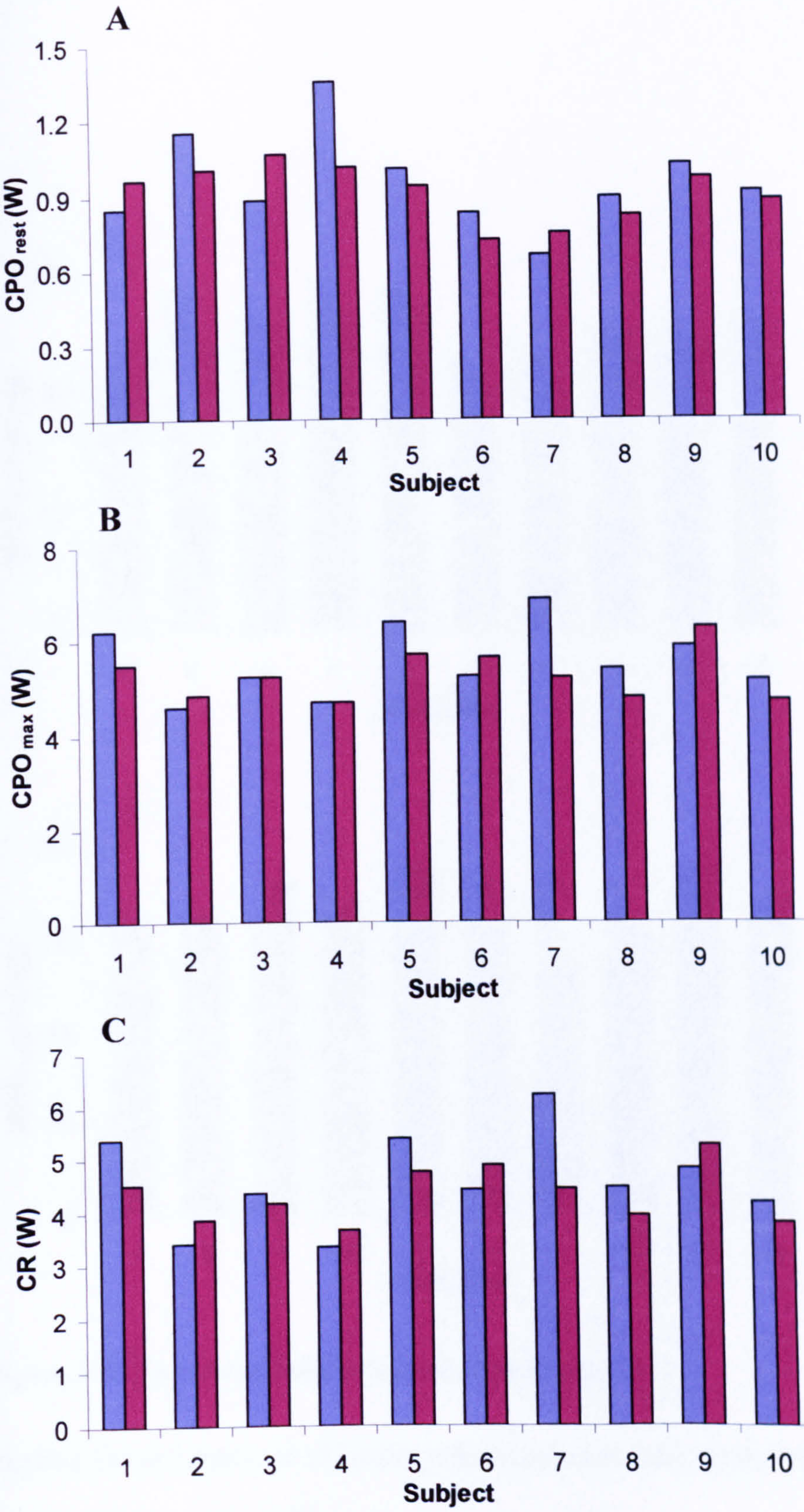
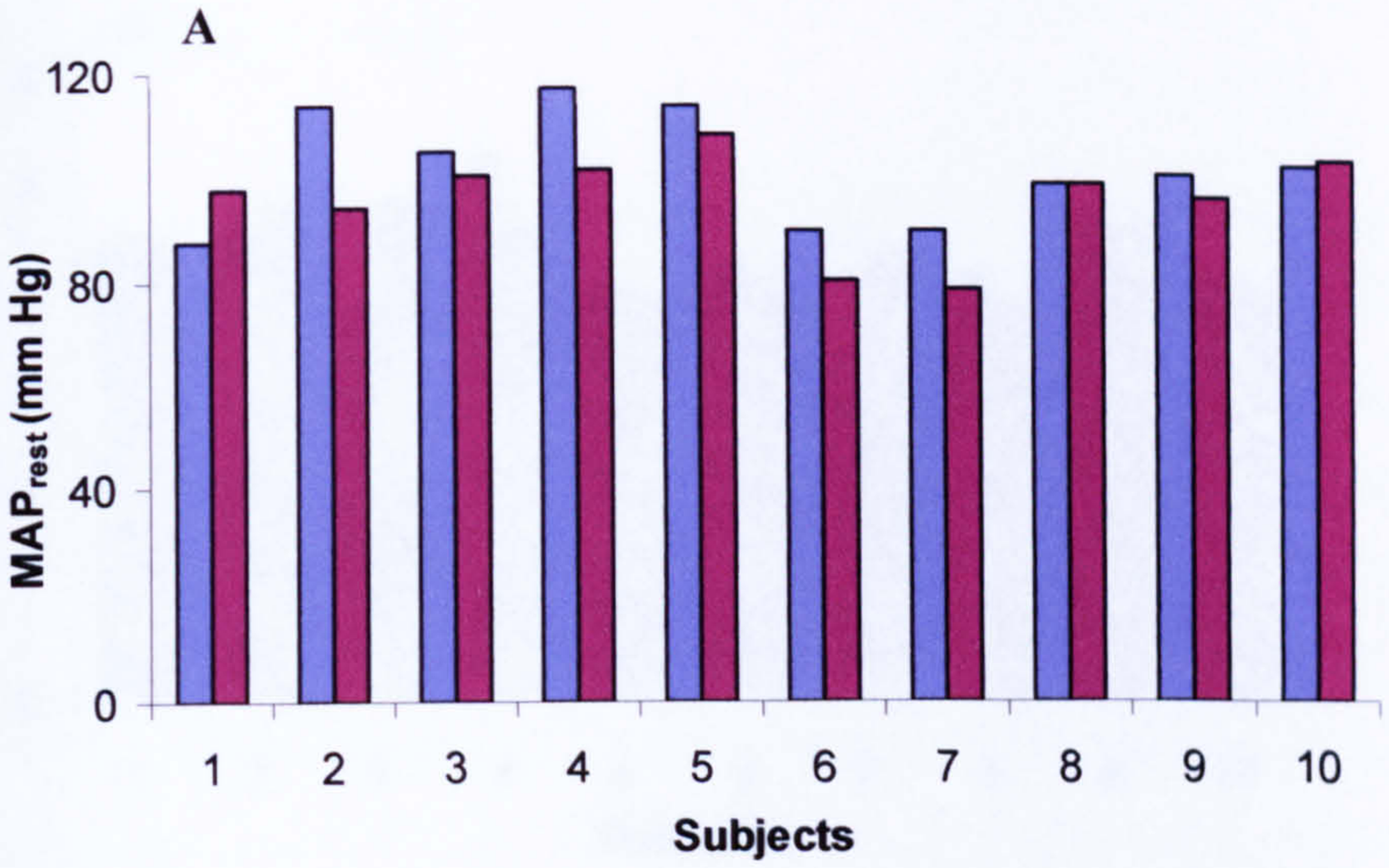


Figure 3.44. Individual subject's values of cardiac power output.

Resting (A) and maximal (B) cardiac power output, and (C) cardiac reserve were measured at the end of the placebo (■) or creatine (■) trial.



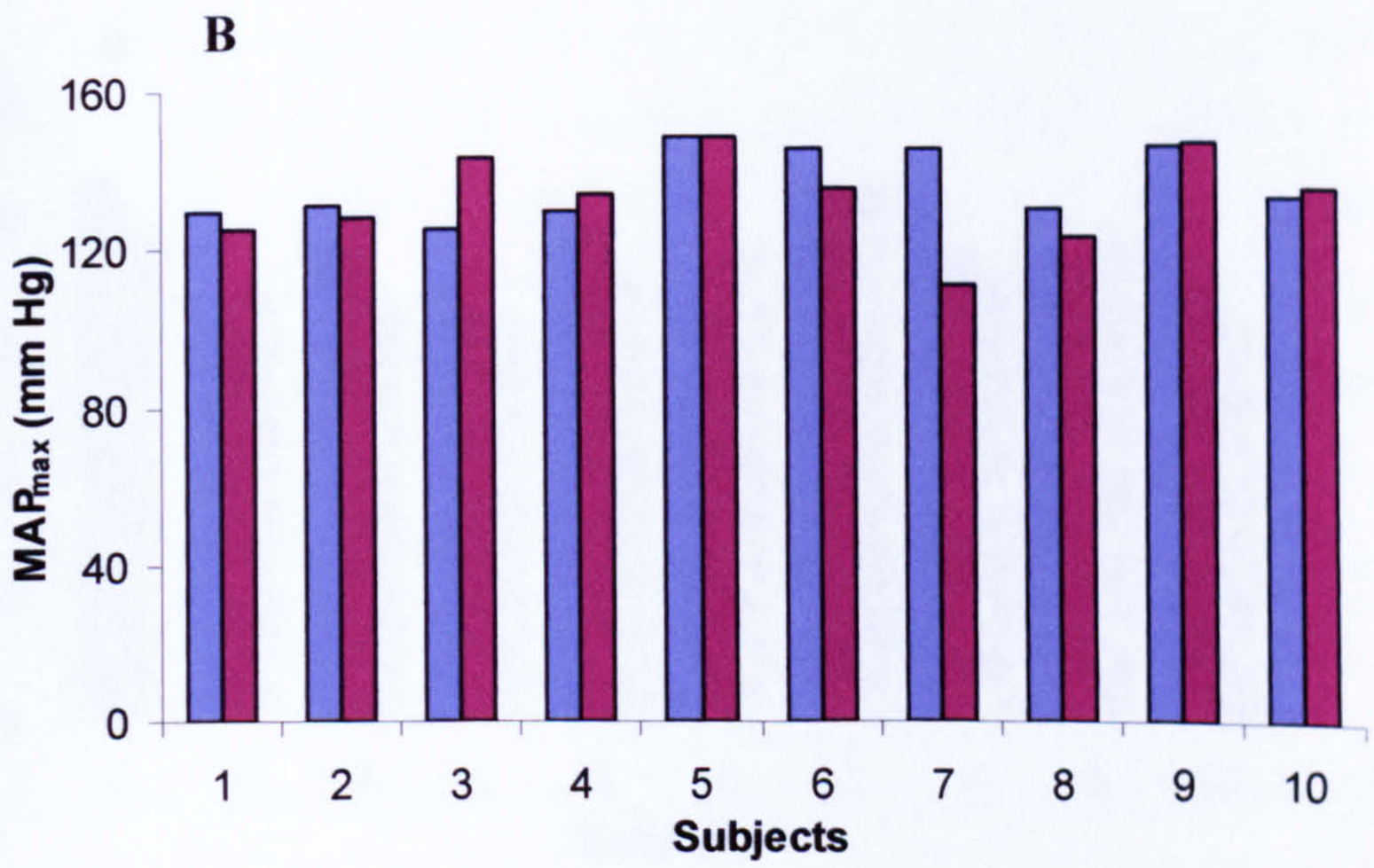
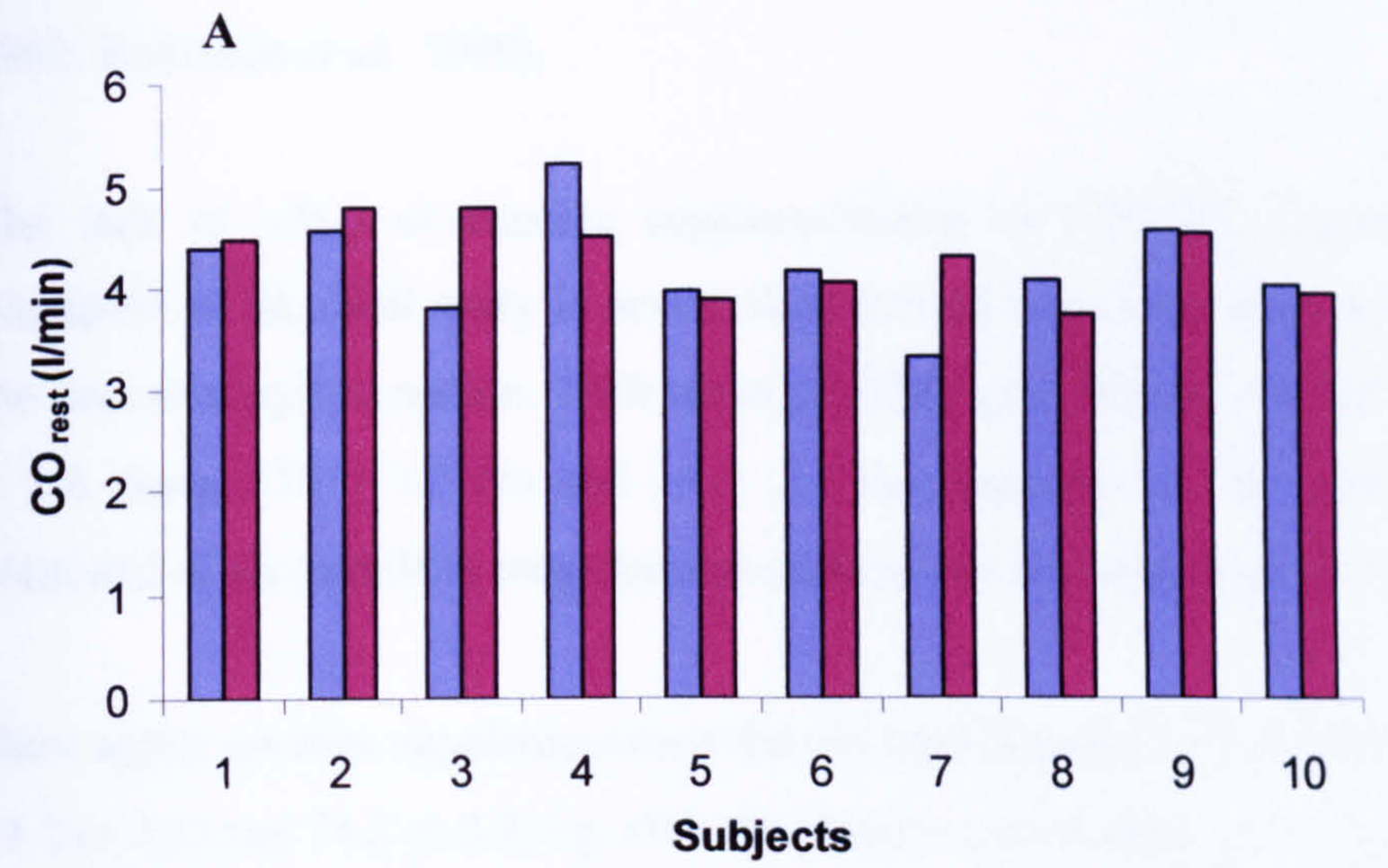


Figure 3.45. Individual subject's mean arterial pressure.

Resting (A) and maximal (B) mean arterial pressure were measured after the placebo (■) or creatine (■) trial.



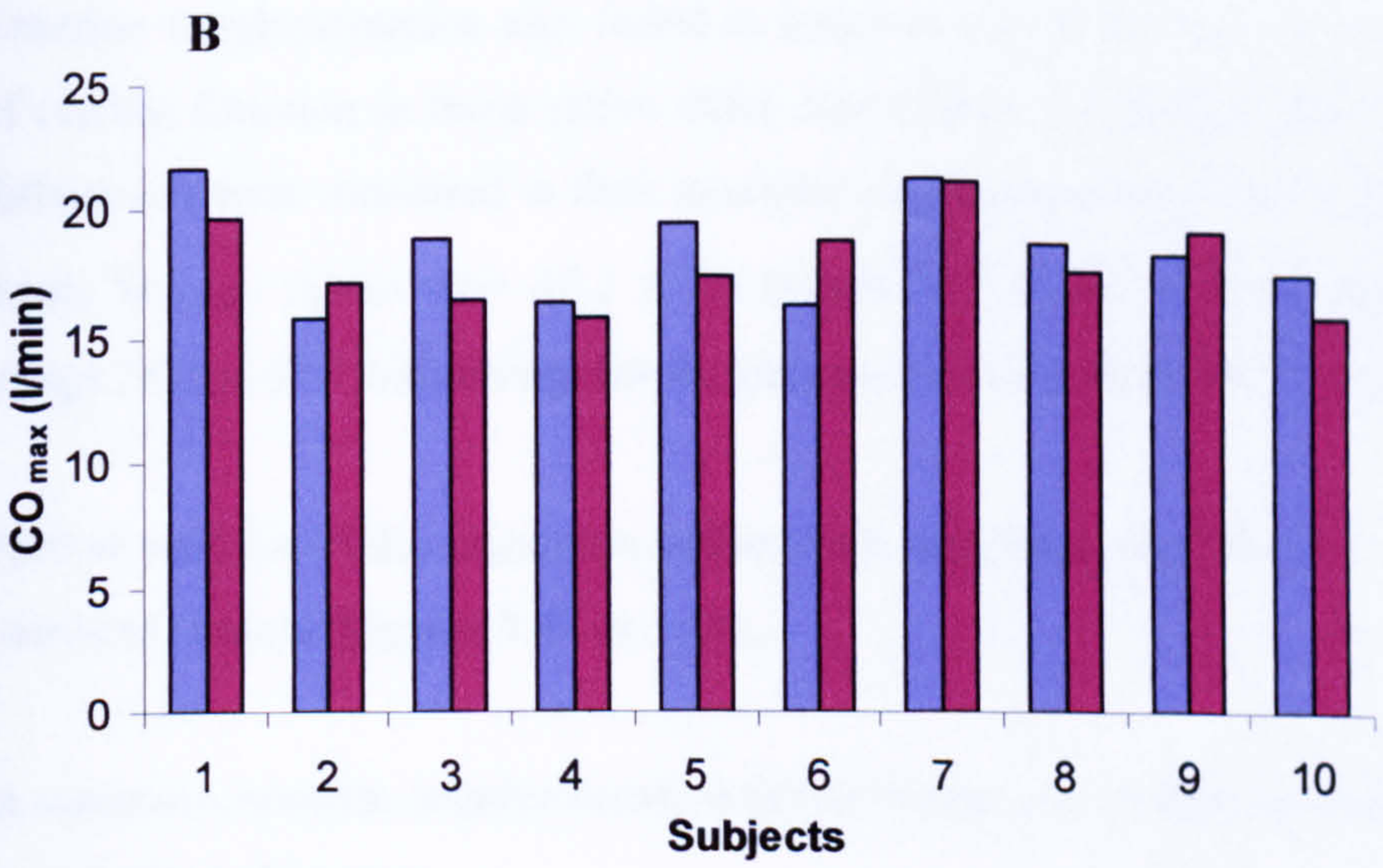


Figure 3.46. Cardiac output in individual subjects.

Resting (A) and maximal (B) cardiac output were measured after the placebo (■) or creatine (■) trial.

3.4.2. Creatine supplementation in active older men

Past research has identified that exercise training improves the uptake of creatine into the skeletal muscles, with resultant improvements in muscle performance (Harris *et al.*, 1992; Robinson *et al.*, 1999).

The lack of effect of creatine supplementation on CPO, in sedentary older men, prompted an identical study in seven older trained men, who were actively training at the time of supplementation. Their mean (± SEM) ages, heights and body mass' were 56 ± 1.8 years, 172 ± 1.7 cm and 74 ± 2.1 kg, respectively. The active male runners consisted of six middle to long distance runners and one long distance cyclist.

Once again, creatine supplementation did not significantly increase the subjects BM, i.e. 73.2 (± 3.1) and 74.2 (± 3.2) kg, after the placebo and creatine trials, respectively.

Creatine supplementation also failed to improve any of the resting or maximal aspects of cardiac function in these active older men (Table 3.14). Furthermore, no significant differences were measured in their maximal oxygen uptakes between the two trials. The mean $\dot{V}O_{2\ max}$ values were 42.2 ± 2.6 (range 36.3 to 51.6 ml/min/kg) and 43.2 ± 2.7 (range 36.5 to 55.7 ml/min/kg) for the placebo and creatine trials, respectively.

Further analysis of the responses within each individual also failed to demonstrate any consistent trends (Figures 3.47 to 3.49).

In summary, creatine supplementation failed to improve cardiac function in either active or sedentary older men.

Table 3.14. Cardiac function after either placebo or creatine supplementation in active older men.

	Supplementation		
	Placebo	Creatine	P-Value
Heart Rate (b/m)			
At Rest	50 ± 1.6	51 ± 1.6	0.51
At Maximal Exercise	164 ± 2.6	162 ± 2.3	0.46
Stroke Volume (ml)			
At Rest	90.8 ± 3.4	93.1 ± 4.4	0.90
At Maximal Exercise	133.6 ± 2.9	137.2 ± 6.5	0.83
Cardiac Output (l/min)			
At Rest	4.6 ± 0.2	4.7 ± 0.2	0.80
At Maximal Exercise	21.7 ± 0.6	22.2 ± 0.6	0.81
Systolic Pressure (mm Hg)			
At Rest	128 ± 7.2	116 ± 3.5	0.24
At Maximal Exercise	202 ± 8.3	208 ± 6.1	0.29
Diastolic Pressure (mm Hg)			
At Rest	81 ± 3.3	78 ± 2.0	0.11
At Maximal Exercise	72 ± 4.2	72 ± 4.0	0.87
Mean Arterial Pressure (mm Hg)			
At Rest	100 ± 4.0	95 ± 2.2	0.13
At Maximal Exercise	125 ± 4.7	128 ± 4.1	0.08
Cardiac Power Output (Watts)			
At Rest	1.0 ± 0.1	1.0 ± 0.1	0.91
At Maximal Exercise	6.2 ± 0.2	6.3 ± 0.3	0.97
Cardiac Reserve (Watts)	5.2 ± 0.2	5.3 ± 0.3	0.97

Data are expressed as mean ± SEM, n = 7

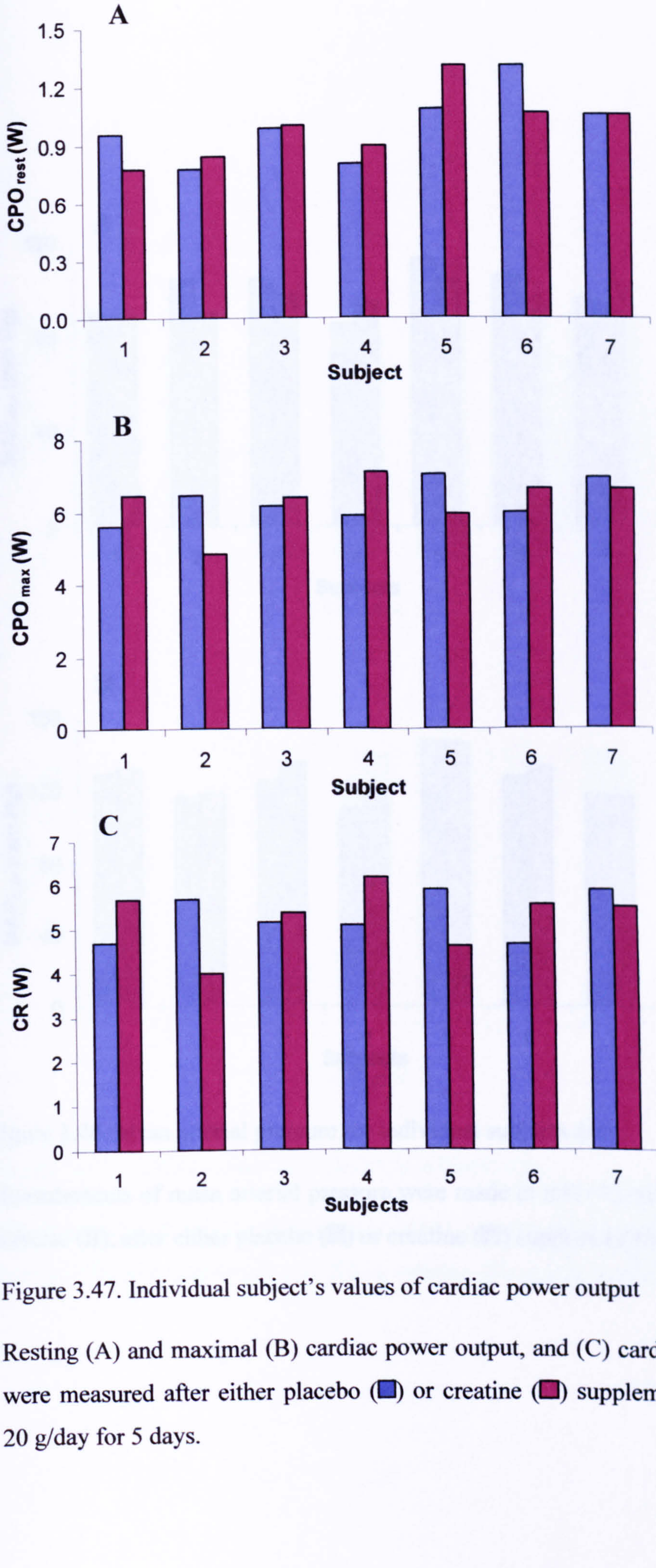


Figure 3.47. Individual subject's values of cardiac power output

Resting (A) and maximal (B) cardiac power output, and (C) cardiac reserve were measured after either placebo (■) or creatine (■) supplementation at 20 g/day for 5 days.

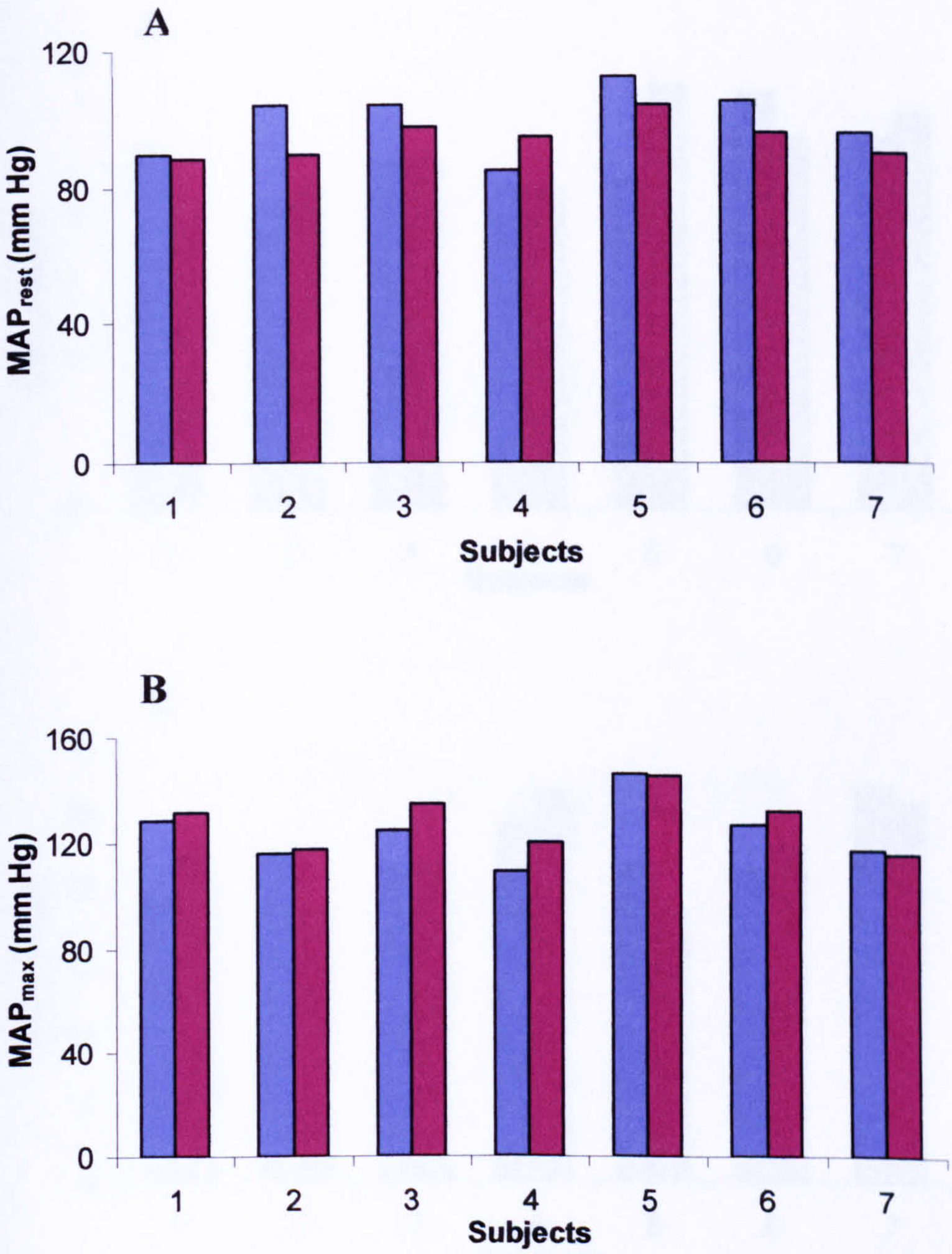


Figure 3.48. Mean arterial pressure for individual subjects data

Measurements of mean arterial pressure were made at rest (A) and at maximal exercise (B), after either placebo (■) or creatine (■) supplementation.

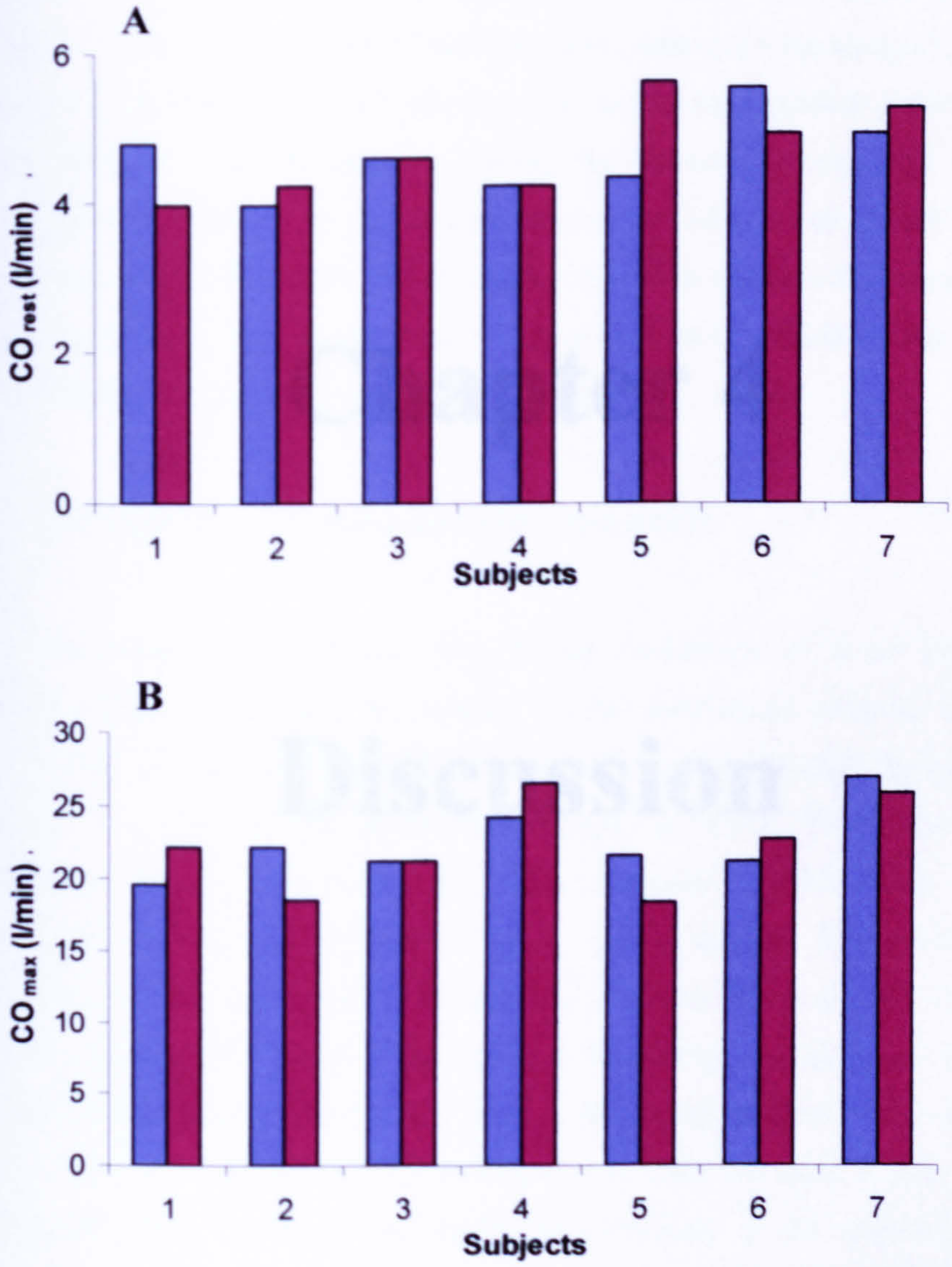


Figure 3.49. Cardiac output for individual subjects data

Measurements of cardiac output were made at rest (A) and at maximal exercise (B), after either placebo (■) or creatine (■) supplementation.

Chapter 4

Discussion

Four main findings emanate from this thesis. First, the way cardiac power output (CPO) was scaled was critical in the interpretation of the results. For example, in the sedentary women the age-related decline in CPO_{max} was lost when scaled for fat free mass (FFM^{b}). In contrast, in the sedentary men the decline in CPO_{max} was still evident. This significant age-related difference between men and women was the next novel aspect of this thesis. Third, it was evident that long-term endurance training, as shown in the veteran athletes, helped to ameliorate the loss in maximal cardiac function seen over approximately 40 years of ageing. Fourth, the increase in maximal mean arterial pressure (MAP) with age helped to ameliorate some of the loss in CPO_{max} with age. Therefore, if maximal cardiac output (CO) alone was used as the marker of cardiac function, as routinely used in past research, then the loss in overall cardiac function with age would have been overestimated.

4.1. Limitations of the current research

Before discussing these findings some of the limitations of these studies will be examined. When interpreting the results several limitations need to be taken into account. One limitation relates to the use of a cross-sectional designed study in measuring the age-and fitness-related changes in CPO. There are two major confounding factors associated with cross-sectional studies. First, the cohort (generational) effects, e.g. the lower CPO_{max} values attained in the older sedentary subjects compared to the sedentary 20 year olds, could be due to the less active lifestyle, rather than ageing per se. Second, the effects of selectivity. As one is carefully selecting subjects that are free of cardiovascular disease, the results obtained will relate to a small fraction of the older population. Furthermore, it is often the more active, middle-class older people who volunteer more readily to participate in the research, rather than inactive individuals. Therefore, the changes with age may appear to be attenuated through subject availability or selectivity. In the current studies, attempts were made to prevent such factors from occurring by ensuring the subjects were relatively sedentary, based on their answers to the physical activity questionnaire and their measured $\dot{V}O_{2max}$. The vast majority of investigations into the changes in cardiovascular function with age employ the cross-sectional study. This is not too surprising as the studies can be executed relatively quickly, and are relatively inexpensive.

Although longitudinal studies circumvent some of the problems described above they are costly both in terms of time and money. Also, they require a stable population of subjects, available over a long period of time with a stable reliable analytical methodology throughout the entire study. The latter includes the training and research skills of the investigators, as well as the confounding effects of repeatedly exposing the subjects to a measurement and possible leading to 'training' effects. Furthermore, environmental or lifestyle changes within the subject population over the course of the study can substantially influence the interpretation of the process of ageing. For example, changes in the quantity and quality of diet from decade to decade can affect cholesterol concentrations and be inappropriately interpreted as an effect of ageing.

Other limitations include the measurements per se. For example, in the current studies the measurement of MAP using the manual auscultation method. At rest, the measurement of arterial BP using the auscultation method is relatively easy to perform and has been shown to closely reflect central aortic blood pressure (Lightfoot, 1991). The absolute value recorded is of course influenced by the amount of tissue in the arm that has to be compressed by the inflated cuff in order to occlude the brachial artery before establishing systolic pressure. The use of manual auscultation to measure BP during dynamic exercise is even more technically challenging (Lightfoot, 1991) and requires extensive practice to overcome problems with treadmill vibrations and noise. Consequently, measurements made at maximal exercise have been shown to be less representative of the aortic pressures, compared to invasive techniques (Lightfoot, 1991). In addition, ageing is associated with an increase in arterial stiffness (Lakatta, 1993), which can therefore increase the amplification of the pulse wave. To date the only alternative method of measuring BP is the intra-arterial method. However, such a technique is potentially dangerous for the subject especially when exercise is involved. In addition, this invasive technique itself could physically limit the subjects' attainment of true maximal exercise etc. Therefore, until a more representative technique is developed, the manual auscultation method remains the best non-invasive technique available to measure MAP.

Another possible limitation to the current data concerns the use of the CO_2 rebreathing technique to measure CO. This measurement of CO is dependent on the subjects' ability to breath adequately to facilitate the mixing of the gases in and across the lungs and

blood stream. This could conceivably be less accurate in individuals with pulmonary abnormalities. Such individuals were however not invited to participate in the study and therefore this, apart from poorer respiratory function in the elderly, was probably not a major problem. In addition, the CO_2 rebreathing technique is based on some assumptions, e.g. that the effects of differences in pH, venous oxygen saturation and temperature are negligible. To overcome these assumptions, past research has taken blood samples to account for the differences in haemoglobin concentrations (Coyle *et al.,* 1986; McHardy, 1967) and have oxygenated the mixed venous blood with high concentrations of O_2 (Coyle *et al.,* 1986; Rebuck *et al.,* 1983). However, this limits the non-invasive nature of the CO_2 rebreathing manoeuvre. Also the values of CO derived in this way are similar to those recorded after rebreathing acetylene (Spina *et al.,* 1993).

Despite these limitations, most of the 'errors' are built in and will be consistent throughout as the same techniques etc were employed from the beginning to the end of these studies. In addition, by being aware of such limitations, every effort was made to minimise their impact on the studies and emphasis was placed on careful measurements being made and protocols followed faithfully. Many earlier studies in related areas have clearly been less rigorous.

4.2 Blood pressure is a critical component in the measurement of CPO

Despite recent advances, our understanding of the basic physiological mechanisms responsible for the changes in body structures and functions remains rudimental. Many of the publications concerning the age-related changes in cardiovascular function have neglected to control for the fundamental effects of disease and/or lifestyle. Such confounding factors have clouded the issue of ageing per se. It is therefore imperative that both disease and lifestyle variations are controlled for, so that the effects of healthy ageing on overall cardiac function are examined in relative isolation. Although, this may be difficult to achieve, as it is widely believed that ageing is synonymous with disease (Lakatta *et al.,* 1987). Although examining the age-associated changes in a normal healthy population may be difficult, if not impossible. In light of current theories, we attempted to perform such a task. In this thesis, the term 'Healthy ageing' was used to

represent the process of ageing in individuals in the absence of overt clinical diseases, and in particular cardiovascular abnormalities or diseases. Therefore, only subjects who met our criteria were selected.

Another factor that has hindered interpretations in this important area of research, concerns the validity of the measurement variables used to describe the age-related changes in cardiac function. Cardiac power output, a measure of overall cardiac function was proposed as it takes into account both the pressure and flow generating capacities of the heart and can be measured at rest and at maximal exercise. From the values the reserve capacity of the heart (CR) can be calculated ($CPO_{max} - CPO_{rest}$). Therefore, CPO has been shown to be a more representative and comprehensive indicator of overall cardiac function (Cooke *et al.*, 1998).

The acceptance of CPO as the best measurement of overall cardiac function, will affect the way we interpret age-related functional changes. For example, by ignoring the pressure generating capacity of the heart and focusing solely on cardiac output (CO), as previously used in most of the literature, the changes in cardiac function are either under-or over-estimated depending on the health status of the subjects or patients examined (Figure 4.1). That is, in a healthy ageing population a greater decline in cardiac function would be reported if CO was solely used, thus overestimating by 5% to 7% the changes compared to these reported for CPO_{max} (Figure 4.1A). This is because unlike CO_{max}, MAP_{max} increases with age. In contrast, the detrimental effects of heart failure (HF) will be underestimated by 15% compared to age-matched healthy controls. These HF patients express an inability to increase both their flow and pressure generating capacities of the heart to the same extent as healthy controls at maximal exercise thereby showing an inability to maintain cardiac function (Figure 4.1B).

Furthermore, the importance of including the heart's pressure generating capacity in a measure of cardiac function was highlighted in a recent communication (Schlosshan *et al.*, 2004). In a group of HF patients undergoing cardiac resynchronisation therapy, the authors identified an increase in CPO_{max} independent of any changes in maximal CO or SVR. It was therefore concluded that cardiac pressure-generating capacity must be a primary manifestation of improved cardiac function. Such data highlight the importance of incorporating pressure in the measurement of overall cardiac function. This is an

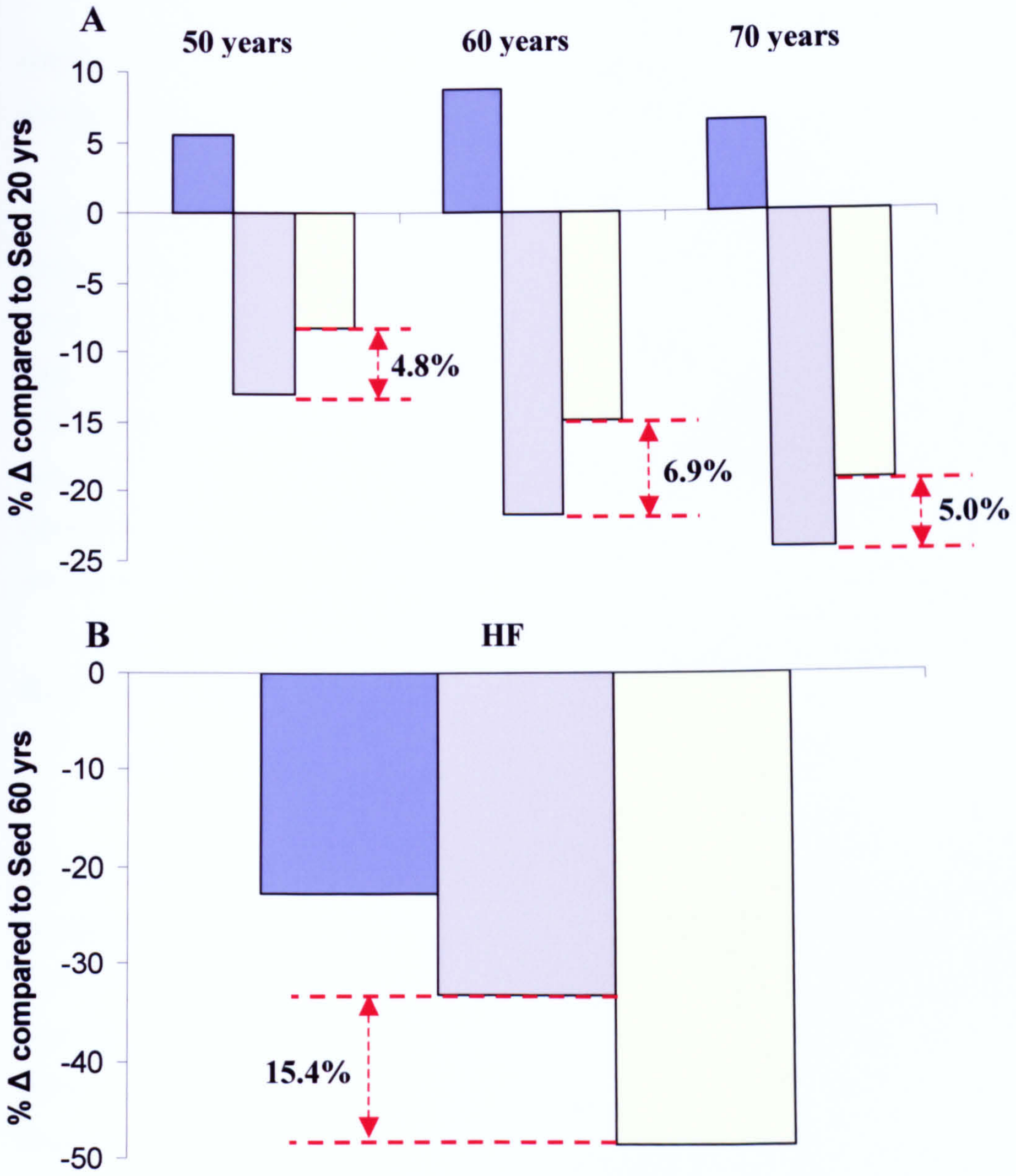


Figure 4.1. Schematic diagram illustrating the potential errors associated in measurements of cardiac function when the pressure generating capacity is ignored.

A) Data from sedentary 21 year-old men (Figure 3.41) have been used here to generate the baseline values (0%; x-axis) from which percentage differences in MAP_{max} (blue bar), CO_{max} (grey bar) and CPO_{max} (cream bar) have been calculated for 50, 60 and 70 year-old sedentary men. Using CO_{max} only overestimates the decline in cardiac function by 5-7%, compared to CPO_{max}.

B) The percentage differences in MAP_{max} (blue bar), CO_{max} (grey bar) and CPO_{max} (cream bar) for 60 year-old heart failure (HF) patients (NYHA class II-III) were calculated against data from 60 year-old healthy men (Figure 3.41) reduced to 0% baseline values (x-axis). Measuring CO_{max} alone, in this study would underestimate by 15.4% the decrease in cardiac function. These data for the HF patients were obtained from Dr L-B Tan (personal communication).

extremely important point as most current studies in a clinical or exercise physiology setting measure cardiac function based only on measures of flow.

Prior to examining the main aim of the thesis, it was important to optimise the reliability and reproducibility of measurements of CPO. Optimising the experimental conditions becomes all the more crucial when documenting the critical changes that occur with age, which may eventually lead to a pathological state. The methodological advances of CPO from an initial invasive to a non-invasive protocol have provided opportunities to measure CPO in a non-clinical setting (Cooke *et al.*, 1998). As a natural progression of previous work, we conducted some further validation studies as a precursor to conducting the main investigations on the processes of ageing.

4.3. The effects of time of day on the measurement of cardiac power output

One possible consideration that needed to be addressed at the outset concerned the possibility that the measurements of CPO were influence by a circadian rhythm. Evidence to support this possibility is conflicting. Several studies have measured the component parts of CPO (i.e. CO and MAP) and have produced variable results which either support or refute the influence of circadian rhythms (Cohen and Muehl, 1977; Cugini *et al.*, 1991; De Scalzi *et al.*, 1984; Deschenes *et al.*, 1998; Wang *et al.*, 1992). Resting CPO is only a fraction of CPO_{max} and may therefore be sensitive to changes in body temperature or fluctuating hormonal concentrations. For example, research has tended to find rhythms in CO and MAP at rest (Atkinson *et al.*, 1994; Cugini *et al.*, 1991; De Scalzi *et al.*, 1984; Furlan *et al.*, 1990; Reilly *et al.*, 1984; Reilly and Brooks, 1990; Wang *et al.*, 1992). In contrast, at maximal exercise the whole body, and its regulatory pathways, will be maximally activated and probably no longer susceptible to stimuli associated with the time of day. Therefore, it has been suggested that circadian rhythms are not evident at maximal exercise (Davis and Sergeant, 1975; Deschenes *et al.*, 1998a). In addition, $\dot{V}O_{2max}$, a measure of the maximal cardiovascular function and an indirect measure of cardiac function, has been reported to be stable and independent of the time of day (Reilly and Brooks, 1990). Indeed, in the current study, there was no suggestion of $\dot{V}O_{2max}$ being affected by the time of day at which it was measured.

Past research has reported that older individuals show a blunted circadian response compared to younger individuals (Otsuka *et al.*, 1989; Weizman *et al.*, 1982). It has been found that the amplitude of the circadian rhythms for rectal temperature (Atkinson *et al.*, 1994; Deschenes *et al.*, 2002) and resting pulse pressure (Atkinson *et al.*, 1994) were significantly reduced in older subjects. Also, no such differences have been reported for resting BP, HR_{rest} or the response of HR to exercise between 08:00 and 20:00 hours (Deschenes *et al.*, 2002). Therefore, the lack of a circadian response for CPO identified in the young subjects, together with the reported blunted circadian response in older individuals, suggest that CPO will not be affected by a circadian rhythm in older subjects.

In addition, it has been shown that circadian rhythms are highly influenced by other factors such as sleep, posture, ingestion of food and activity patterns (Pickering, 1988). Such influencing factors raise the question as to whether an endogenous component exists at all.

Such discrepant results, and the lack of significant changes at maximal exercise, highlight the lack of precise knowledge of how circadian rhythms may affect cardiovascular function. As far as possible, the confounding effects of posture, food ingestion and digestion, and prior physical activity were controlled for in the current study to minimise such effects. It was therefore concluded that resting and maximal CPO were not affected by the time of day that they were measured (Table 3.1). Even when the subject data were treated separately and examined for individual trends, there was no suggestion of a circadian response to any of the resting or maximal haemodynamic data (Figures 3.1 to 3.3). It can therefore be concluded with reasonable confidence that the measurements of CPO were not affected by circadian variations and can be measured with reliability at any time point during the day. This was reassuring, since if such a pattern had appeared the implications would have been very restrictive, limiting the number of subjects who could have been tested per day. Also, if the measurements of CPO had to be made according to an optimal time this would have impacted on cross-sectional studies and the pooling of such values.

4.4. Scaling of physiological variables

It has been well documented that a number of physiological entities are influenced by body size (Batterham *et al.*, 1999, de Simone *et al.*, 1997; Nevill *et al.*, 1994). Cardiac output, a vital component of CPO, has been shown to increase in accord with an increase in body mass (de Simone *et al.*, 1997; Lakatta, 1993). It was therefore highly likely that CPO would be affected in a similar way to that reported for CO. Indeed, all variables of CPO were positively influenced by the various measures of body dimensions (Figures 3.5 to 3.7). In addition, the sex differences highlighted between men and women, and with age per se, also influence the measurement of CPO. Therefore, to obtain meaningful inter-or intra-group comparisons the effects of body size must be corrected for (Batterham *et al.*, 1999).

This is the first study that has examined the relationship between CPO and body dimensions. It was found that the allometric approach was the best scaling model to compare data from male and females, as the assumptions of this scaling model were satisfied. That is, the relationship between the variables of body dimensions and CPO, were similar for men and women, which allowed common ***b*** exponents to be calculated. The assumption of homoscedasticity was achieved and the allometric model completely corrected for the effects of body composition on the data for CPO (Table 3.6).

However, it was also desirable to find the best scaling variable which would further improve the quality of such data. Often for convenience, body mass (BM) has been routinely used for the scaling of physiological function. In cardiology, body surface area (BSA) has been widely used as it incorporates some estimates of body composition. However, BSA is rarely measured and calculations of BSA introduce errors (Martin *et al.*, 1984). Although the use of BM or BSA reduces the differences between men and women, despite having similar physical fitness and health backgrounds, significant differences often remain. These differences can be partially attributed to the incorrect selection of the scaling model and due to the wrong choice of scaling variable. The current study identified that fat free mass scaled allometrically (FFM^{b}), was the best scaling variable for the independent removal of body dimensions on CPO values. Indeed, such an approach dramatically reduced the differences in CPO between men

and women (Table 3.8). Furthermore, no differences were found between men and women for CR. In contrast, large differences were still evident between men and women when BM^b or BSA^b was employed for the scaling of CPO.

Although, the use of FFM as the scaling variable is an improvement on the conventional approach of scaling physiological functions to BM, it is not perfect. That is, FFM is composed of metabolically active constituents (i.e. skeletal and cardiac muscle etc) and low-metabolically active tissues or organs (i.e. tendons, ligaments, intestines, pancreas etc). Although at rest, the liver, kidneys and gastrointestinal tract are considered to be organs with high metabolic rates (Muller *et al.*, 2002), their energy expenditures represent a significantly smaller proportion during vigorous exercise. Therefore, an ideal scaling variable would be one that solely takes into account the most metabolically active tissues, i.e. skeletal and cardiac muscle.

The selection of FFM^b as the scaling variable was based on the statistical evidence and importantly its biological relevance. That is, statistically FFM presented with the strongest relationship of all body dimensions when correlated to CPO (Table 3.7). Further information was gained by examining the confidence intervals surrounding the *b* exponent. Body surface area produced wider confidence intervals than either FFM or BM for all variables of CPO (Table 3.7). This suggested that the exponents calculated for BSA were less stable, and hence potentially less applicable to other populations when compared to exponents of FFM or BM. In the absence of FFM, when used allometrically, BM may be the next best alternative in a similar population of subjects. That is, although both BM and BSA had similar R^2 and root-mean-squares error values, the width of the confidence intervals for BM were tighter compared to BSA, which means the values are more generally acceptable to other populations. However, the fact that BM does not differentiate between the differences in body composition, e.g. a large proportion of metabolically active muscle versus metabolically inert adipose tissue, will therefore not fully correct for the changes in body composition. This was highlighted in Table 3.8, whereby highly significant sex-related differences remained once the differences in BM between groups were accounted for.

The use of FFM as a scaling variable is not a new concept, a number of studies have shown its superiority compared to BM or BSA (Batterham and George, 1998; Bella *et*

al., 1998; Collis *et al.,* 2001; Döbeln, 1956; George *et al.,* 1999). The physiological basis for the selection of FFM as the scaling variable was that it allows the independent removal of body dimensions that are related to metabolically active tissues from CPO, e.g. muscle.

On a cautionary note, the use of FFM is dependent on the accuracy by which it can be measured. For the current study, Dual Energy X-ray Absorptiometry (DEXA) was used to measure FFM, which has been recognised as a precise technique for the measurement of body composition (Kelly *et al.,* 1997; Khort, 1998; Makam *et al.,* 1997). Unfortunately, in practice the use of FFM for the scaling of CPO may be limited by the availability of equipment and hence how accurately it can be measured. Although increasingly popular, DEXA machines and other reliable technique are not widely available. Although techniques to measure FFM, such as skinfold thickness and bioelectrical impedance, are more freely available they possess inherent errors. Additionally, these techniques measure fat and not FFM. Therefore under circumstances when FFM can not be measured accurately, other scaling variables may be warranted.

Although scarce, aspects of cardiac function, i.e. CO and SV, have previously been examined. These may provide some insight into the results obtained for CPO. To my knowledge, the study of de Simone and colleagues (1997) is the only one that has correctly examined the relationship between body size and CO using the allometric model. Even then, this was only performed under resting conditions. In a similar population to the one used in the current study, de Simone *et al.* (1997) scaled CO and SV for BM to the power of 0.71. Their value of the ***b*** exponent was higher than that calculated for CPO_{rest} when scaled to BM (***b*** = 0.33) or FFM (***b*** = 0.47). In addition, as illustrated in section 3.3.1, resting and maximal CO were scaled to FFM to the power of 0.36 and 0.64 respectively (Figures 3.12B and 3.18B), both of these ***b*** exponents are different to that reported by de Simone *et al.* (1997). Possible explanations for the differences between the exponents calculated in this study and those of de Simone *et al.* (1997) could relate to the different techniques used to measure CO and SV. de Simone *et al.* (1997) measured CO and SV using echocardiography, whereas the CO_2 rebreathing technique was employed in the current study. Differences in results may also have been due to the health status of the subjects. We rigorously examined the subjects for any signs or symptoms of clinical diseases. Therefore as far as we can

ascertain, the population studied were disease-free. However, of the subjects used in the study by de Simone *et al.* (1997) only hypertension was ruled out by BP measurements. These factors could account for the differences between the two studies.

Although the data for CPO was completely normalised for body size using the allometric model of scaling, a cautionary note still needs to be made. First, allometric scaling should be population specific, i.e. the allometric exponents should be calculated for each new data set to ensure that such data are completely normalised. Second, the allometric equations cannot be used for extrapolation beyond the range of the data at which they are based. Furthermore, as these results are novel further examination of the relationships between CPO and variables of body dimensions are warranted. This should help to establish the normal range of exponents for the allometrically scaling of CPO.

By removing the confounding affects of body size on CPO, and scaling in the most appropriate way, valid inter-and intra-group comparisons could be made with greater confidence and age-related changes in CPO examined in both men and women.

4.5. The effects of ageing

Although the differences in cardiovascular function between young and old have been extensively documented, failure to acknowledge or control for the confounding influences of disease and lifestyle have clouded many issues. In fact some argue that ageing is intrinsically linked with disease. However, many achieve old age with little evidence of disease (Lakatta and Levy, 2003). Hence, it was necessary to study healthy subjects in well-defined groups separated according to sex, age, levels of physical fitness and training status. This was considered to be a very important aspect of these studies.

At rest the heart, like other aspects of the cardiovascular system, operates at a fraction of its total capacity. Therefore changes at rest, unless the patients are in heart failure, are unlikely to have serious implications on the ability of the heart to cope with daily stresses. However, a deterioration in maximal cardiac function will have a substantial

affect on daily living. Maximal exercise is a commonly used experimental tool employed in studies in exercise physiology because it allows quantification of the limits of an individual's physiologic function. It is, therefore, perhaps more important to document the changes that occur at maximal exercise with increasing age. In so doing, one is defining the functional reserve capacity of the heart.

It has been reported that there is a progressive decline in the functional capacity of the cardiovascular system with ageing (Gerstenblith *et al.*, 1976; Pimentel *et al.*, 2003). This deterioration has been demonstrated by a decrease in $\dot{V}O_{2max}$ (Astrand, 1960; Dehn and Bruce, 1972; Ogawa *et al.*, 1992). However, $\dot{V}O_{2max}$ is a composite measure of many organ/bodily functions, whereas CPO_{max} measures just the overall function of a single organ (i.e. the heart). To date, the changes that occur in CPO_{max} and CR with age, and the differences between the sexes, have not been documented.

Although, in absolute terms (i.e. data not normalised for FFM^b), men and women behaved similarly in terms of the age-related changes in maximal cardiac function, on an age for age basis, men presented with higher values of CPO_{max}, CR, CO, SV and a lower SVR_{max} than women. Such sex-related differences in CO and SV are well known (Fleg *et al.*, 1990, 1995; Lakatta, 1993). However this is the first study to find a sex-related difference in CPO_{max} and CR in absolute terms. It is generally believed that men and women are distinctly different in terms of physiological function. However it is difficult to try and explain why healthy men and women, who have similar fitness levels, should be so vastly different, apart from the obvious differences in body size. Indeed, once the body compositional differences were accounted for, the differences in CPO_{max}, CR, $SVRi_{max}$ and SV_{max} were less evident and the differences in CO_{max} were substantially reduced (i.e. from 22% to 5%). These findings clearly show that the sex-related differences on maximal cardiac function and other heamodynamic variables could be mostly explained by differences in body composition in a sedentary population.

The progressive age-related decline in CPO_{max} identified in the current study for both sexes are therefore novel. It was also found that the rate of decline was greater in men than women (Figure 3.16A). Such change in maximal cardiac function impact on the

reserve capacity of the heart. Both men and women expressed a decline in CR with age. However, the 10% decline in CR for the sedentary women was not found to be statistically significant (Figure 3.17A).

The age-related decline in maximal cardiac function in men was still evident after normalising CPO_{max} for FFM^b (Figure 3.16B). The age-related decline in CR in men is likely to result in a reduced exercise capacity and gradually an increased incidence of functional disability and an impaired quality of life. The age-related decline in CR would also mean that those older individuals engaging in physically demanding occupations may be working closer to their maximal capacity (CPO_{max}) and that could result in fatigue, acute cardiovascular events, etc (WHO, 1993).

Interestingly, in women the decline in CPO_{max} with age disappeared once normalised for FFM^b, leaving only a non-significant 8% decline in CPi_{max} and CR. These changes or lack of them, in CPO_{max} and CR for the sedentary women has not previously been reported. It has been assumed that women behave in a similar fashion to men in terms of a loss in maximal functional capacity, as evidenced by a decline in $\dot{V}O_{2max}$, CO, stroke work index (Fleg *et al.*, 1994, 1995; Ogawa *et al.*, 1992). However, such measures don't take into account the pressure generating capacity of the heart; a vital component in the measurement of overall cardiac function.

Although CPi_{max} did not decline with age in the sedentary women, decreases in CO_{max} were reported, which were similar to those of sedentary men. However, unlike their male equivalents the decline in CPO_{max} disappeared when scaled appropriately. That is, in women, the increase in MAP_{max} was effective in preventing any loss in maximal cardiac function. Once again appropriate methods of scaling crucially influence data outcome and interpretations.

In terms of the age-related changes in CPi_{max}, why should women of similar fitness levels, behave differently to men? These functional differences are consistent with structural changes in the heart as reported previously. Between 20 and 95 years-of-age the total number of viable cardiomyocytes in the female heart, remains essentially constant (Figure 1.1). In contrast, a 30-35% loss of the cardiomyocytes over the same age has been documented in men. Although the remaining viable cardiomyocytes

undergo hypertrophy in men, this adaptive response clearly does not fully compensate for the progressive decline in cardiomyocyte numbers (Olivetti *et al.*, 1995). This was clearly evident in the current study, as an age-related decrease in maximal cardiac function was still evident in the men. Currently there is no good explanation for this interesting sex difference. If women are able to maintain approximately the same number of contractile cells in the heart with increasing age, it may therefore not be too surprising that there is little or no change in their maximal cardiac function.

The traditionally held belief that the heart has little or no regenerative capacity has recently been challenged. The recent detection of cardiac stem cells capable of giving rise to primitive myocytes, together with small myocytes still capable of dividing, suggest that a potential for cardiomyocyte regeneration does exist (Nadel-Ginard *et al.*, 2003, Sussman and Anversa, 2003). Whether this regenerative capacity in the heart declines with age, and between men and women, will be important areas for future work (Sussman and Anversa, 2003).

The current study was able to measure certain structural changes of the heart, which may provide further insight into the changes in maximal cardiac function. Unfortunately, echocardiographic data were only available for sedentary men at the specific age groups of 20, 50, 60 and 70 years. Although not significantly different, these data suggested a gradual decline in LVM from 50 years-of-age onwards (Figure 3.43). If this is true, the minor loss in LVM in the sedentary men may have accounted for some of the decline in CPO_{max}. On a cautionary note the measurement of LVM was performed using the technique of 2D M-mode echocardiography. This non-invasive technique samples only a single small area of the LV posterior wall or LV septum. These are then extrapolated to represent the global thickness of the LV; and inevitably carries with it a certain amount of variability. Left ventricular mass was then estimated, assuming a constant ventricular geometry at all ages. Furthermore, the use of echocardiography can not disclose important information concerning the compositional changes of the heart, such as the number of cardiomyocytes, the content and types of collagen etc. Such adaptations can occur without observable changes in LVM.

Research examining the age-associated changes in LVM has been conflicting (Dannenberg *et al.*, 1989; Ensor *et al.*, 1983; Kitzman *et al.*, 1988; Potter *et al.*, 1982;

Smith *et al.*, 1991). By employ the technique of magnetic resonance imaging (MRI), a recent study by Hees *et al.* (2002) provided further insight into the age-associated changes in LVM. This 'gold standard' technique identified that ageing was associated with left ventricle remodelling in both men and women along the heart's long axis. However, in women a decrease in long axis length was countered by an increase in wall thickness, resulting in an altered shape of the heart but not in LVM. However, in men the decrease in long axis length was not accompanied by an increase in wall thickness. Thus, LVM decreased by about 10% between 20 to 80 years. Such data may help to explain the differences found in CPO_{max} between men and women, and with age.

Further investigations need to be carried out in this area to provide more insight into the mechanisms governing the changes in cardiac function in women. Furthermore, it will be important to identify if the menstrual cycle affects cardiac function and what consequences, if any, the menopause and hormonal replacement therapy, has on CPO. Due to insufficient numbers and other priorities in the current study, it was not possible to examine the effects of the menstrual cycle or the menopause on CPO. Evidence from animal research suggests that oestrogen influences cardiovascular haemodynamics, both at rest and during exercise (Magness *et al.*, 1989; Schaible *et al.*, 1984; Scheuer *et al.*, 1987). However, studies in humans have been conflicting, with Green *et al.* (1997) suggesting that oestrogen supplementation may be associated with higher peak CO in exercise-trained, postmenopausal women due to alterations in the peripheral vascular and oxygen kinetic responses to maximal exercise. However, the differences between the oestrogen and non-oestrogen replacement therapy group only became significant once expressed relative to BSA (RES model). Furthermore, maximal CO was not measured. Rather it was calculated using the regression of CO on oxygen uptake at each stage of submaximal exercise and by extrapolating the CO to $\dot{V}O_{2peak}$. In addition, subjects were not matched for fitness levels or years of training. Therefore, the conclusion by Green *et al.* (1997) must be treated with some caution. A subsequent cross-sectional study highlighted that hormone replacement therapy (HRT) had no effect on CO_{max} in postmenopausal women (McCole *et al.*, 1999). In addition, no differences were reported for maximal MAP, SBP, or DBP in postmenopausal women who were either on HRT or not. These findings were also independent of physical fitness, i.e. sedentary, physically active or master athletes (McCole *et al.*, 1999).

Therefore, further investigations are warranted before a valid conclusion can be made concerning the effects of HRT on cardiovascular function.

In the current study, men and women seemed to have similar mechanisms associated with the age-related changes in CO and MAP. At maximal exercise, CO is affected by multiple pathways, including HR and SV, which in turn are regulated by other determinants. For example, SV is dependent on preload, afterload, myocardial contractility and coronary blood flow, whilst HR is dependent on the autonomic nervous and endocrine systems etc. In turn these regulatory factors are themselves affected by determinants at multiple levels, such as the central nervous system, vascular and blood properties (for afterload). All of these are highly interrelated, thus highlighting the complexity of such a system, particularly when viewed from the perspective of ageing.

Although the precise mechanisms underlying the observed age-related differences in central cardiac responses to maximal exercise could not be ascertained to any great extent in this study, the complex interactions between SVR, MAP and CO are likely to offer partial explanations.

In addition, the control of BP during exercise involves complex interactions between the peripheral vasculature and the heart, which is carefully modulated through the central nervous system (Schrager *et al.*, 1983).

Under normal circumstances, the cardiovascular system is designed so that MAP is relatively constant through a range of exercise intensities, although at maximal exercise an increase in arterial pressure occurs. Because the pressure gradient driving CO is relatively constant, increases in blood flow to active muscle is achieved by reductions in SVR (Tanaka *et al.*, 1996). The current study identified a decline in SVR from rest to maximal exercise. This reduction in SVR_{max} was substantially less in the older men, compared to their younger controls. A corresponding increase in MAP_{max} was also found with increasing age. Such changes may have lead to the reduction in CO_{max}. Systemic vascular resistance is commonly used as a surrogate of pump afterload (Milnor, 1975). Thus, the changes noted in the current study suggest that older sedentary individuals have an impaired ability to vasodilate their resistance vessels leading to a higher SVR at maximal exercise, i.e. a higher afterload. This increased

pump afterload is likely to reduce the maximal pumping performance of the heart in these subjects, via its affects on CO. Indeed, an inverse relationship was identified, whereby an increase in SVR_{max} was associated with a decline in CPO_{max} (Figure 3.38).

The gradual increase in SVR_{max} with increasing age, correlated with similar increases in MAP, SBP and DBP at maximal exercise (Figure 3.39). Therefore, based on Ohms law, it may be concluded that the primary manifestation of an increase in MAP_{max} with increasing age would be due to an increase in SVR_{max}. Such changes may be adaptive in nature. That is, part of the heart's work directed to blood flow in the younger individuals may be replaced by work directed towards blood pressure in these older subjects. Support for the theory comes from Ogawa *et al.* (1992), who measured the changes in stroke work (i.e. the product of SV and MAP), and found that the maximal stroke work was either similar or greater in older, compared to young subjects. Ogawa *et al.* (1992) indicated that the decline in SV_{max} with age was associated with a higher MAP_{max}. They concluded that less work was expended in SV and more in pressure generation in the older subjects.

Several mechanisms may have accounted for the age-related increase in SVR_{max}. One possibility concerns structural changes to vessels walls, e.g. greater deposition of collagen, proteoglycans, and less elastin, making them less responsive to vaso-active agents (Challah *et al.*, 1997; Li *et al.*, 1999). Changes affecting the humoral and endothelial regulation of vascular smooth muscle tone can also affect the responsiveness of the vascular smooth muscle. That is, senescent vessels show an increased endothelial permeability and reduced nitric oxide-dependent vasodilatory response to acetylcholine (Taddei *et al.*, 1995). This has been consistently observed in different regional beds, including the coronary bed, of both animals and humans (Egashira *et al.*, 1993). Also, the vasodilator responses to β_2-adrenoceptor agonists are attenuated due to a reduced number and affinity of specific receptors. Also, but probably to a less extent, vasoconstrictor responses to α-receptor stimulation have been found to be diminished in 'aged' arteries (Elliot *et al.*, 1982).

The age-related changes identified in maximal CO were also associated with changes in maximal HR and SV. It has long been appreciated that, older subjects have a smaller increase in their HR during maximal exercise (Figure 3.19A). It has been postulated that

the decline in HR_{max} with age is due to an increase in elastic and collagenous tissue in all parts of the conductive system and fat accumulation around the SA node (Lakatta, 1993). It has been identified that by the sixth decade there is a pronounced decrease in the number of pacemaker cells in the SA node, such that by age 75+, less than 10% of the original cell number found in the young adult remain (Fleg *et al.*, 1988). This age-related decline in HR_{max} is one of the factors, contributing to the observed age-related decline in CO_{max}. Whether SV_{max} declines remains controversial (Fleg *et al.*, 1990; Higginbotham *et al.*, 1986; Julius *et al.*, 1967; Kuikka and Lansimies, 1982). Such variability between studies can be attributed to the study design, measurement techniques, and the subject profiles used. There are at least two studies that have found an increased maximal SV index, which was sufficient to compensate for the decline in HR_{max}, thus maintaining maximal cardiac index with age (McGuire *et al.*, 2001; Rodeheffer *et al.*, 1984). In the current study maximal SV (or SVi_{max}) was maintained with increasing age, therefore the decline in CO_{max} was solely attributable to the decline in HR_{max}.

Unfortunately we were unable to measure the left ventricular end diastolic (LVEDV) and systolic (LVESV) volumes at maximal exercise. Such data would have provided important information regarding the mechanisms by which SV_{max} was maintained with age. However, it has been previously postulated that an augmentation of LVEDV during exercise may be an adaptation through which SV_{max} is maintained (Fleg *et al.*, 1990, 1995; Lakatta, 1993). The maintenance of SV_{max} illustrates an important mechanism by which the ageing heart attempts to adapt to changes in function. In younger individuals there is a greater reliance on increasing HR and probably a reduction in LVESV to increase CO. However, with increasing age there is a greater reliance on the Frank-Starling mechanism, which is probably manifested by an increase in LVEDV and SV (Gerstenblith *et al.*, 1987). Because of such changes, it has been suggested that the heart of the older individual behaves like that of a younger one subjected to β-blockade (Lakatta and Yin, 1982).

A possible mechanism that affects both the changes in maximal HR and SV concerns the age-associated diminution in the sympathetic modulation of the cardiovascular response to exercise. That is, the decline in HR_{max} and inability of SV_{max} to increase, and therefore compensate for this reduced rhythmicity, may be due to a down regulation

of β-adrenergic receptors in response to the age-related increases in circulating concentrations of catecholamines (Pugh and Wei, 2001).

For many years $\dot{V}O_{2max}$ has been used as a marker of cardiovascular function and therefore an indirect marker of cardiac function, providing that other organ systems (e.g. lungs, musculoskeletal system) are not limiting factors influencing exercise ability (Tan *et al.,* 1997). It is axiomatic to state that despite all other systems and organs functioning normally, if the heart is incapable of performing its normal function, $\dot{V}O_{2max}$ will be compromised. Equally, $\dot{V}O_{2max}$ is influenced by the performance of the heart, particularly the flow generating capacity of the heart. Therefore, changes to CPO_{max} can be expected to be a major determinant of $\dot{V}O_{2max}$. It was, therefore, not surprising to identify an age-related decline in $\dot{V}O_{2max}$ in the current study. Several studies have also identified an age-related decline in $\dot{V}O_{2max}$ at approximately 10% per decade (Drinkwater *et al.,* 1975; Inbar *et al.,* 1994; Jackson *et al.,* 1995; Toth *et al.,* 1994). This figure was not too different from that reported in the current study. That is, $\dot{V}O_{2max}$ declined by 7.6% per decade in the sedentary men from 20 to 70 years of age.

Interestingly, the age-related rate of decline in $\dot{V}O_{2max}$ was greater than that reported for CPO_{max}, such that in advanced age the $\dot{V}O_{2max}$ of sedentary subjects reaches levels not to dissimilar to those with moderate heart failure. However, as mentioned earlier $\dot{V}O_{2max}$ is a composite measure of many organ/bodily functions, whereas CPO_{max} measures just the performance of a single organ. Therefore, age-related changes to the skeletal muscles, heart and liver will have a combined affect on the changes in $\dot{V}O_{2max}$ with age. For example, there is evidence that the skeletal muscles in older subjects have a reduced aerobic capacity, which is independent of changes in lean body mass (Proctor and Joyner, 1997). Whether this reflects less oxygen delivery to the muscles, or an inability of muscle machinery e.g. decline in the number of mitochondria to utilise the oxygen, is at present unclear. In the current study the greater rate of decline in $\dot{V}O_{2max}$ could be attributed to a combined loss of central cardiac (CO) and peripheral (a-v O_2 difference) factors (Figure 3.26).

In addition to the changes identified in maximal CPO, an age-related decrease in CPO_{rest} was also measured in both male and female subjects (Figure 3.11A). This reduction in CPO_{rest} has never been reported before. However, the reduction in CPO_{rest} is unlikely to have an appreciable effect on either the performance of the heart or the individual concerned.

The importance of accounting for differences in body composition has previously been addressed. If such data on body composition (i.e. FFM) were not available, one might reasonably conclude that resting CPO is reduced with age. However, a very different conclusion was obtained by scaling the data for the differences in FFM^b. That is, no reduction in CPO_{rest} was found (Figure 3.11B). This highlights the importance of accounting for relevant body size and composition. Why should changes in body composition affect resting CPO? In adults, it has been shown that at rest, 70-80% of energy expenditure is derived from organs which comprise only ~5% of BM, i.e. brain, heart, kidneys, liver etc. In contrast, the mass of all the skeletal muscles (approximately 40% of body mass) roughly accounts for the remaining 20-30% (Muller *et al.*, 2002). The measurement of FFM will therefore take into account only the changes in the most metabolically active organs. Tzankoff and Horris (1977) actually found that the decline in basal metabolic rate, with age, was abolished when oxygen consumption was normalised (using RES model) for lean muscle mass. Therefore, the changes in resting CPO may relate to an age-related reduction in muscle mass and the functional requirements of less active skeletal muscles, with less mitochondria and hence oxidative capacity.

Despite the lack of changes in CPO_{rest} once scaled to FFM^b, a significant reduction in resting Ci_{rest} was still evident (Figures 3.12B). However, this rate of decline was reduced and consequently, was sufficient for the increase in MAP_{rest} to prevent an age-related decline in CPi_{rest}.

The changes in peripheral blood flow are usually proportional to a tissue's metabolism (Lakatta, 1993). However, the decline in FFM did not fully account for this age-related decline in CO_{rest} (Figure 3.12B). Therefore, other factors must have also contributed to the decline in CO (or Ci) with age, e.g. increases in resting MAP and SVR. When Ohm's law is applied to the circulation, increases in resistance and pressure would

result in a decrease in CO. This increased vascular loading on the heart may therefore contribute to the decline in resting CO (and Ci) in all populations, with advancing years.

The mechanisms behind the gradual increase in resting arterial pressure with age are dependent on which aspect of pressure is analysed. Arterial pressure can be divided into steady (MAP) and pulsatile components (pulse pressure; PP) (Safar, 1989). Mean arterial pressure is determined by CO and SVR. The PP component, representing the variation in pressure around the mean, is influenced by left ventricular ejection, large artery stiffness, early pulse wave reflection and HR. Both increased resistance and wall stiffness elevate SBP. In contrast, DBP rises with increased resistance but falls with increased stiffness; the relative contribution of each determining the net effect on DBP (Franklin and Weber, 1994; Franklin, 1995; Safar, 1989).

It is believed that the changes in pressure are a result of alternations in the vasculature. That is, age-associated structural changes in compliance arteries (Gerstenblith *et al.*, 1977; O'Leary *et al.*, 1999) and impaired relaxation of smooth muscle tone following β-adrenergic stimulation lead to a reduction in arterial compliance with ageing (Lakatta, 2002). Such changes are associated with an increase in SBP_{rest} within the clinical normal range (Pearson *et al.*, 1997). An increase in both SBP and DBP were identified in the current study and may well be due to an increase in arterial stiffness and resistance, respectively (Miyachi *et al.*, 2003; Tanaka *et al.*, 1998). Consequently, increasing age has been referred to as a muted form of hypertension (Lakatta, 1989).

It has been well documented that SVR_{rest} increases with age in patients with clinical hypertension, which elevates DBP and MAP (Kawamoto *et al.*, 1977; Lund-Johansen, 1991; Messerli *et al.*, 1981; Messerli *et al.*, 1984). However, the changes in SVR_{rest} for normotensive subjects are inconsistent (Brandfonbrener *et al.*, 1955; Fleg *et al.*, 1990; Julius *et al.*, 1967). An increase SVR_{rest} with age has only been reported to occur in healthy women and not men (Fleg *et al.*, 1990, 1995). However, an increase in SVR_{rest} with age in both sexes was clearly evident in the current study (Figure 3.15).

The changes that are identified in resting cardiac function (CPO_{rest}) seem to be governed by a complex interplay between CO, MAP and SVR. In addition to the age-related differences in CPO_{rest} significant sex-related differences were evident. It was also

interesting to note that, age for age, women had lower resting CPO, CO, SV and higher SVR values compared to men. These differences were solely related to the differences in body composition and once CPO and SV were normalised for FFM^b, no sex-related differences were found. Therefore, the differences in FFM seem to be the principle reason for the apparent differences between sedentary men and women at rest. The lack of changes identified in resting CPO, (i.e. once normalised to FFM^b) between men and women of various ages and fitness levels, further demonstrates that such measurements at rest are unlikely to be of any real discriminatory value. The same is also true of patients with moderately to severe heart failure (Cotter *et al.*, 2003; Goldspink *et al.*, 2003).

4.6. The effects of endurance training

A challenging question that has puzzled many physiologist, concerns whether the deterioration in physiological function is due to ageing per se or a less active lifestyle that accompanies ageing. It is well known that as individuals become older they gradually become less physically active. Consequently it can be difficult to separate this trend towards a more sedentary lifestyle from the intrinsic changes associated with ageing (Lakatta, 1993; Seals *et al.*, 2003). We attempted to examine this question by looking at a specific experimental model. For this purpose aerobically active men were examined in relation to age-matched sedentary controls.

The findings of the current studies illustrated that maintaining an active lifestyle was not sufficient to prevent an age-related decline in maximal cardiac function or CR (Figures 3.32 and 3.33). The mechanisms behind these age-related declines were similar to those identified in the sedentary men. That is, the primary factor that contributed to the decline in CPO_{max} was a corresponding decline in CO_{max}. An increase in MAP was also observed at maximal exercise in these active men, which helped to ameliorate the loss CPO_{max} with age.

Interestingly looking at the raw data, it would appear that the active men expressed the greatest rate of decline in CPO_{max} and CR, compared to their sedentary counterparts. Such data suggest that the benefits of aerobic training are lost with advancing age.

However, this may well be misleading. It was interesting to see that the older (60+ years) endurance trained men were physically smaller than their sedentary counterparts, i.e. on average they had lower BM and FFM values (Table 3.9). Such differences in body composition have been shown to affect CPO. It was therefore not surprising, that once these values were normalised for FFM^b the rate of decline for both CPO_{max} and CR were similar between the sedentary and active men (i.e. 14 to 18%, respectively).

The heterogeneous sample of male fitness levels in section 3.3.2 has made it difficult to conclude whether the changes in cardiac function were attributed to ageing per se or due to other confounding factors. Therefore, two groups of long distance veteran athletes (50 and 58 years-of-age) were examined and compared to age-matched sedentary controls. However, these veteran athletes who had trained for an average of 18 years with a weekly running distance of ~32 miles were unable to shed any further light on this question. That is, the age-related decline in CPO_{max} from 50 to 58 years-of-age in these veteran athletes was similar (14 to 17%) to that found in the sedentary and active men (Figure 3.32A). This would suggest that irrespective of fitness levels, a decline in CPO_{max} is almost inevitable with increasing age in men. However, caution is warranted when comparing the age-related decline in CPO in these veteran athletes, because of the small sample size (n = 20) and the narrow age (46-64) range.

It has been widely advocated that the age-associated decline in $\dot{V}O_{2max}$ can be partially offset with aerobic exercise training (Ehsani *et al.*, 1991; Seals *et al.*, 1984; Stratton *et al.*, 1994). However, others have shown that the age-related decline in $\dot{V}O_{2max}$ is greater in endurance trained individuals, compared to their sedentary counterparts (FitzGerald *et al.*, 1997; Pimentel *et al.*, 2003; Wilson and Tanaka, 2000). However, in the current study, the rate of decline in $\dot{V}O_{2max}$ (l/min) with age was similar for the sedentary and active men (Figure 3.25A).

A possible explanation for the decline CPO_{max} identified in these veteran athletes could be due to changes in the exercise-training stimulus. That is, with increasing age the athletes are not able to perform the same intensity or volume of habitual aerobic exercise that they performed in their youth. Evidence for this comes from data obtained for the changes in $\dot{V}O_{2max}$ with increasing age. Pimentel *et al.* (2003) found that the

frequency of training decreases with increasing age and that correlated with the decline in $\dot{V}O_{2max}$ in the endurance trained men. Furthermore, longitudinal data have shown that $\dot{V}O_{2max}$ values were preserved when the exercise training stimulus was maintained over periods of 10-20 years (Katzel *et al.*, 2001; Marti and Howald, 1990; Pollock *et al.*, 1987). Data to either refute or confirm this explanation is difficult to obtain, especially in cross-sectional studies because precise documentation would be required of the subjects' volume and intensities of training.

The current study obtained information regarding race times (i.e. 10k, half-and full-marathons) over the past year, training volume, intensity, and the number of years the subjects had been regularly participating in this form of training. However, details were not obtained concerning how their current training stimulus, compared to that over the past 10 years. It is therefore difficult to ascertain whether the subjects had reduced their training volume. Even if such data were available it would be difficult to elucidate whether the decrease in training stimulus with age caused a smaller decline in CPO_{max}. Alternatively, with the age-related reductions in CPO_{max}, the perception of exercise difficulty may be increased and the training stimulus consequently decreased.

In addition, with increasing age, there is a likelihood of sub-clinical illnesses, which would confound the findings and may account for the changes in CPO_{max}. Despite this possibility, we still observed significant perseveration of cardiac function with training in the older age-groups.

It would therefore be interesting to establish how maximal cardiac function would vary with age if the training stimulus could be maintained. For this purpose, longitudinal studies that monitor the training stimulus would be required to provide further insight into this possible mechanism. Alternatively, cross-sectional studies that employ a wide age-range, large number of subjects, exclusion of any diseases, and a stringent training status criteria for subject selection of the may also provide some insight into the affects of training status on overall cardiac function.

Despite all of these shortcomings the beneficial adaptations of long-term endurance training were clearly evident at maximal exercise. These veteran athletes who have

trained for ~18 years had substantially greater CPO_{max} and CR values, than their age-matched controls (Figure 3.41). These beneficial differences were still evident when expressed relative to FFM^b and cannot therefore be attributed to confounding affects of body composition.

Although no differences were found for resting CPO, CO, or MAP between the veteran athletes and their sedentary controls, positive adaptations were present for resting SV and HR. These changes associated with long-term endurance training have been well documented (Blomqvist and Saltin, 1983; Saltin, 1969). The larger SV_{rest} (or SVi_{rest}) found in the veteran athletes of the current study has previously been attributed to a larger resting LVEDV. In turn, such adaptations are thought to be directly related to expanded intravascular volumes, particularly plasma and total blood volumes (Hagberg *et al.*, 1998). The larger LVEDV is thought to evoke the Frank-Starling mechanism, thereby increasing SV. The limited echocardiography data we have suggested that those veteran athletes had greater LVEDV than their age-matched counterparts. Although not statistically significant (Figure 3.43), this observation was consistent with findings by others (Pluim *et al.*, 2000; Spirito *et al.*, 1994). Any myocardial hypertrophy could also result in increased force of contraction leading to a reduction in the LVESV, thereby increasing SV_{rest}. However, the echocardiography data suggest no changes in cardiac structure in the veteran athletes, with left ventricular diameter and wall thickness no larger in the veteran athletes, compared to their sedentary age-matched controls. Changes in cardiac structure are common in endurance trained athletes and enable the heart to adapt to both pressure and volume overload (Pluim *et al.*, 2000; Spirito *et al.*, 1994). It was therefore surprising not to establish differences between these two extreme populations.

Resting bradycardia was also identified in the current study. This again is another common adaptation to training. It is thought that the bradycardia results from increased parasympathetic activity in the heart, while decreasing sympathetic activity (Dowell, 1983; Saltin, 1969). Such antagonistic changes in SV and HR at rest means that the resting CO was not significantly different between the veteran athletes and their age-matched controls.

Past research has clearly identified that endurance training results in physiological stress, which induces adaptations to the heart. These are characterised by increased diastolic filling, left ventricular hypertrophy and SV_{max} (Astrand, 1960; Blomqvist and Saltin, 1983; Clausen, 1976; Levy *et al.*, 1993; Longhurst *et al.*, 1989; Saltin *et al.*, 1968). Indeed, in the current study the active men had greater CO_{max} values which were solely attributed to a larger SV_{max}, because HR_{max} did not differ between the subjects (Table 3.12). No differences were found in MAP_{max}. Therefore, it is likely that CO plays a greater role in the adaptive increase in CPO_{max} in trained men.

The increased SV_{max} in these endurance trained men could be due to a variety of beneficial adaptations. These could include an enhanced inotropic state which can result from enhanced sensitivity to catecholamines, a larger end diastolic volume (hence preload) thus evoking the Frank-Starling mechanism, left ventricular hypertrophy, or any combination of these variables (Ehsani *et al.*, 1991; Fleg *et al.*, 1994; Lakatta, 1993; Ross, 1976). Milliken *et al.* (1988) demonstrated that LVM was greater in highly trained athletes and that this accounted for 40% of the variance in $\dot{V}O_{2max}$. Although no statistical differences were found in our data for LVM (Figure 3.43D), the values tended to be greater in the veteran athletes, and may account for some of the greater SV_{max} in these subjects.

There are some suggestions that endurance trained individuals can obtain higher maximal BP values than untrained individuals (Ekblom *et al.*, 1968; Stratton *et al.*, 1994; Tanaka *et al.*, 1996). However, others have found no such differences before and after endurance training (Svedenhag *et al.*, 1986), and between trained and untrained subjects (Steinhaus *et al.*, 1988). It is thought that in trained athletes, the increase in maximal SBP is an adaptive response to maintain the perfusion pressure to widely dilated skeletal muscle and vital organs under conditions of low SVR (Rowell, 1991). However, the effect of endurance training in determining BP responses to dynamic exercise remains controversial. The veteran athletes examined in the current study had similar maximal BP values, compared to their age-matched controls (Table 3.12).

The evidence in the literature suggests that elevated SBP in response to maximal exercise may only be apparent in younger endurance trained individuals (Ekblom *et al.*, 1968; Steinhaus *et al.*, 1988; Stratton et al., 1994; Svedenhag *et al.*, 1986; Tanaka *et al.*,

1996). Such evidence questions whether older endurance trained individuals have a similar response to their younger counterparts. We examined trained subjects who were into their fifth and sixth decade of life, which may have accounted for the lack of differences in MAP_{max}. It may be that overtime this adaptive response is either lost or that older trained subjects adapt differently to the training stimulus. Another possible explanation concerns the inability to adequately differentiate between the veteran athletes and their age-matched controls. That is, the high SBP in the veteran athletes may be a result of an adaptive response to the training stimulus, whereas in the sedentary older men it may be due to a greater reduction in compliance of the large elastic arteries. This is one of the reasons why MAP, and not SBP, is used in the calculation of CPO. However, one cannot rule out the fact that the arteries of the veteran athletes may also become stiffer with age, although past research has indicated that regular endurance training can attenuate the age-associated increase in arterial stiffness (Miyachi *et al.*, 2003; Tanaka *et al.*, 2000). Indeed, in the current study the veteran athletes had lower SVR_{max} than their sedentary peers, which indicates greater maximal vascular dilatation, or less alterations in vascular structure (Clausen, 1977; Snell *et al.*, 1987). Therefore, further evidence is required to clarify whether endurance training in older individuals enhances the pressure generating capacity of the heart.

The greater CPO_{max} values in these veteran athletes were associated with a lower SVR_{max}. This is an important adaptation to endurance training as it highlights a lower vascular load on the heart, thereby allowing a greater volume of blood to be ejected from the ventricles. Such changes suggest improvements in peripheral function as well as positive central cardiac adaptations.

The enhanced maximal cardiac function observed in these veteran athletes, compared to their age-matched controls has an important health-related outcome. Such individuals have a greater CR and should be able to cope better with the stresses of day-to-day life. More importantly, for the same size of myocardial infarction they should perhaps retain a greater cardiac functional reserve (CR) than a sedentary individual with a smaller initial CR. It is therefore obvious that an active lifestyle is vitally important.

How well the aged heart responds to aerobic exercise training is an important question that needs to be ascertained. Past research has demonstrated that older individuals do in

fact maintain the ability to adapt to endurance exercise training, as indicated by an increase in the $\dot{V}O_{2max}$ (Ehsani *et al.*, 1991; Hagberg *et al.*, 1989; Kohrt *et al.*, 1991; Meredith *et al.*, 1989; Stratton *et al.*, 1994). Initial responses suggest the CPO_{max}, and thus CR, can also be enhanced in older individuals by endurance training. A recent study by Ehsani *et al.* (2003) examined frail octogenarians (both men and women) who participated in a training programme of physical therapy for 6 months e.g. strength training, and walking followed by 3 months of more intense endurance exercise at 78% peak HR. These results contained pressure and flow changes both at rest and at maximal exercise. However like many studies, the two components were not combined to provide a marker of overall cardiac function. If CO and MAP been combined to calculate CPO, then the authors would have found that the trained group had increased their maximal cardiac function by 21%, compared to the insignificant 3% change identified in the control group. At present the only study to examine directly the changes in CPO was performed by Marshall *et al.* (2001). After performing 20 minutes of cycling at 75-80% of their $\dot{V}O_{2max}$ for 5 days a week for 8 weeks, 58 year-old men significantly improved their CPO_{max} and CR by 16 and 21%, respectively.

Another interesting point would be to ascertain whether the total number of cardiomyocytes declines in individuals who maintain endurance training over many years. The reports of Olivetti *et al.* (1995; Figure 1.1) lead us to believe that ageing is associated with a loss of contractile cells, especially in men. Unfortunately, these investigators did not have any information relating to the lifestyle (e.g. sedentary of active) of these individuals prior to their death. Therefore, it may be that long-term endurance training attenuates or prevents such a loss of myocytes by apoptosis and/or necrosis. It has been well documented that the cardiac muscle of endurance trained athletes undergoes considerable hypertrophy as a result of the training stimulus. Whereas the cardiomyocyte hypertrophy identified by Olivetti *et al.* (1995) presumably represents an attempt to compensate for the loss of heart cells, this hypertrophy clearly is not sufficient as CPO_{max} declines in the men, with age. If the age-related death and loss of myocytes occurs irrespective of fitness levels, it may be possible that the degree of hypertrophy in long-term endurance trained individuals may be sufficient to attenuate these losses and preserve overall cardiac function at least for some years, e.g. between 20 and 60 years.

Several studies have shown that older endurance trained athletes have markedly higher $\dot{V}O_{2max}$ values than their sedentary peers (Hagberg *et al.*, 1985; Heath *et al.*, 1981; Pollock *et al.*, 1987; Seals *et al.*, 1994). Others have also shown that the $\dot{V}O_{2max}$ values of veteran athletes can be greater than younger sedentary individuals (Heath *et al.*, 1981; Ogawa *et al.*, 1992). The latter agrees with the current study (Table 3.10). Not only were the benefits of long-term endurance training apparent on measuring maximal cardiac function in relation to men of the same age, but also in relation to sedentary 21 year-old men (Figure 3.41). These positive findings indicate that endurance training can delay the loss in $\dot{V}O_{2max}$ and cardiac functional reserve which normally occurs over 40 years of ageing in inactive individuals.

Compared to the sedentary 21 year-old men, these veteran athletes exhibited a training-induced preservation of cardiac function without a concomitant reduction in afterload, i.e. an improved CPO_{max} but no differences in SVR_{max} (Figure 3.42). These findings imply that the improvement attained in CPO_{max} in the veteran athletes were due preliminary to central adaptations (i.e. increased SV) rather than driven by peripheral factors such as oxygen demand and extraction or a reduction in afterload.

It is well known that the vascular component of afterload greatly influences cardiac pump function. That is, at either extreme of the spectrum of vascular impedance, there would be no hydraulic energy output from the heart (Cotter *et al.*, 2003; Tan, 1986; Tan, 1987; Williams *et al.*, 2001a). In the current study the increase in SVR with age could be associated with the decrease in CPO (Figure 3.38). These results provide further evidence to suggest an increase in SVR_{max} may have contributed to the decline in CPO_{max} with increasing age.

By divorcing the effects of SVR from CPO_{max} we were able to identify an important relationship. It was found that the ability of the heart to perform external work was greater in the active men compared to their sedentary peers for a given vascular resistance. Hence, CPO_{max} was not totally dependent on SVR (Figure 3.38). A similar relationship was also identified in the ability of the heart to generate pressure (Figure 3.39), that is the active men had a greater ability to generate pressure for a given SVR

compared to their sedentary controls. Therefore, the greater MAP_{max} in the active men was also not totally dependent on SVR.

These novel findings are important as they illustrate that improvement in CPO_{max} in these active men was more likely to be a direct result of increased cardiac performance rather than a reduction in the pump afterload, which could also increase CPO.

4.7. The effects of creatine supplementation on CPO

Perhaps a simple and less energetic way of attenuating this age-related decline in maximal cardiac function is through creatine supplementation. Dietary creatine supplementation of 20g/day for 5 days has been shown to improve the performance of the skeletal muscles (Harris *et al.*, 1992). Furthermore, it has been shown that creatine concentrations decline in a normal human heart, with age (Nascimben *et al.*, 1996). Additionally, creatine supplementation in the rat has been shown to increase myocardial ATP and phosphocreatine concentrations (Brzezinska *et al.*, 1998). Such evidence links the possibility that a decline in the heart's immediate energy system may affect its function. In these studies we examined whether it would be possible to 'rejuvenate' the ageing heart by "topping up" its creatine, and hence phosphocreatine (PCr) concentrations. This would have provided an easy, cheap and painless means of increasing cardiac functional reserve. However in the current study, there was no evidence to suggest that creatine supplementation had any beneficial effect in improving cardiac performance in 50-60 year-old inactive men. Subsequent to this investigation a group of 60 year-old active men were also examined, as creatine combined with exercise training has been shown to augment the uptake of creatine into skeletal muscles (Harris *et al.*, 1992; Robinson *et al.*, 1999). However, once again creatine supplementation failed to improve cardiac performance in these active older subjects.

There may be a number of possible explanations for the lack of apparent improvement in cardiac performance. One such explanation is that the majority (95%) of the creatine stores are located in the skeletal muscles (Wyss and Kaddurah-Daiuk, 2000). This may explain why a number of studies have demonstrated significant increases in skeletal muscle creatine content and performance. However, of the remaining 5% in the body

the highest concentration is located in the heart (Wyss and Kaddurah-Daiuk, 2000). Whether, the cardiac store of creatine can be enhanced sufficiently to improve performance remains to be established. Also, Rawson *et al.* (2001) postulated that older individuals may have either a poorer ability to absorb creatine from the gut into the blood stream, or an inability of the muscle to take up creatine. Further to this, Neubauer *et al.* (1999) identified that the total creatine and number of creatine transporter proteins were significantly reduced in autopsied failing human hearts. It is currently unknown whether normal healthy ageing is associated with a decline in the number of creatine transporters in the heart. If this is the case then this could affect creatine uptake into the heart.

Another possible explanation concerns the sensitivity of using CPO as the measurement tool. To measure CPO requires the subject to exercise to exhaustion (~9 minutes), before maximal limits are reached and CO and MAP measured. This process is then repeated for duplicate or triplicate measures. Walter *et al.* (1997) has indicated that creatine concentrations are reduced to less than 40% of the resting concentrations within 10 seconds of maximal exercise, after which glycogenolysis becomes the prime energy supplier (Hultman and Sjoholm, 1983; Jacobs *et al.*, 1983). It is therefore conceivable that any beneficial improvements would have occurred at the very beginning of the high intense exercise when the PCr system is being utilised as a major source of ATP. At present the current CPO protocol cannot provide continuous measures of cardiac power, which is perhaps one of its limitations. Therefore it may not be sensitive enough to have identified any short-lived improvements. Furthermore, Terjung *et al.* (1999) indicated that marginal increases in performance due to creatine supplementation could be difficult to detect given the experimental variability of performance measurements in different individuals. This may well be true for the measurement of CPO. Any, such beneficial effects of creatine on CPO could conceivably be identified using the invasive CPO technique, which instantaneously measures flow and pressure generation from the heart.

The negative results in the current study are similar to those found in an animal model where biological and environmental variables are more easily controlled. Data from Horn *et al.* (1998) demonstrated that increasing dietary creatine, and thus both extra-and

intra-extracellular creatine concentrations, did not affect cardiac performance or coronary blood flow in normal rats. Horn *et al.* (1998) concluded that in the normal heart the energy reserve provided by creatine kinase is not regulated by extracellular creatine concentrations. Furthermore, a study by Neubauer *et al.* (1999) examined the haemodynamic changes after 8 weeks of feeding β-guanidinopropionate. This synthetic analogue depletes the PCr and total creatine pool by ~80 and ~70%, respectively (Neubauer *et al.*, 1999). Despite these dramatic losses in creatine concentrations no differences were found in peak haemodynamic variables such as left ventricular developed pressure, CO or SVR. Unknown to the authors, CPO could have been calculated from their data. Once determined, no differences were found in peak CPO. Such data suggest that the role between creatine and cardiac energy metabolism plays a relatively minor role in determining peak cardiac function in the rat. This may also be true in humans. It therefore appears that endurance exercise training remains the best approach to improve CR.

Chapter 5

Conclusion

The aim of this thesis was to determine if healthy ageing was associated with a decline in maximal cardiac function and functional reserve capacity. In the past many of the techniques used were invasive or measured only specific aspects of cardiac function. For example, CO alone has been commonly used in both exercise physiology and clinical medicine as an index of cardiac function. The pressure generating capacity of the heart is a vital element of cardiac function and must be incorporated when addressing overall cardiac function. These studies here highlight that by ignoring blood pressure and examining only blood flow the changes in cardiac function will be overestimated with healthy ageing. Furthermore, when examined in heart failure patients (NYHA II-III), the detrimental impact of the disease on cardiac function will be underestimated. It is therefore imperative to incorporate both the pressure and flow generating capacities of the heart when examining its overall function. Therefore, CPO, as a more representative and comprehensive indicator of cardiac function (Cooke *et al.*, 1998; Nicholls and Reilly, 2001) was employed throughout to document the changes associated with ageing. Since this can be achieved non-invasively, it represents a powerful research tool.

Prior to embarking on this large study, it was important to ascertain whether the measurement of CPO, like other physiological measures, was affected by a circadian rhythm. However, by measuring resting and maximal CPO at the extremes of 04:30 and 16:30, it was established that there were no influences due to the time of day. In addition to its physiological importance this has huge practical benefits concerning the number of subjects that were reliably tested each day, and for cross-sectional studies of this nature.

Hence, the optimisation of the CPO protocol, i.e. time of day has significantly improved the precision and reproducibility of this non-invasive technique.

Changes in body composition, particularly the amounts of metabolically active skeletal muscle mass, strongly influenced the interpretation of these results with respect to both age and gender. The physiological basis for this association is assumed to be a direct relation between skeletal muscle mass and its capacity to consume oxygen (Fleg and Lakatta, 1988; Toth *et al.*, 1994). The current results highlighted that both $\dot{V}O_{2max}$ and variables of CPO were affected by differences in body composition in a way similar to

that reported for CO. Therefore, to permit meaningful comparisons of inter-or intra-groups of data the current studies identified that it was critical that CPO should be scaled to FFM, using the allometric model of scaling.

Exactly how the process of ageing affects CPO is unknown. Past research has either tended to examine the age-related changes using incomplete measures of overall cardiac function, or the results have been difficult to interpret due to the confounding influences of disease, gender, fitness, or differences in body composition. Here, original observations on the effects of healthy ageing on overall cardiac function (CPO) have been reported. It is clear that healthy ageing is associated with a decline in both resting and maximal cardiac function, in both sedentary men and women. The primary mechanism for this decline in both resting and maximal cardiac function was a corresponding decrease in CO. Such a decline in resting and maximal CO has been reported in the past (Fleg *et al.*, 1990, 1995; Rodeheffer *et al.*, 1984, 1986). Although an age-related increase in resting MAP is well known, the increase in MAP at maximal exercise with age is seldom reported, which is a crucial component in measuring CPO.

An age-associated decline in CPO_{rest} has not been reported before. However, the decline in resting CPO, as experienced by both men and women, was entirely due to the age-associated changes in body composition. Hence, no differences remained when these data when normalised for FFM^b.

The age-related decline in maximal cardiac function was anticipated. However, interestingly after the female CPO_{max} data had been normalised for FFM^b, no significant decline was observed. In contrast, a significant decline in maximal cardiac function was evident in the male data. At present it is not known why women behave differently to men. It may be a direct result of the female heart loosing substantially less cardiomyocytes with time, compared to men (Olivetti *et al.*, 1991). This could also be in agreement with the maintenance of LVM (Hees *et al.*, 2002). Although, 89 women were studied between the ages of 19 to 76 these were not sufficient to determine with any accuracy whether the menopause and HRT exert any direct effects. It would be important therefore to repeat these findings in both cross-sectional and longitudinal studies to consolidate these findings of CPO_{max} in ageing for postmenopausal women.

In an attempt to improve cardiac metabolic performance through oral creatine supplementation, this ergogenic aid was given to two groups of 60 year-old men. However, the dietary creatine supplementation had no effect on cardiac performance, in either sedentary or active men even though it has been reported that exercise training augments the uptake of creatine into the skeletal muscles (Harris *et al.*, 1992; Robinson *et al.*, 1999). These results suggest that creatine supplementation does not metabolically 'rejuvenate' the hearts of older men.

This thesis also compared aerobically active and veteran endurance trained athletes to sedentary, age-matched men, to determine whether an active lifestyle could prevent or attenuate the changes associated with ageing. Although, the active men reported a similar decline in maximal cardiac function to their sedentary counterparts, important physiological adaptations were evident. Maximal CPO and CR were greater in the veteran athletes compared to their age-matched counterparts. Not only were these benefits of long-term endurance training apparent relative to men of the same age, but also when compared to sedentary 20 year-old men. These findings indicate that maximal cardiac function was more than fully preserved against the process of ageing by long-term endurance training.

Animal experiments, involving sedentary versus long-term endurance trained animals, could be undertaken and the number of cardiomyocytes in their hearts counted to determine if cell loss is attenuated by exercise. If not, then all adaptations would appear to occur through different degree of myocyte hypertrophy.

An unexpected outcome was the finding that for any given SVR the active men had greater CPO_{max} and MAP_{max} values, compared to the sedentary men. This indicated that maximal cardiac performance in these subjects was not totally dependent of SVR. This adaptive response suggests that the changes due to endurance training directly improve cardiac performance, rather than by reducing afterload.

The results described in this thesis have progressed the understanding of the age-and exercise training changes in overall cardiac function. In addition, improvements have been made towards the CPO protocol that should further improve the quality of the measurements of CPO, and hence CR. Also advances have been made towards how best

to normalise CPO measurements in relation to changes in body composition thereby improving the validity and interpretation of data for inter-and intra-group comparisons. Despite this, much still needs to be accomplished.

Chapter 6

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Appendix

Appendix 1

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
☐	☐	☐	☐	☐	☐

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

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

19. Do you ever lose consciousness? Yes No

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

If yes, was the ECG normal? Yes No

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

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

If yes, which one? Low High

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

If yes, give name and dosage _____

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

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

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

If yes, state name and dosage _____

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

If yes please specify condition and medication _____

_____

27. 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 ☐

28. 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

29. 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

30. Do you know of any other reason why you should not undertake physical activity?

If yes, why _____

31. 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

32.Do you smoke? Yes No

What do you smoke (please circle) cigarettes cigars pipe

If yes,

How long have you smoked for? _____

How many per day? _____

Have you ever smoked? Yes No

If yes,

How long did you smoke for? _____

How many per day? _____

When did you stop? _____

Section Three

Physical Activity Assessment

33. 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)	_____	_____

34. 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
☐	☐	☐

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

If yes, please detail training schedule including, type of activity, intensity, number of sessions per week and duration of each session on the attached sheet at the end of the questionnaire.

36. 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 four

Diet Assessment
(please circle)

37. Are you a vegetarian Yes No

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

_____

_____

_____

39. Do you take any food supplements Yes No

If yes, please specify _____

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

Participant signature: _____

Thank you for completing this questionnaire

Question 35 continued.
Please give details of current training schedule.

Appendix 2

American College of Sports Medicine, percentile values for maximal aerobic capacity (ml/min/kg).

	Age (years)				
Percentile	**20-29**	**30-39**	**40-49**	**50-59**	**60+**
Men					
90	**51.4**	**50.4**	**48.2**	**45.3**	**42.5**
80	**48.2**	**46.8**	**44.1**	**41.0**	**38.1**
70	**46.8**	**44.6**	**41.8**	**38.5**	**35.3**
60	**44.2**	**42.4**	**39.9**	**36.7**	**33.6**
50	**42.5**	**41.0**	**38.1**	**35.2**	**31.8**
40	**41.0**	**38.9**	**36.7**	**33.8**	**30.2**
30	**39.5**	**37.4**	**35.1**	**32.3**	**28.7**
20	**37.1**	**35.4**	**33.0**	**30.2**	**26.5**
10	**34.5**	**32.5**	**30.9**	**28.0**	**23.1**
Women					
90	**44.2**	**41.0**	**39.5**	**35.2**	**35.2**
80	**41.0**	**38.6**	**36.3**	**32.3**	**31.2**
70	**38.1**	**36.7**	**33.8**	**30.9**	**29.4**
60	**36.7**	**24.6**	**32.3**	**29.4**	**27.2**
50	**35.2**	**33.8**	**30.9**	**28.2**	**25.8**
40	**33.8**	**32.3**	**29.5**	**26.9**	**24.5**
30	**32.3**	**30.5**	**28.3**	**25.5**	**23.8**
20	**30.6**	**28.7**	**26.5**	**24.3**	**22.8**
10	**28.4**	**26.5**	**25.1**	**22.3**	**20.8**

Data are presented by institute for Aerobics Research, Dallas, TX (1994). Study population for the data sets were predominately white and college educated. A modified Balke treadmill test was used with $\dot{V}O_{2max}$ estimated from the last grade/speed achieved. The following may be used as descriptors for the percentile rankings: well above average (90), above average (70), average (50), below average (30), and well below average (10).