The Effects of Pregnancy and Weight Changes on Cardiovascular Pathophysiology

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The candidate confirms that the work submitted is his own and that appropriate credit has been given where reference has been made to the work of others.

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Declaration

Diane Barker performed her MD with Lip-Bun Tan entitled "*Cardiovascular function in pregnancy in subjects with and without Heart disease"* and completed her thesis in 2009. This work was in part, a pilot study to my more comprehensive study in healthy pregnancy. I chose not to use any of Diane's data however, I was able to amend her ethics approval and her ground breaking work established the safety of exercise testing in pregnant women and so paved the way for my research. On the other hand I did allow Diane to use some of my data on healthy pregnant women, to allow her to make comparisons between data she had collected on pregnant women with heart disease.

The normal healthy data that was used in Study VIII was a mixture of healthy females I had studied and data from other healthy controls collected by my colleague, Lisa Sharp in Liverpool.

Abstract

Pregnancy is a major physiological stress of the cardiovascular system. Weight gain significantly contributes to physical limitations. This thesis examines the effects on both physical and cardiac performance of weight gain in pregnancy. Utilising cardiac power output at rest and maximal exercise, I measured the effects of (i) inert weight loading (ii) pregnancy and (iii) obesity in the non-pregnant state, to determine the acute, chronic and also reversible changes.

Weight loading using a pregnancy simulator suit ("*Empathy Belly"*) showed reduced physical performance, whilst showing an improvement in cardiac performance, predominantly by increasing the pressure generating capacity of the heart. Additional load carriage with the "*Empathy Belly"* and a rucksack, showed further reduction in physical performance, but no further improvement in cardiac performance. Pregnancy revealed significant reductions in physical performance and maintenance in cardiac performance compared to the non-pregnant post-partum. Contrary to this, there were significant reductions in both physical and cardiac performance in pregnancy, compared to pre-conception. Changes in cardiac performance throughout pregnancy gradually improved, whilst there was a deterioration in overall physical performance. Obesity in the non-pregnant state, showed significant reduction in physical performance with a marked increase in cardiac performance. This was primarily driven by an increase in the flow generating capacity of the heart; the cardiac output.

Inert weight loading, weight carriage in pregnancy and non-physiological weight gain in obesity in the non-pregnant state, all reduce physical performance. In contrast to this, both inert weight carriage and weight carriage in obesity increase cardiac performance. Acute weight loading induces an increase in pressure generating capacity, whilst chronic weight carriage leads to an increase in flow generating capacity.

For the first time, I have shown that peak cardiac performance reduces in pregnancy from pre-conception, although this gradually improves throughout pregnancy and is likely to be in part caused by an increase in weight gain.

Publications from the PhD

Lewis NT, Hothi SS, Tan DK, Tan LB. (2015) Discordant changes in peak O_2 consumption and peak cardiac power during weight loaded treadmill exercise. Int J Cardiol. Apr 15;190:185-186. **(Appendix D)**

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Glossary

ANOVA	Analysis of variance
AT	Anaerobic threshold
BMI	Body mass index
ECG	Electrocardiogram
CEMACH	The Confidential Enquiry into Maternal and Child Health
CircP	Circulatory power
CO	Cardiac output
CO_2	Carbon dioxide
CoR	Coefficient of repeatability
CPO	Cardiac power output
CPX	Cardiopulmonary exercise
CR	Cardiac reserve
CV	Coefficient of variance
DBP	Diastolic blood pressure
$ETpCO_2$	End tidal partial pressure of carbon dioxide
ExDur	Exercise time
Hb	Haemoglobin
HF	Heart Failure
HR	Heart rate
ICC	Intra-class correlation coefficient
LVEDV	Left ventricular end diastolic volume
LVEDP	Left ventricular end-diastolic pressure
LVEF	Left ventricular ejection fraction
MAP	Mean arterial blood pressure
Max	Value achieved at maximal exercise
MHO	Metabolically healthy obese

MRI	Magnetic resonance imaging
NYHA	New York Heart Association (functional class)
PC	Pre-conception
PP	Post-partum
RER	Respiratory exchange ratio
SEM	Standard error of measurement
SBP	Systolic blood pressure
SD	Standard deviation
SF-36v2	Short form health survey questionnaire
SV	Stroke volume
SVR	Systemic vascular resistance
SW	Stroke Work
T1	First trimester
T2	Second trimester
T3	Third trimester
TTE	Transthoracic echocardiography
VE	Minute ventilation
VE/VCO_2	Ratio of minute ventilation to carbon dioxide production
VCO_2	Carbon dioxide production
VO_2	Oxygen consumption
V_t	Tidal volume

Chapter 1

Literature review

1 Literature Review

Weight is defined as "*a body's relative mass or the quantity of matter contained by it, giving rise to a downward force*" [Oxford Dictionary 2010]. When considering weight in humans, it is deemed in society as a sign of being healthy, if one is a normal weight and unhealthy if one is underweight or especially overweight. Society commonly stigmatises those individuals outside of the normal range and often leads to mocking and social isolation for those involved. Moreover, changes in body mass can occur for a number of reasons: from a growing child, to a pregnant woman, or self induced weight gain or loss seen in obesity and anorexia. Interventions can lead to dramatic changes in body mass: dieting; bariatric surgery where patients can lose up to 40% of their body mass [Buchwald *et al* 2004]; childbirth; amputation of a limb due to injury or severe peripheral vascular disease. It is often also necessary to carry external weight, which may be because of one's occupation, such as a soldier carrying a rucksack or in everyday life, carrying a school or work bag or even carrying one's own children. Some individuals choose to train their body, through weight lifting or performing dynamic exercise carrying weight, such as ankle weights or a weight suit. All of these weight changes inevitably lead to a change in stress on the cardiovascular system.

1.1 Cardiovascular response to stress

The human cardiovascular system is able to dynamically respond to stress, by having a reserve capacity to generate more force when necessary. This is prompted by neurohormonal and sympathetic activation and vagal inhibition. This results in a significant increase in heart rate, cardiac contractility, blood pressure, skeletal muscle blood flow and venous return with a drop in systemic vascular resistance, whilst peripheral vasoconstriction diverts blood away from the non-essential organs and inactive muscles. Different types of stress and exercise lead to varying levels of response. When more muscle groups are used, such as in weight bearing exercise, the fall in peripheral vascular resistance can be considerable. However, the blood pressure and cardiac output rises in parallel to the amount of work [Berne *et al* 2010].

The cardiovascular system also has limits to its response in heart rate, stroke volume and oxygen consumption, all reaching a plateau at maximal exertion. It is traditionally accepted that stroke volume plateaus at 40-50% of VO_{2max} [Astrand *et al* 1964]. However, current research suggests there is a range of responses, with some trained individuals showing a progressive rise in stroke volume up to VO_{2max}. [Vella & Robergs 2005]. VO_{2max} is generally considered as the best measure of the functional limitation (physical performance) of the cardiovascular system and is often used as an indicator of cardiopulmonary fitness. Seminal work by AV Hill showed that oxygen consumption reached a maximum level during peak physical work [Hill & Lupton 1923]. Subsequently, a plateau in VO_2, despite increase in work, has been used to determine a subject's maximum VO_2 (VO_{2max}). However, considerable variation in achievement of the plateau has been reported in the literature, therefore some investigators have chosen to test blood lactate levels or use a cut off respiratory exchange ratio as the key criterion of having attained VO_{2max}. [Rossiter *et al* 2006, Howley *et al* 1995]. There is also considerable debate about what ultimately limits VO_{2max}, between either a cardiac (circulatory) or neural (central governor model) regulation. The widely held view is that exercise is limited by the heart's inability to pump blood to the skeletal muscle. The evidence for this, is the drop in blood flow in the legs when arm exercises are superimposed on maximal bilateral leg exercise, leading to a fall in tissue and blood pH from the build up of lactic acid in the muscles. [Brink-Elfegoun *et al* 2007, Ekblom 2009]. The opponents of this suggest that there is a centrally mediated mechanism during exhaustive exercise that limits exercise in order to limit myocardial ischaemia [Noakes & Marino 2009]. Further to this discussion a very recent trial examined whether cardiac performance, namely Cardiac Power Output (CPO_{max}), limited VO_{2max} by assessing trained athletes during cycle exercise using 2 different rates of work. Despite similar VO_{2max} and cardiac output (CO), the study showed that mean arterial pressure (MAP) was significantly higher and that increases in CPO_{max} also approached significance (8.1 v 8.5, $p < 0.06$) in the group with the higher work rate, suggesting that the heart works sub-maximally during incremental exercise tests [Elliott *et al* 2015].

1.2 Cardiovascular changes of inert increase in body weight

When the increase in body mass is inert, in other words an external non-perfused increase in mass, such as seen with external weight carriage, one can clearly

establish how the cardiovascular system responds to weight alone. For many years the military has tried to establish the optimum pack weight for the soldiers going to war. In 1897, a British Royal Commission recommended a maximum fighting load of 40 pounds. In World War I this rose to 80% of body weight. In 1923, Cathcart *et al* found that the rate of oxygen consumption (referred to as energy cost), with weight loading, increases significantly when more than 40% body weight is carried, under laboratory conditions and therefore, under service conditions, a limit of one third of body weight was accepted, to maintain efficiency and health [Cathcart *et al* 1923]. Interestingly, in a recent study in Afghanistan, soldiers carried a fighting load of 29kg and march loads up to 57.5kg [Orr 2010]. It is well recognised that the rate of oxygen consumption increases with the amount of load carried, as well as the amount of work performed [Haisman 1988; Abe *et al* 2004]. Borgols *et al* studied loading up to 30kg and showed that for each kilogram of weight increased, VO_2 increased by 33.5ml/min [Borgols *et al* 1977]. Soule *et al* also showed that, at a given speed, with every increase in weight carriage, there was an increase in VO_2 up to 70kg [Soule *et al* 1978]. Bhambhani *et al* examined the physiological differences in healthy men carrying 2 different weighted boxes (15 and 20kg) during submaximal treadmill exercise, and showed that there was an increase in oxygen consumption with the higher weight, but no change in cardiac output and blood pressure [Bhambhani *et al* 1997]. Bhambhani then went on to compare gender differences using the same methods and showed that the rate of oxygen uptake was significantly higher in women, compared to men, and that cardiac output and maximum heart rate rose in women only with higher weight carriage [Bhambhani *et al* 2000]. Sagiv *et al* also compared the differences in load carriage, using heavy backpacks (38kg and 50kg) in healthy male volunteers performing 4 hours of treadmill walking. He found significantly higher values of VO_2, CO, HR, MAP and diastolic blood pressure (DBP) and significantly lower systemic vascular resistance (SVR) [Sagiv *et al* 1994]. Sagiv confirmed these findings in an older population (mean age 66 years) using two weights of 20 and 30kg, performing 30 minutes of submaximal treadmill exercise. They similarly showed a significant increase in CO, HR, MAP and DBP [Sagiv *et al* 2002].

What is not clear, is whether additional weight carriage will help us differentiate between indirect and direct changes in peak cardiac performance and overall cardiac function, namely VO_{2max} and CPO_{max}. It is also not clear whether cardiac performance can in fact supersede what is felt to be maximum functional performance at VO_{2max}.

1.3 Cardiovascular changes to perfused increase in body mass

The cardiovascular system also has the ability to adapt to changes in actual body mass over time. This generally occurs through a process of remodelling, caused by increased neurohormonal activation and vagal inhibition. If the increased body mass is perfused, as is the case in pregnancy and obesity, remodelling is further promoted by an increase in circulating blood volume. In the non-pregnant state, there is a curvilinear relationship between body mass and skeletal muscle mass [Janssen 2000], which further leads to increased muscle perfusion and venous return. However, the major difference in cardiovascular response between obesity and pregnancy is the dramatic change in haemodynamics seen in the first few weeks of pregnancy, even before body mass has changed.

1.3.1 Cardiovascular changes in pregnancy

1.3.1.1 Resting cardiovascular changes in pregnancy

Cardiovascular changes in pregnancy have been extensively studied since the first measurement of resting cardiac output in pregnancy was reported by Lindhard in 1915 [Lindhard 1915]. A number of investigators, including Stander and Cadden in 1932 and then Burwell *et al* in 1938, measured the changes in cardiac output in pregnancy, using the acetylene method. They found that cardiac output increased rapidly during the first half of pregnancy and reached a maximum by the 32nd week of pregnancy (increase of 45-85%) [Stander and Cadden 1932; Burwell *et al* 1938]. Hamilton then went onto perform a single CO measurement, using the direct Cournand cardiac catheterization technique, on 75 pregnant women throughout pregnancy and compared them to 32 non-pregnant controls. In the 6-9th week of pregnancy, CO was unaltered, but then suddenly increased by the 10th week, reaching a peak at the 29th week, then plateauing until the 37th week and falling in the last 2 weeks. [Hamilton 1949]. In 1989 Clark *et al* examined the longitudinal resting haemodynamic changes in 10 women from third trimester to 12 weeks post-partum, using the direct Fick technique. They found that pregnancy was associated with a significant rise in cardiac output and heart rate. They also reported a significant fall in systemic vascular resistance, but no significant change in ventricular stroke work index or mean arterial pressure [Clark *et al* 1989]. In 1990

Pivarnik *et al* performed a similar longitudinal study, examining the changes in cardiac output in 7 women between 37 weeks and 12 weeks post-partum, using the direct Fick technique at rest and during sub-maximal exercise. They found that responses of VO_2, cardiac output and stroke volume during exercise were greater in pregnancy [Pivarnik *et al* 1990]. During a similar period a number of other longitudinal studies were performed using non-invasive methods to measure resting cardiac output using M-mode echocardiography, Doppler echocardiography and impedance cardiography [Rubler *et al* 1977; Katz *et al* 1978; Capeless & Clapp 1989; Caton & Banner 1987; Easterling *et al* 1990; Robson *et al* 1989; Atkins *et al* 1981]. There was intensive discussion about which non-invasive test provided the most accurate assessment of cardiac output, in keeping with invasive methods. Easterling *et al* found that impedance techniques correlated poorly with the thermodilution method [Easterling *et al* 1989], whereas echo Doppler techniques were shown to correlate well with thermodilution techniques [Rose *et al* 1984]. Robson's study [Robson *et al* 1989], which assessed cardiac output in 13 subjects using the echocardiography Doppler technique from pre-conception, then at 5 weeks gestation and every 4 weeks through gestation to term, was felt to be the most valid study and therefore has been used to characterise the pattern of changes in cardiac output through pregnancy. Robson showed that cardiac output rose from 5 weeks and continued to rise to a maximum at 32 weeks by nearly 50%, and then fell slightly until term. He also showed that heart rate rose from week 5 until 32 weeks by 17% and then remained constantly elevated until term. Stroke volume rose by week 8, reaching maximum values at 20 weeks, and was then maintained to term. Left ventricular and left atrial dimensions became enlarged by week 12, until the end of the second trimester, by 7% and 16% respectively and remained constant until term, while LV wall thickness progressively increased from week 12 to term by 28%. He also showed that SBP remained constant during pregnancy until 36 weeks, when there was a slight rise, whilst DBP fell, reaching a significant nadir by 20 weeks and then rising progressively and increasing above pre-conception levels by 38 weeks. SVR also progressively fell from the start of pregnancy until 20 weeks, before slowly rising to term, albeit with levels that remained significantly lower at 38 weeks than pre-conception [Robson *et al* 1989].

Using post-partum as the non-pregnant state, both Mabie *et al* [Mabie *et al* 1994] and Desai *et al* [Desai *et al* 2004] performed echo studies, which showed that cardiac output increased by approximately 50% and that half of the increase had occurred early in the first trimester. However, they also showed that cardiac output then continued to steadily rise until term, rather than peaking in the early third

trimester. More recently, Ducas *et al* [Ducas *et al* 2014] made a comparison between transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging in pregnancy and post-partum. 34 women underwent scans at approximately 34 weeks and 16 weeks post-partum and these showed that cardiac output increased by 80-85% using both techniques. However, TTE underestimated the values compared to MRI. There was a similar increase in left ventricular end-diastolic volume (LVEDV) by 20-30% and LV mass by 45-50% between techniques, but again volumes and mass were underestimated by TTE. These differences are merely a reflection of the different imaging analysis techniques. Most recently Mahendru *et al* [Mahendru *et al* 2014] examined the longitudinal changes in resting cardiac output and blood pressure from pre-conception, through pregnancy and then again in post-partum, using a non-invasive validated inert gas re-breathing technique (Innocor, Innovision, Odense, Denmark). They showed a gradual rise in CO up to the second trimester, with a plateau in the third, before falling to pre-conception levels by 12 weeks post-partum. As well as seeing a rise in heart rate throughout pregnancy by 20%, there was also a significant rise in stroke volume in pregnancy. However, they also identified a significant increase in SV in post-partum, in comparison to the third trimester. Left ventricular ejection fraction did not significantly change throughout assessments. Blood pressure (systolic, diastolic and mean arterial) and systemic vascular resistance fell in pregnancy, reaching a nadir in the second trimester, before climbing again in the third trimester and post-partum. However, systolic blood pressure in post-partum remained significantly lower than in pre-conception. They found no relationship between weight gain and cardiovascular changes.

1.3.1.2 Exercise testing in pregnancy

1.3.1.2.1 Maximal exercise testing in pregnancy

A number of studies have examined the effects of pregnancy on VO_{2max} using cycle, treadmill exercise and swimming [Artal *et al* 1986; South-Paul *et al* 1988, Sady 1989; Lotgering *et al* 1991; Morton 1991; McMurray *et al* 1991; Spinnewijn *et al* 1996; Heenan *et al* 2001]. Lotgering *et al* [Lotgering *et al* 1991] performed the only longitudinal study using treadmill exercise in all three trimesters and post-partum, whilst, at the same gestation, also compared differences with cycle exercise. They found no significant difference in VO_{2max} between any trimester and post-partum, and no difference between exercise methods when VO_{2max} was expressed in litres/ minute. Maximal heart rate either appeared to be similar or slightly reduced. Other

studies have shown similar results, showing no change in VO_{2max} during maximal cycle exercise [Sady 1989; Spinnewijn *et al* 1996; Heenan *et al* 2001]. If VO_{2max} was scaled by body mass, then one would have seen a fall in aerobic capacity, which would have been a false interpretation.

Only one study in the literature, by Sady [Sady 1989], examined the longitudinal effect of CO in pregnancy during maximal cycle exercise. Sady used the acetylene re-breathing technique to measure CO and found that CO was higher in the third trimester in comparison to post-partum. Maximal heart rates were unchanged, thereby suggesting that an increase in SV was responsible. Sady also measured CO and VO_2 at two submaximal levels and found the CO/ VO_2 relationship was linear both during and after pregnancy, and suggested that there was a coupling mechanism between oxygen utilisation and oxygen delivery that was maintained in pregnancy.

1.3.1.2.2 Submaximal exercise testing

Many more studies examining the effects of pregnancy on submaximal exercise haemodynamics have been performed. The first comprehensive study was performed by Bader *et al* in 1955 [Bader *et al* 1955]. They measured CO, using the Fick technique in 46 pregnant women during supine cycling. No post-partum tests were performed, but they found that CO increased by 30-40% from rest with sub-maximal exercise and was similar to a reference control group, although exercise was not standardised. Ueland and Hansen [Ueland & Hansen 1969] performed a study with standardised upright cycle exercise in 11 women throughout pregnancy and post-partum and measured CO using the dye dilutional method. They found at 16 watts, there was a significant increase in CO and SV, that peaked at 20-24 weeks and was then maintained until term. However, at higher intensity, cycling at 32 watts, CO and SV still peaked at 20-24 weeks, but was not sustained and fell towards term. In contrast, Guzman and Caplan [Guzman & Caplan 1970] showed that CO remained elevated in pregnancy at all levels of cycle exercise (24, 41 and 57 watts), while $VO_{2,}$ on the other hand, only increased during the lowest intensity exercise in pregnancy. Knuttgen and Emerson [Knuttgen & Emerson 1974] compared both cycle and treadmill sub-maximal exercise in 13 women throughout pregnancy and post-partum. They measured VO_2 at peak using both methods of exercise and then CO at peak cycle exercise, using the CO_2 re-breath technique. They found that VO_2 was significantly elevated with weight bearing treadmill

exercise in pregnancy, but was unchanged with cycling. CO was not significant higher in pregnancy, but was increased (9.48 ± 0.25 $l.min^{-1}$ versus 8.79 ± 0.31 $l.min^{-1}$). Pivarnik *et al* [Pivarnik *et al* 1990] examined 7 women in the third trimester and post-partum, using both submaximal treadmill and cycle exercise and measured CO using the direct Fick technique. They showed a significant increase in VO_2 and CO with both cycle and treadmill exercise in pregnancy and that the response became greater as exercise intensity increased. Stroke volume increased with the intensity of treadmill walking, regardless of pregnancy status. Spatling *et al* [Spatling *et al* 1992] examined the differences in response to VO_2 between trimesters and post-partum during light and moderate cycle exercise and found that most of the change in VO_2 occurred in the first trimester, whereas in the second trimester there was either a fall or plateau in VO_2, before a gradual increase in VO_2 at term.

1.3.1.3 Non-pregnant controls

Most studies have used post-partum as a surrogate for the non pregnant control and have tended to choose 12 weeks post delivery as a time at which cardiovascular changes are felt to have returned to baseline [Gammeltoft 1926; Burwell *et al* 1938; Palmer and Walker 1949; Adams 1954; Roy *et al* 1966; Walters *et al* 1966; Ueland *et al* 1969; Katz *et al* 1978; Caton *et al* 1987; Atkins *et al* 1981; Davies *et al* 1986; Clark *et al* 1989; Sady *et al* 1989; Pivarnik 1990; Easterling *et al* 1990; Lotgering 1991; McMurray *et al* 1991; Spinnewijn *et al* 1996]. Robson *et al* [Robson *et al* 1987] examined cardiac output using the Doppler echocardiography technique in late pregnancy and then continued to compare this post-partum at 2, 6, 12 and 24 weeks. They showed a significant fall in cardiac output of 27-29% by 2 weeks with a much more gradual decline up to 24 weeks. This was accompanied by similar structural changes in end diastolic left ventricular and left atrial dimensions by 2 weeks with no significant change therafter. When the post-partum measurements at 24 weeks were compared to age-matched non-pregnant controls, they had significantly higher measures of left ventricular mass and reduced ejection fraction, suggesting that even at 24 weeks, not all cardiovascular changes had returned to normal. Capeless and Clapp [Capeless and Clapp 1991] examined the serial changes in cardiac output and stroke volume, using m-mode echocardiography, in 13 women at pre-conception and then again at 6 and 12 weeks post-partum and found that cardiovascular measures had not returned to pre-conception baseline at this stage. They then went on to examine serial resting

changes using the same method from pre-conception, through pregnancy and at 12, 24 and 52 weeks post-partum. As well as showing that changes in CO occurred early, from at least 8 weeks, and progressed into mid-third trimester, they also showed that although changes in cardiac output reduced post-partum, they also remained elevated above pre-conception levels, even at 1 year post-partum. They also showed that those who had had previous pregnancies had an increased response to CO throughout pregnancy and post-partum, despite not having different baseline pre-conception CO. Sady *et al* [Sady *et al* 1990] examined the differences in resting, submaximal and maximal haemodynamics using the acetylene re-breathing method, whilst pregnant (25 ± 3 weeks) and then at both 2 and 7 months post-partum. They showed that at rest VO_2, HR, SV and CO were higher in pregnancy, whereas there was no significant difference in these parameters between post-partum tests. During submaximal testing the same haemodynamic measures were generally higher antepartum, however the only significant difference was that in the CO/ VO_2 relationship between antepartum and 7 months post-partum, but not at 2 months. At maximal exercise, CO and SV were higher antepartum compared to 2 and 7 months, but arterial-venous difference was lower at 7 months. The authors suggested that the majority of cardiovascular changes reduced by 2 months post-partum, but further time was needed for complete resolution.

1.3.1.4 Effect of maternal weight gain on cardiovascular function

Maternal weight gain occurs because of the combination of a growing fetus, amniotic fluid, an enlarged placenta and breast tissue, increase in fat mass, extracellular fluid and blood volume. Although there are established guidelines recommending weight-gain ranges, up to a maximum of 18kg [Rasmussen *et al* 2009], 20-40% of women in the US and Europe exceed this [Cedergren 2006; Olson & Strawderman 2003]. High gestation weight gain is generally inversely proportional to pre-pregnancy weight and can lead to larger babies, maternal obesity and hypertension later in life [Edwards *et al* 1996; Fraser *et al* 2011]. The amount of weight gain successively increases with gestation from 1-3 kg in the first trimester, then by 300-500g a week from the second trimester to term. [Queensland Dieticians 2013]. These changes do not include any increase in skeletal muscle mass and, so cannot assist with the ability to perform physical work [Lynch *et al* 2007].

Non pregnant overweight females have significantly reduced cardiorespiratory fitness compared to normal weight females [Shazia *et al* 2015] and so the ability to perform work decreases, unless there is a significant increase in muscle mass or significant training. Direct measures of cardiac function, including CPO and CO, are both linearly correlated with VO_2 in observation studies of healthy females [Goldspink *et al* 2009]. Therefore, it is likely that CO would fall in overweight individuals when performing maximal exercise. In contrast to this, Ahokas *et al* [Ahokas *et al* 1983] showed that pregnant rats who were starved by 50% had a 20% maternal weight reduction in comparison to rats fed ad libitum displayed a 30% reduction in CO at the same stage in gestation. This therefore suggests that weight is a factor in causing an elevation in cardiac output. Carpenter *et al* [Carpenter *et al* 1990] attempted to estimate the effect of weight gain on exercise performance by performing both submaximal cycle and treadmill exercise with 10 pregnant women and then repeating these exercises post-partum and also performing treadmill exercise wearing weighted belts to equalise their body weights to that experienced in pregnancy. Absolute measures of VO_2 and CO were higher during pregnancy than in post-partum for all forms of exercise, including weighted exercise. However, the decrease in VO_2 during non-weight bearing cycle exercise was half that of weight bearing treadmill exercise. These changes were not significant when VO_2 was scaled by body mass per kg. The relationship of VO_2 and CO remained similar during and after pregnancy. Therefore, the authors concluded that body weight accounts for 75% of the increase in VO_2 during weight bearing exercise and contributes to reduced exercise capacity due to the higher baseline VO_2 and CO and additional work of weight carriage in pregnancy.

Although the standard practice when reporting VO_2 is to scale it by body mass and express it per kg, all the studies in the literature display absolute VO_2 in $ml.l^{-1}$, as suggested by Lotgering *et al* [Lotgering *et al* 1985], or should be normalised to lean body mass. Otherwise aerobic capacity would appear more unfairly limited in pregnancy, due to the increase in weight gain which, as previously stated, is not all related to an increase in muscle mass.

1.3.2 Obesity prevalence, risk and assessment

Obesity is a growing epidemic across the western world in both adults and children. In England, the prevalence has risen from 13% in men and 16% in women in 1993 to 24% in men and 26% in women in 2011. Severe obesity (Obesity III, BMI ≥ 40

kg/m2) has now reached a prevalence of 2% in both men and women in the England and 4.1% in men and 6.7% in women in the US [HSCIC 2011, Sheilds *et al* 2011]. It is well known that obesity is associated with increased mortality, however there is significant debate about whether those who are overweight (BMI ≥ 25-30 kg/m^2) or obesity class I (BMI ≥ 30-35 kg/m^2) are at a higher risk. This was borne out in a large meta-analysis, which showed the lowest mortality group were those in the overweight category, with a 6% lower mortality than those with a normal BMI [Flegal *et al* 2013]. However, there are significant problems with using BMI alone to categorize individuals and ascribe risks to them. Firstly, it is known that BMI is a crude tool used to estimate body fat percentage and does not account for the natural variation in body composition [Rothman 2008]. Moreover, the presence or absence of metabolic health (abnormal glucose levels or lipid profiles) appears to have a more significant effect on risk of cardiovascular events than weight. Two large meta-analyses have shown that, although there is a slightly increased risk of cardiovascular events in metabolically healthy obese (MHO) patients compared to metabolically healthy normal weight individuals, normal weight individuals, who have metabolic dysregulation, have a significantly higher mortality than obese patients who are metabolically healthy [Kramer *et al* 2013; Fan *et al* 2013]. These normal weight individuals with high body fat percentage are part of a phenomenon called normal weight obesity, which has a higher risk of developing metabolic syndrome and cardiometabolic dysfunction [Oliveros *et al* 2014]. Individuals with MHO are more likely to have higher cardiorespiratory fitness than obese individuals with metabolic dysregulation and those individuals with high fitness levels have been shown to have a 30-50% lower risk of mortality than those with low fitness [Ortega *et al* 2013].

In the same way that high cardiovascular risk is commonly ascribed to obese individuals, poor cardiopulmonary fitness and cardiac performance is often predicted to be poor in obese patients. Due to the altered body geometry and physical demands on the body, obese individuals often complain of exercise limitation, breathlessness, fatigue and limb pains. Physicians regularly struggle to assess cardiac function accurately due to limitations in the techniques used to assess function [Poirier *et al* 2006]. These limitations are commonly seen with echocardiography, nuclear perfusion, CT and MRI scanning, which may either not be technically possible because the individual can not fit in the scanner or un-interpretable due to poor image acquisition or artifact. Patients are then often stigmatized due to the physicians' anecdotal personal experience with these diagnostic challenges. Healthcare providers often have both explicit and implicit views about obese patients that are regularly negative and can lead to impaired patient-centred communication in those who they believe will not be adherent to

advice. This can then lead to patient stress and avoidance and mistrust of healthcare providers. Patient disengagement and difficulties in assessing function accurately can then lead to poor management and outcomes [Phelan *et al* 2015]. It is essential to make an attempt to establish cardiac function in obese patients, either to assist with a decision to start treatment for heart failure or provide an assessment of risk and optimisation for a surgical procedure and anaesthetic, which inevitably requires some knowledge about an individual's cardiac reserve. Independent factors associated with surgical mortality in obese patients undergoing bariatric surgery include age, male sex, cardiorespiratory fitness, electrolyte disorders and congestive cardiac failure [Livingston & Langert 2006; McCullough *et al* 2006]. The routine assessment of obese patients undergoing surgery should include a comprehensive medical history and examination, routine blood tests, an ECG and a chest x-ray [Poirier *et al* 2009]. Unfortunately, cardiac symptoms such as dyspnoea, exercise intolerance and leg swelling, are non-specific. Also clinical examination and assessment of the ECG often underestimates cardiac pathology in obese patients [Poirer *et al* 2006]. Therefore an attempt is made to obtain a more objective assessment, usually by performing cardiac imaging, when symptoms are suggestive of heart failure or if high risk surgery is to be performed. As already mentioned, imaging is often confounded by technical difficulties resulting from the patient's body habitus [Lotia & Bellamy 2008].

In order to both interpret and understand the physiological basis of changes in cardiac function in obesity, one must have knowledge of the merits and pitfalls of the current methods of assessment of cardiac function, as well as the current literature in this area in obesity.

1.3.2.1 Changes in cardiac morphology and resting function in obesity

In 1847, William Harvey was the first to describe the phenomenon "*Obesity Cardiomyopathy*", when he recognised symptoms of heart failure in a severely obese man, who shortly afterwards died. He went on to describe his cardiac pathological autopsy findings as "large, thick and fibrous, with a considerable quantity of adhering fat, both in its circumference and over its septum" [Alexander 1998a]. The first major post mortem series, by Willlius and Smith in 1933, confirmed the finding of enlarged cardiac weight with excess epicardial fat in obese individuals, but found no myocardial fat [Smith & Willius 1933]. They found that heart weight increased linearly with body weight up to 105kg and then levelled off. Subsequent post-mortem series have shown that the increase in weight is

secondary to uniform symmetric left ventricular hypertrophy. Biventricular dilatation has also been noted in many cases [Alexander & Pettigrove 1967; Warnes & Roberts 1989]. Most of these post mortem studies were performed in obese individuals who suffered from coronary artery disease or heart failure. Following the advent of non-invasive studies, obese individuals without cardiovascular disease were also evaluated and then compared to findings in lean individuals.

Obesity is characterised by a build up of fat mass, as well as growth in fat-free mass - predominantly skeletal muscle and viscera. Although fat is less metabolically active than lean tissue, the overall oxygen consumption is higher at rest in obese individuals [Ravussin 1995; Frayn 1992]. However, when VO_2 is scaled by body mass (per kilogram), it is lower in obese individuals [De Divitiis *et al* 1981]. Total blood volume also increases in proportion to weight gain [Alexander *et al* 1962; Messerli *et al* 1983] and leads to increased LV filling and stroke volume [Wikstand *et al* 1993; Carabello & Gittens 1987]. Heart rate remains unchanged and so cardiac output also increases and again appears to be proportional to the amount of weight [Backman *et al* 1973; Messerli *et al* 1982; Licata *et al* 1991, Messerli *et al* 1983]. If CO is scaled by body surface area, it remains to be within normal range [Messerli *et al* 1982; Messerli *et al* 1983]. Reduced SVR also accompanies and facilitates these changes in normotensive obese individuals [Alexander *et al* 1962; Messerli *et al* 1982; De Divitiis *et al* 1981].

The first response to increases in blood volume and metabolic demand is an increase in stroke volume, leading to LV dilatation. This causes increased wall stress over time and stimulates myocardial growth and hypertrophy [Alpert 2001]. Hypertension occurs in 50% of obese individuals and can further stimulate increases in LV mass [Wong *et al* 2007]. Moreover, right ventricular dilatation and hypertrophy has been seen in extreme obesity [Alpert *et al* 1985]. In addition left atrial dilatation can occur. The incidence of structural changes varies in incidence and severity and is likely to be related to the severity of obesity, duration of obesity and presence of co-morbidities. These changes are often accompanied by impaired diastolic filling [Chakko *et al* 1991; Stoddard *et al* 1992] and high LV end-diastolic pressure (LVEDP) [Alexander et al 1962, De Divitiis 1981]. There appears to be a positive correlation with relative weight and BMI and indices of LV mass.

LV systolic function, measured by ejection fraction, has been reported as either normal or hyperdynamic. Even in severe obesity, LV systolic dysfunction is uncommon in the absence of cardiovascular disease [Alpert *et al* 1993; Tumuklu *et al* 2007].

1.3.2.2 Changes in cardiac function with exercise in obesity

Alexander understood that at a given level of activity, cardiac workload was greater for an obese subject, in comparison to a subject of ideal body weight. He demonstrated that at varying grades of moderate treadmill exercise those oxygen requirements of obese individuals were much greater. He also showed that the increase in CO and its relation with oxygen consumption was similar to that in lean individuals, [Alexander 1964]. However, at high workloads (> 5 times baseline), CO decreased to a low-normal level [Alexander *et al* 1998b]. Kaltman reported normal or high resting CO with high oxygen consumption appropriate to body weight in 12 severely obese individuals. During exercise (passive leg raises) there was a consistent rise in stroke volume, parallel with an abnormal increase in LVEDP. Stroke work and central blood volume were also uniformly increased, consistent with a hyperdynamic and hypervolaemic state. Four patients were studied again after weight loss and 3 of the 4 had a normal response in LVEDP to exercise, i.e. no increase in LVEDP [Kaltman & Goldring 1976]. Alpert assessed the response of ejection fraction to exercise via radionuclide ventriculography and found a significant increase in those with normal LV mass, but no increase in those with increased LV mass [Alpert *et al* 1989]. More recently the effects of weight loss after bariatric surgery have shown significant incremental improvements in relative, but not the absolute aerobic capacity at 6 and then 12 months post surgery [de Souza *et al* 2010; Wilms *et al* 2013]. One however has to be cautious when interpreting data using oxygen consumption scaled by body mass in obese patients. Hothi showed in 152 obese patients with heart failure that although the mean $VO_{2max/kg}$ was lower in obese compared to absolute lean heart failure patients, the absolute VO_{2max} was higher in the obese patients and direct markers of function, CPO_{max} was also significantly higher [Hothi *et al* 2015].

1.4 Measures of cardiac function

In 1628, William Harvey published De Moto Cordis, and described the finding that blood circulated around the body, driven by the heart [Franklin 1933].

“For it is by the heart's vigorous beat that the blood is moved.”

He then went onto develop a measure of the heart’s function (cardiac output), by multiplying heart rate by stroke volume. One problem with this concept was that it did not tell us how the heart performed as a displacement pump and how it maintained the circulation.

In 1908, Sir Arthur Mackenzie described two types of heart force: one at rest, sufficient to meet the needs of the body and a second reserve force, otherwise known as cardiac reserve, to be used only when needed during stress. He further went on to describe the importance of myocardial dysfunction and stated that *"Heart failure is simply the inability of the heart muscle to maintain circulation".* He sought an explanation of this and came to the summation that heart failure was "*the exhaustion of the reserve force of the heart"* [Mackenzie 1921].

In 1981 Lip-Bun Tan developed a new paradigm for evaluating overall cardiac pumping performance. He described the heart as a mechanical pump, which generates a continuous supply of hydraulic energy needed to maintain circulation to meet the metabolic demands of the body. Utilising the laws of physics, the rate of energy needed to move a volume of fluid (blood) continuously, is the product of pressure generation and flow rate. This rate at which the heart imparts this energy is the power output and as such is the ideal measure of cardiac performance. The maximal cardiac performance (pumping capability) is hence the maximum cardiac power output (CPO_{max}) during maximal stimulation [Tan *et al* 1981; Tan *et al* 1987]. CPO_{max} is the product of cardiac output and arterial pressure and hence encompasses not only the flow generating capacity (CO), but also the pressure generating capacity of the heart (MAP). Cardiac reserve is the difference between resting cardiac function and the maximum cardiac pumping capability.

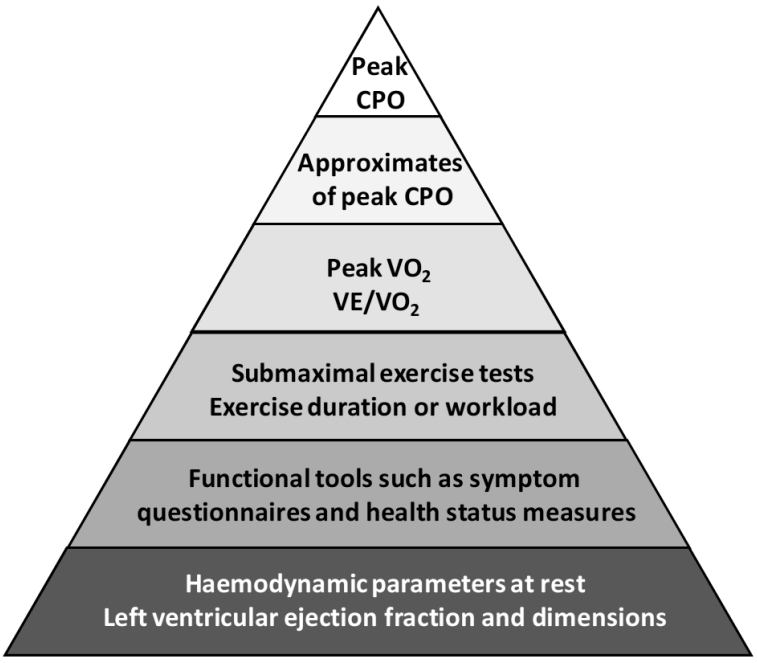
Evaluation of central haemodynamics, including cardiac output and central arterial and cardiac pressures, by invasive methods was a prominent feature of cardiovascular assessment in the middle part of the 19th century however, became less commonly used as newer and more non invasive technologies became available. Evidence also suggested that exercise capacity alone correlated poorly with newer measures of cardiac function, nominally ejection fraction [Benge *et al* 1980; Franciosa *et al* 1981]. The most commonly used measures of cardiac function thereafter were left ventricular ejection fraction (LVEF) and fractional shortening, and have been used in multiple clinical trials and guidelines to assess treatment response or to act as a cut off point for therapy.

In 1991 Mancini et al published a landmark study showing that a $VO_{2max.kg}$ above 14 ml/min/kg gave prognostic value in patients with heart failure referred for cardiac transplantation, in addition to knowing the LVEF [Mancini *et al* 1991]. The explanation for this, is that according to the Fick principle, VO_2 is determined by cardiac ouput and arteriovenous difference. VO_{2max} was confirmed by multiple studies to be of prognostic value and has lead to the routine use of cardiopulmonary exercise testing in heart failure patients. The issue with VO_2 is that

many other factors can influence it, including haemogloblin content, muscle mass and peripheral oxygen extraction and pulmonary disease. Cooke et al then confimed that it was possible to measure CPO_{max} non invasively using a CO_2 rebreathing technique, based on the indirect Fick principle [Cooke *et al* 1998]. Williams et al then went onto show that CPO_{max} was a more powerful prognostic indicator of survival than VO_{2max} [Williams *et al* 2005]. This was confirmed by Lang et al, using an inert rebreathing technique (Innocor). More recent evidence has suggested that CPO is independent of VO_2. Although VO_2 is an indirect indicator of peak cardiac performance, this needs to be interpreted with some caution, particularly in stroke patients and patients with obesity and heart failure [Jakovljevic *et al* 2012; Hothi *et al* 2015].

Other surrogate indices of cardiac performance include circulatory power (CircP = product of VO_2 and MAP), cardiac output, stroke volume (SV) and stroke work (SW = product of SV and MAP). As with VO_{2max}, these indicies are indirect measures of peak cardiac performance, as opposed to the *"gold standard"* direct measure. Figure 1.1 demonstrates the hierarchy of measures of cardiac function.

Figure 1.1 Heirarchy of measures of cardiac function



[Adapted from Schlosshan 2007]

CPO has not previously been studied with inert weight carriage or obesity. Pilot work analyzing CPO in pregnancy has been performed by my predecessor, Diane Barker. Although not reported in the literature, she established that maximal exercise testing and measurement of CPO_{max} is feasible and safe, upto 40 weeks

gestation. Much of her work focused on comparing the cross sectional difference between women with and without heart disease in pregnancy. She hypothesised that a cut off value of a CPO_{max} of greater than 2.6 watts may signify acceptable cardiac function for completion of pregnancy and child birth [Barker 2009]. Therefore using this technique may allow the possibility to individualise the cardiac reserve in pregnant patients with cardiac disease.

Chapter 2

Methods

2 Methods

Pregnancy can be viewed as a state of protracted cardiac stress and is associated with enormous physiological changes, induced not only by the enlarging gravid uterus, but also by neurohormonal and metabolic changes. The cardiovascular system is then further stressed during daily physical activities, and culminates in an extreme stress during labour. Impairment of any cardiac component and overall function will limit the ability to augment the requisite circulation. On top of these physiological demands, if there were any superimposed obstetric complications, such as bleeding, pre-eclampsia, embolism, then the inadequate cardiac reserve may present insurmountable problems. It can be presumed that cardiovascular systems with less reserve are more unlikely to cope well with these challenges.

Characterizing the physiological changes in healthy women are fundamental in order to understand how the cardiovascular system adapts to this stress throughout pregnancy and is vital to identify those who have maladaptive responses and are potentially at risk. Much has been discovered about the cardiovascular physiology of pregnancy, but to date, almost all information in humans have been derived from evaluations made at rest, in different postures and only a few during submaximal exercise [Hennessy 1996; Khodiguian 1996; Mabie 1994; Hunter 1992; Easterling 1990; Robson 1989; Ueland 1969; Vorys 1961] and many invasively [Clark 1989; Pirvarnik 1990; Duvekot 1994]. Although haemodynamic measurements at rest are much easier to perform, it has long been known that resting data often correlate poorly with organ function and clinical outcomes [Benge, 1980; Franciosa, 1981; Tan 1986; Tan 1990], in contrast to values obtained at peak stress, which are more predictive of physical function and outcomes [Cooke 1998; Cotter 2003; Cohen-Solal, 2002; Scharf 2002].

2.1 Questions and hypothesis

The key question:

What effect does pregnancy have on peak physical and cardiac performance and functional cardiovascular reserve in humans?

Hypothesis:

Peak cardiac performance and functional cardiovascular reserve improves in and throughout pregnancy because of neurohormonal changes and weight gain.

My aim was to assess the magnitude and modulators of the cardiovascular responses to pregnancy. I therefore designed a series of studies to answer a number of sub questions necessary to meet this objective.

2.1.1 Sub Questions and Studies

Chapter 3

1. *What is the most reliable way to assess resting cardiac function in pregnant women?*

Study I: Validity and reproducibility of resting measurement of cardiac output using CO_2 and inert gas rebreathing methods and transthoracic echocardiography

2. *What is the most reliable way to assess peak cardiac performance and functional reserve in pregnant women?*

Study II: Comparison of two techniques to measure cardiac output during exercise, using CO_2 rebreath and inert gas rebreathing methods

3. *How reproducible is measurement of cardiac output at peak exercise?*

Study III: Reproducibility of measurement of cardiac output at peak exercise using Medgraphics Ultima

Chapter 4

4. *What is the effect of weight on peak cardiac performance and functional reserve in simulated pregnancy?*

Study IV: Cardiovascular effects of weight carriage using an *"Empathy Belly"*

Chapter 5

5. *Does the magnitude of response in peak cardiac performance and functional reserve change with additional loading in simulated pregnancy?*

Study V: Cardiovascular effects of differential weight carriage

Chapter 6

6. *What is the effect of pregnancy on peak cardiac performance and functional reserve, compared to post-partum?*

Study VI: Longitudinal cardiovascular effects of pregnancy compared to post-partum

Chapter 7

7. *What is the effect of pregnancy on peak cardiac performance and functional reserve, compared to pre-conception and how does this response change with gestation?*

Study VII: Longitudinal cardiovascular effects of pregnancy from pre-conception through to post-partum

Chapter 8

8. *How do changes in body weight affect peak cardiac performance and functional reserve in the non-pregnant state?*

Study VIII: Cross sectional study to determine the cardiovascular effects of obesity

2.2 Ethics

The experimental procedures, simulated pregnancy and pregnancy studies were all approved by the Leeds (West) Ethics Committee (Appendix A). The recommendations from the Declaration of Helsinki (World Medical Association General Assembly 2008) concerning the use of human subjects were followed carefully because of the nature of the subjects studied. In addition, the experimental protocols were anonymously examined by two external reviewers from two distant Universities/Hospitals. One of these reviewers was a Consultant Obstetrician with a background of research in pregnancy and the other a Consultant Cardiologist with a background of research in patients with heart disease. The study and its aims were described in detail to all potential participants and interested subjects received a

written information sheet. All participating pregnant women gave their written informed consent.
The obesity study was a retrospective analysis of clinical exercise tests used to aid patient management and therefore I did not seek approval by the ethics committee.

2.3 Power calculations

This was a pilot study and there are no previously reported studies of cardiac power output in pregnancy to guide sample size calculation. In the longitudinal study, the subjects acted as their own controls. Differences in VO_{2max} were estimated to be similar to a previous exercise study in a group of patients with heart failure, requiring a sample size of 30 [Cooke *et al*., 2002]. Sady et al [Sady *et al* 1990] commented that with the differences between their pregnant and postpartum data, they would need ”an additional 3 – 32 subjects for a power of 0.8”. They had a sample size of 9, so assuming that our data would be similar, we would need 12 – 41 subjects in each group to show a significant difference in longitudinal data.

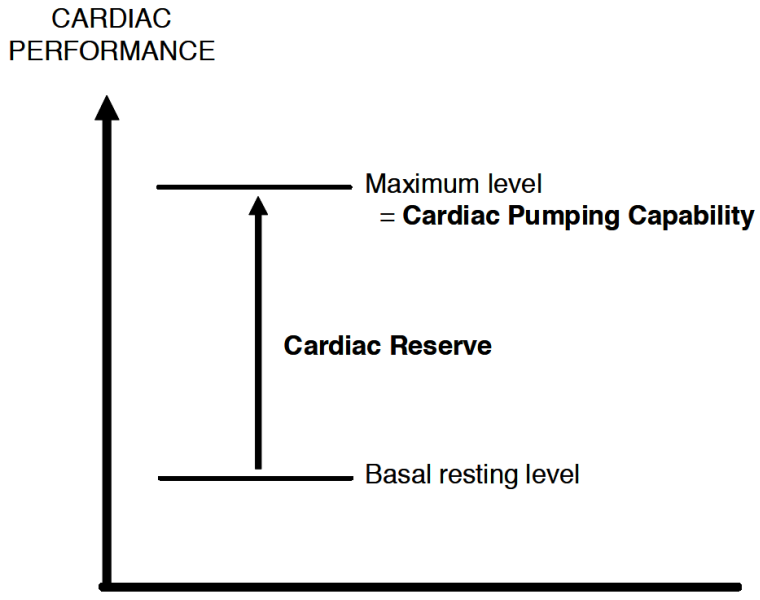
For the cross sectional study of obese patients, to demonstrate a conservatively estimated difference in the peak exercise VO_2 of 150 $ml.min^{-1}$ between the two groups (obese versus normal weight), with a 5% two-sided significance level and 80% power, assuming a standard deviation of 326 $ml.min^{-1}$, a sample size of 76 subjects per group (152 in total) would be needed.

Due to the inherent difficulties of the study tests, and the conflicting domestic, work, social and in some cases medical circumstances of the young subject group, I anticipated that not all those recruited would be able to complete the longitudinal studies. Therefore, I estimated that there would be a ‘dropout’ rate of 40%.

2.4 Measurement of cardiac power output and cardiac reserve

Cardiac power output (CPO) is determined by the product of cardiac output and aortic pressure. It can be defined as the rate at which the heart imparts hydraulic energy into the arterial system to maintain circulation of blood. It is calculated as the product of mean arterial pressure (MAP) and the cardiac output (CO), multiplied by a correction factor (2.22×10^{-3}) and is expressed in watts [Tan 1987]. The span of cardiac performance is depicted by cardiac reserve (CR), which is calculated by subtracting the resting CPO from the maximal CPO [Tan 1991].

Figure 2.1 Relations of cardiac functional capability and cardiac reserve when assessing cardiac performance.



(Modified from Tan LB, (1986) Cardiac pumping capability and prognosis in heart failure. Lancet)

The above figure shows that cardiac reserve is represented by the difference in maximal cardiac performance (CPO_{max}) and resting cardiac performance (CPO_{rest})

The methods for the non-invasive measurement of CPO at rest and during exercise, using cardiopulmonary exercise testing, was based on work previously performed in the cardiology department at Leeds General Infirmary, led by Professor L.B. Tan. This method was developed, validated and described by Cooke *et al*. [Cooke *et al* 1998].

The measurement of blood pressure was done non-invasively by auscultation and MAP was calculated by the equation DBP + 0.412 (SBP – DBP), where DBP is diastolic blood pressure and SBP is systolic blood pressure [Meaney *et al* 2000].

CO was traditionally measured using invasive techniques (direct Fick, dye dilution and thermodilution) however, due to the impractical nature and potential risks of performing these tests during exercise, many non-invasive methods for measuring cardiac output have been developed. These have included rebreathing techniques using carbon dioxide CO_2 [Collier 1956, Defares 1958] or an inert gas, such as acetylene [Grollman 1929]; Doppler echocardiography [Rawles and Haites 1984] and bio-electrical impedance cardiography [Kubicek *et al.* 1966]. Cooke *et al* chose to use the CO_2 re-breathing technique during treadmill exercise, as it was a reliable and technically feasible to perform at peak exercise [Cooke *et al* 1988].

The process of measuring CPO and CR involves a three-stage procedure:

1) An incremental cardiopulmonary exercise test to exhaustion to measure maximal oxygen consumption (VO_{2max}), carbon dioxide production (VCO_{2max}), and maximal heart rate (HR_{max}).

2) Measurement of CPO_{rest}

3) Measurement of CPO_{max}, i.e. when subjects are exercising at their previously established VO_{2max} (determined in stage 1).

2.5 Cardiopulmonary exercise test

2.5.1 Participant familiarisation

The purpose of the studies and the procedures were explained to subjects in full before they were enrolled into any of the studies. Subjects were familiarized with the exercise equipment and introduced to the staff at the beginning of the study. Two exercise tests were performed at each visit: an incremental and a single stage test. The first test was used as a familiarization study. When there was significant discrepancy between the results of the two tests, the single stage test results were used to reduce the effect of familiarization with the equipment and testing protocol.

2.5.2 Laboratory Conditions

All testing was performed in a dedicated cardiopulmonary-exercise testing laboratory at Leeds General Infirmary. The ambient temperature was maintained at 21 degrees centigrade. The air pressure was measured before each test using a calibrated barometer and input into the software of the testing equipment.

2.5.3 Participants' instructions

Subjects were asked to abstain from any vigorous physical activity for 24 hours prior to testing. They were further instructed to have no food and caffeine for 3 hours and alcohol for 12 hours prior to their attendance. On arrival at the laboratory, the subjects were familiarized with the equipment and the procedures (treadmill, mouth piece, re-breath maneuvers).

2.5.4 Exercise test equipment

All exercise testing was conducted using the Quinton Q-Stress system (Cardiac Science, Pennsylvania, USA) and treadmill (Trackmaster TMX425 Full Vision Inc. 3017 Full Vision Drive Newton, KS 67114, USA) (Figures 2.2 and 2.3 respectively). Exercise protocols were entered into the system and then drove the treadmill. At the beginning of each test subjects were fitted with a 12-lead electrocardiogram (ECG) using the Mason-Likar electrode placements (Table 2.1) specifically designed to reduce the motion artifacts, frequently observed during exercise [Pina

and Chahine 1984]. The Quinton system then recorded and printed 12 lead ECGs at rest and each minute until the end of recovery. Maximum heart rate was determined directly from the R-R interval of the ECG.

2.5.5 Blood pressure measurements at rest and during exercise

Arterial blood pressure was measured using a hand held sphygmomanometer, Welch Allyn Tycos Hand Aneroid Sphygmomanometer (Welch Allyn, New York, USA), at the left brachial artery, via manual auscultation. The appropriate size cuff (width: 40-50%, length: 80% circumference of arm) was chosen for each subject and applied to the bare, upper arm. Measurement of blood pressure was taken in accordance with the British Hypertension Society guidelines [Petrie *et al* 1986]. The stethoscope was placed over the artery, just above the antecubital fossa; the cuff was inflated beyond the estimated systolic pressure, and then deflated at a rate of 2 mmHg per second. Systolic pressure was identified at the first Korotkoff sound (a repetitive, clear tapping sound for >2 consecutive beats) and diastolic at the fifth Korotkoff sound, after which all sounds disappeared [Frohlich, 1988]. Under resting conditions, blood pressure was taken in the seated position with the arm supported at heart level and after at least 3 minutes rest. During exercise, the subject's arm was supported, at the level of the heart on the investigator's shoulder. Blood pressure was then taken every 3 minutes and more frequently towards peak exercise to capture the peak blood pressure. It was also taken immediately post exercise and in recovery.

2.5.6 Exercise Protocols

Exercise protocols were standardised in each of the studies where possible. In studies using healthy and healthy pregnant individuals, the Bruce protocol was used [Bruce 1971]. In obese subjects, a new ramp protocol was devised, as both Bruce and modified Bruce protocols were too severe for most subjects to perform. The ramp protocol adopted a gentle 1 minute incremental rise in speed and gradient after a 2 minute constant run in rate, in order to allow subjects to exercise to their maximum within 10 minutes, in keeping with the recommendations of Buchfuhrer *et al* [Buchfuhrer *et al* 1983]. This was called the Lewis protocol (Table 8.1, Chapter 8).

Table 2.1 Mason-Likar 12-Lead Electrode Placement

Right Arm (RA)	Right deltoid fossa, mid-clavicular
Left Arm (LA)	Left deltoid fossa, mid-clavicular
Right Leg (RL)	Right anterior axillary, mid-clavicular line
Left Leg (LL)	Left anterior axillary, mid-clavicular line
V1	Fourth intercostal space to right of sternal border
V2	Fourth intercostal space to left of the sternal border
V3	Between V2 and V4
V4	Fifth intercostal space mid-clavicular line
V5	Anterior axillary line, in line with V4
V6	Mid-axillary line, in line with V4 and V5

Figure 2.2 Quintin Q stress system

Figure 2.3 Trackmaster treadmill

2.5.7 Breath by breath gas sampling analysis

Continuous sampling of the respiratory gases were obtained during the incremental exercise test, and during the measurement of resting and maximal CPO, using the Medgraphics Ultima cardiopulmonary exercise testing system (Medgraphics Corporation, St Paul, Minnesota, USA) (Figures 2.4 and 2.5). The system performed breath-by-breath gas analysis that was analysed and presented via Breeze Suite version 5 (Figure 2.6).

The gas analyser consisted of a zirconia fuel cell, that measured that oxygen (O_2) and carbon dioxide (CO_2) via an infra-red analyser. The zirconia fuel cell was split into a sample and reference chamber. The cell was semi permeable to oxygen molecules and their movement generated a voltage that was measured by the cell, thereby allowing measurement of O_2 in the gas sample. The CO_2 analyser was split into two chambers (reference and sample) through which beams of infra-red light were focused. CO_2 absorbs infra-red light and so the light absorption in the sample chamber was compared to that in the reference chamber, thus allowing quantification of CO_2 content.

Figure 2.4 Medgraphics Ultima cardiopulmonary exercise testing system

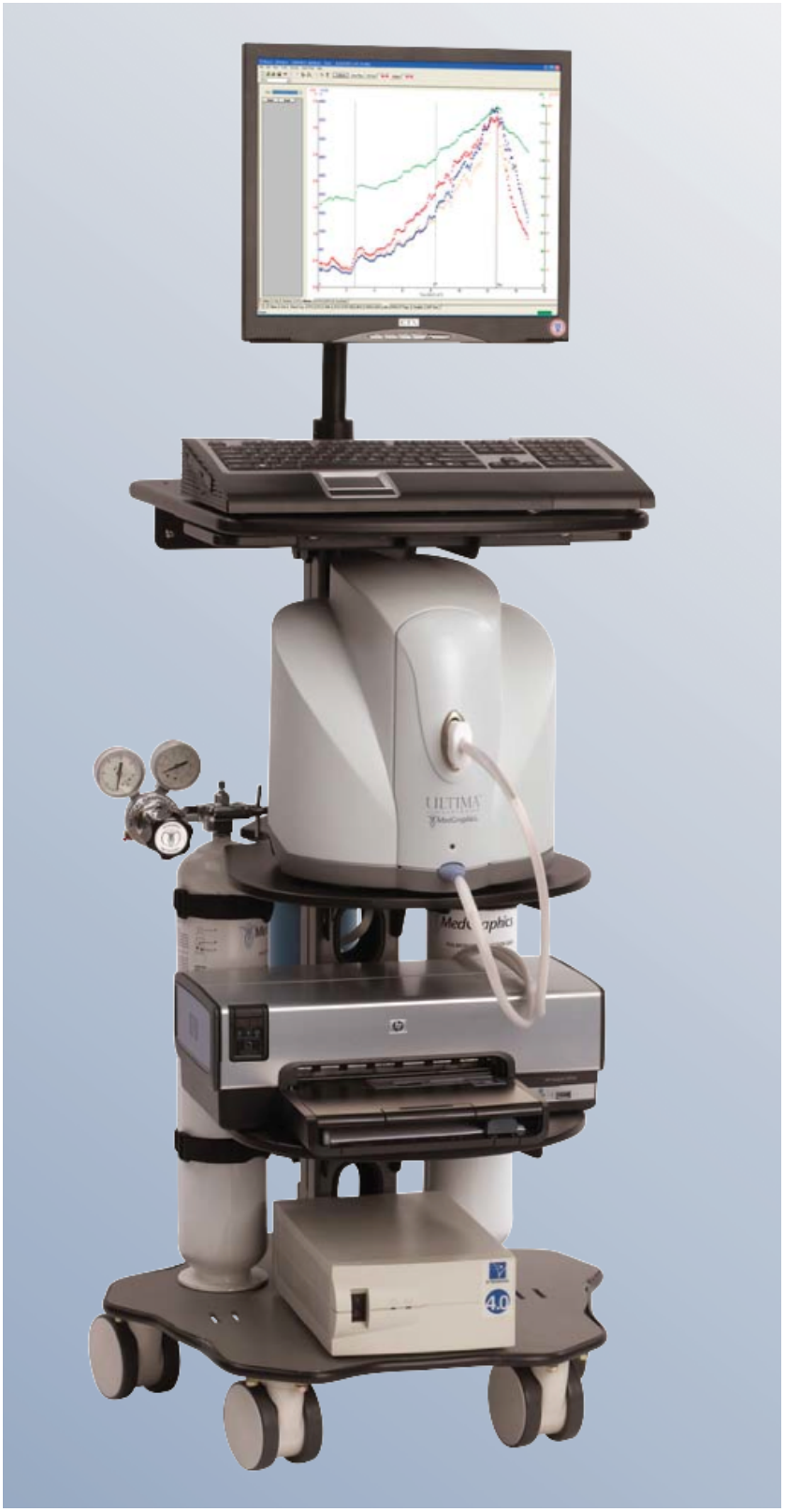
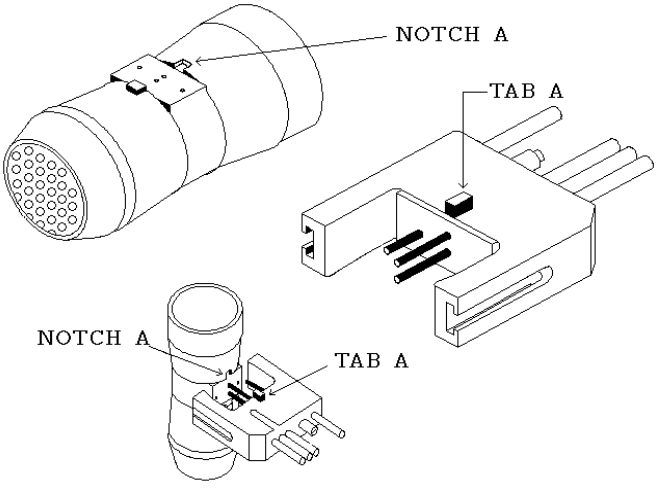


Image of Medgraphics metabolic cart with Breeze suite displayed on a windows PC.

http://www.medicalgraphicsuk.com

Figure 2.5 Medgraphics Ultima equipment

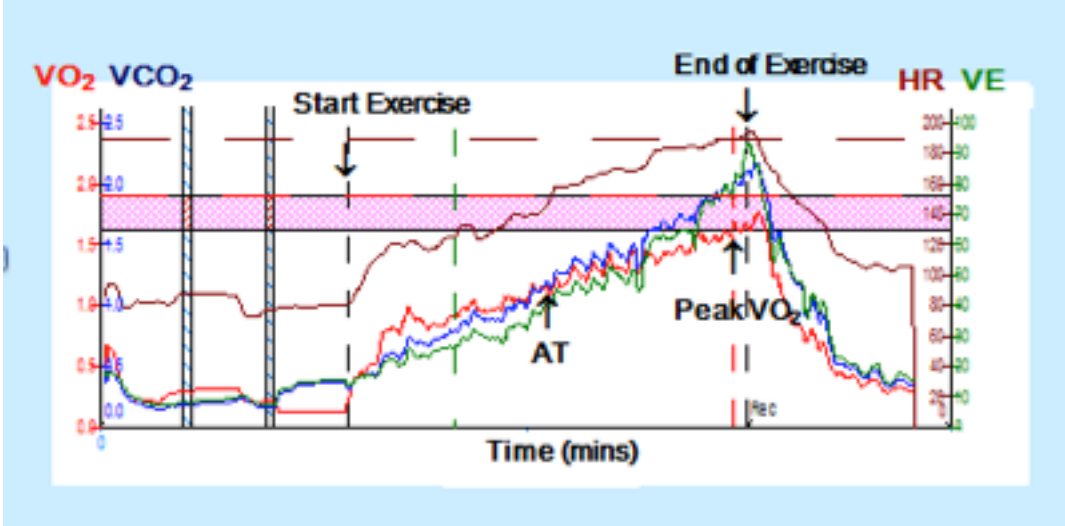


Images in clockwise from top left: Metabolic cart; 3 litre syringe; pneumotachometer; pitot tube and connector.

Bottom: Diagram of pitot connector inserting into pneumotachometer.

http://www.medicalgraphicsuk.com

Figure 2.6 Medgraphics Breeze Suite graphical display of outputs during a cardiopulmonary incremental exercise test



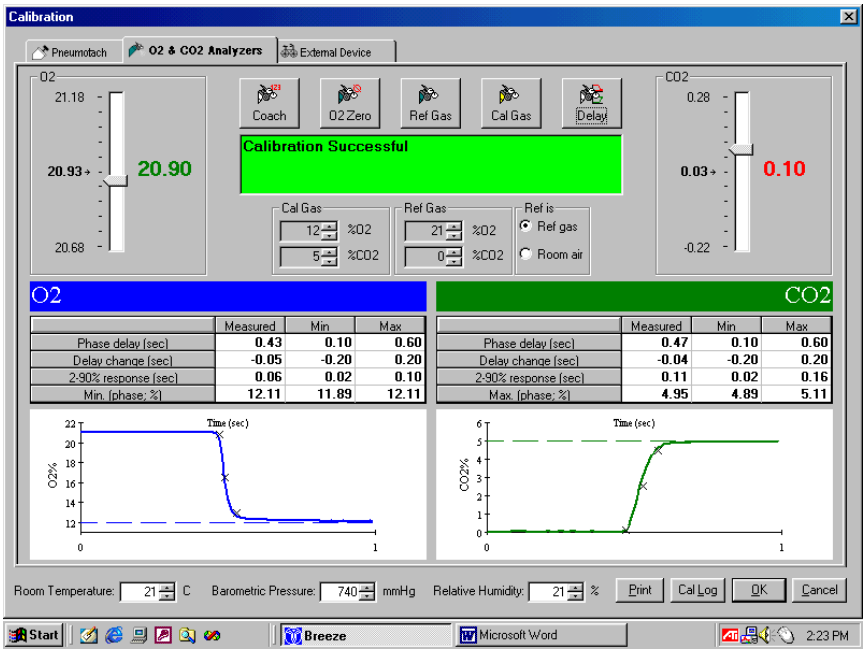
VO_2 (oxygen consumption ($l.min^{-1}$) - red line); VCO_2 (carbon dioxide production ($l.min^{-1}$) - blue line); HR (heart rate (min^{-1}) - dark red); VE (minute ventilation ($l.min^{-1}$) - green line); AT (anaerobic threshold); Peak (peak and maximum are often used interchangably to signify maximal exercise).

The figure shows a standard healthy response to exercise with a gradual increase in all parameters, but most notably VO_2 is greater than VCO_2 until AT is reached, when VCO_2 exceeds VO_2. At peak exercise there is a plateau in VO_2 despite an increase in workload for greater than 1 minute and so VO_{2max} has been achieved. This also falls within the predicted range, as shown by the pink bar. Heart rate has also reached the maximum predicted heart rate (identified as the dashed dark red line). After exercise there is rapid fall in values as the subject recovers.

2.5.8 Calibration of Medgraphics Ultima

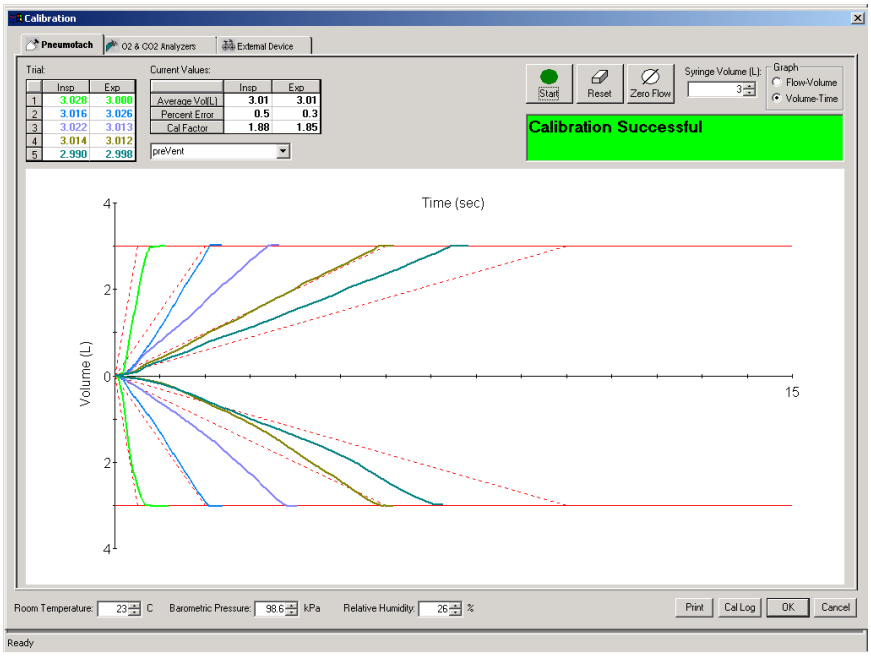
The gas analyser was calibrated prior to every test using both reference (21% O_2 and balanced N_2) and calibration (12% O_2, 5% CO_2 and balanced N_2) gases (Medgraphics Corporation, St. Paul, Minnesota, USA). System response time or "phase delay" was checked and then ambient O_2 and CO_2 measurements were checked using the inbuilt on-line calibration system (Figure 2.7). The air-flow calibration was made via a pitot tube, attached at 90 degrees to a pneumotachometer (pre Vent, Medgraphics Corporation, St. Paul, Minnesota, USA) that measured the differential pressure of gas flow against 2 small tubes. The pressure was dependent on gas density and was therefore, sensitive to changes in gas composition. The pressure measurement was converted to air flow by first establishing a zero flow baseline, then 5 withdrawals and injections of air were made at different speeds using a certified 3-litre syringe (MedGraphics, St Paul, Minnesota, USA). This range of speeds simulated the varying respiratory rates observed throughout an exercise test (Figure 2.8). A correction factor, generated during the calibration, was applied to reduce the variability that exists between pneumotachometer.

Figure 2.7 Medgraphics on-line calibration system



The figure shows the online screen image of the calibration system and system response time or “phase delay”, as well as ambient O_2 and CO_2 measurements within acceptable limits.

Figure 2.8 Medgraphics airflow calibration



The figure shows the screen image of airflow calibration, whereby 5 withdrawals and injections have been performed at varying speeds, guided by the red dotted lines. Similar volumes have been produced, and so calibration was successful.

2.5.9 Stage 1: Incremental exercise test - Measurement of VO_{2max}

Subjects were first weighed and had their height measured. They were then fitted with a 12-lead ECG. A nose clip was placed on the subject's nose and they were then asked to place a rubber mouth-piece into their mouth, that was directly attached to a pneumotachometer with the gas sample line and airflow umbilical. The other end of the umbilical was inserted into the front of the Ultima unit. Air flow was passed through a drying cartridge before entering the gas module, to remove any moisture that may have caused contamination of the infra-red window. Inspired and expired gas samples were analysed breath-by-breath for oxygen uptake (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER), end tidal partial pressure of carbon dioxide ($PETCO_2$), tidal ventilation (VE), tidal volume (V_T) and respiratory rate (RR). Gas analysis output was presented as the mean 5 of 7 breaths to remove the confounding effects of large variations in ventilation. (Figure 2.6)

Baseline heart rate and blood pressure were recorded. After obtaining two minutes of resting data, the exercise test was commenced. Every three minutes, blood pressure measurements were taken and subjects were asked to score their symptoms using a Borg score (Appendix B). Exercise was terminated when the subject reached their maximum, peak volitional exhaustion and an immediate blood pressure was again recorded. Once the subject recovered, they were asked what their reason was for stopping.

2.5.10 Resting period

A rest period of at least 40 minutes was required between the two maximal exercise tests. To prevent hyperthermia, subjects were encouraged to drink water during the rest periods. This period was also utilised for completion of the SF-36v2 questionnaire.

2.6 Measurement of cardiac output at rest

2.6.1 Indirect Fick

The Medgraphics Ultima cardio-pulmonary exercise system (Medgraphics Corporation, St. Paul, Minnesota, USA) was used to measure CO. Non-invasive measurements of CO were obtained using the well-established CO_2 rebreathing techniques developed by Collier (equilibrium) and Defare's (exponential) and the application of the Indirect Fick equation [Collier 1956, Defare 1958]:

$$\mathbf{CO = VCO_2 / CvCO_2\text{-}CaCO_2}$$

VCO_2 = CO_2 production

$CvCO_2$ = CO_2 content of mixed venous blood derived from partial pressure CO_2 during rebreathing ($PvCO_2$)

$CaCO_2$ = CO_2 content of arterial blood estimated from expired end tidal pressure of CO_2 ($ETpCO_2$).

2.6.2 Stage 2 - Cardiac output measurement at rest

The Collier technique, was used to determine resting CO. Previous studies have shown this method to be the most accurate CO_2 rebreathing technique for measuring resting CO (CO_{rest}) [Auchinloss *et al* 1980, Franciosa *et al* 1976, Zeidifard *et al* 1972].

The subject placed a nose clip on and inserted a rubber mouth piece. This was attached to a Hans Rudolph three-way rebreathing valve (Model 2870 series). A respiratory gas sample line was attached just in front of the valve, closest to the subject. A pre-Vent pneumotachometer was then attached to the outflow route of the valve, while a 5 litre anaesthesia bag, which acted as a CO_2 re-breathing bag, was attached to the inferior part of the valve. The valve, which was operated manually by a plunger, allowed the subject to change from breathing atmospheric air, to re-breathing the gas mixture in the anaesthesia bag. The weight of the

equipment was supported by an extendable dog lead suspended from the ceiling (shown in Figure 2.9).

The anaesthesia bag was filled with a medical grade gas mixture comprising 10% CO_2, 35% O_2 and balanced N_2 to provide an initial partial pressure of CO_2 (pCO_2) greater than the subject's mixed venous CO_2 tension ($pvCO_2$). The high content of O_2 (35%) was sufficient to maintain normal arterial saturation throughout the rebreathing procedure. The volume of mixture corresponded to 1.5 to 2 times the subjects resting tidal volume (V_T), which was obtained during a 5 minute seated resting period.

Once satisfied that the subject was fully rested, the investigator inserted the plunger at the end of a tidal breath and instructed the subject to take a deep inspiratory breath and inhale the full volume of gas in the bag. The subject was then asked to continue rebreathing the gas mixture for the next 12 to 15 seconds until a plateau and equilibrium was achieved. The gases in the bag and alveoli mixed, a fall in pCO_2 occurred resulting in equilibrium between the lung-bag system and $pvCO_2$ that was indicative of no further gas exchange. The equilibrium (shown on the capnograph of CO_2 concentration, produced by the Breeze software, Figure 2.10) occurred between 8-12 seconds (or 4 to 5 breaths) from the start of the re-breathing maneuver and had to be maintained within 1mmHg for at least 2 respiratory cycles. At this point pCO_2 was assumed to equal $pvCO_2$. The software recognized equilibrium at the point where the difference between inspired and expired CO_2 was less than 0.1% in two successive breaths. Calculation of the partial pressure of CO_2 in the venous blood was automatically made. The plunger was then pulled out and the subject was able to breath atmospheric air again.

Continuous end-tidal CO_2 ($ETpCO_2$) readings taken for the preceding 30 seconds before the start of the rebreathing maneuver provided a value for alveolar pCO_2 ($paCO_2$) from which arterial CO_2 tension ($paCO_2$) could be derived using tidal volume (VT) from the equation:

$$\mathbf{paCO_2 = 5.5 + 0.9\ (ETpCO_2) - 0.0021(VT)}$$

For the calculation of cardiac output using the indirect Fick equation it was necessary to convert the partial pressures of CO_2 ($paCO_2$ and $pvCO_2$) into the content of CO_2 ($caCO_2$ and $cvCO_2$). This allowed determination of the difference in veno-arterial content ($CvCO_2$-$CaCO_2$) using the CO_2 dissociation curve for whole

blood. In calculating the veno-arterial content difference two assumptions were made for all individuals: i. Haemoglobin content was 15g/100ml of blood and ii. The oxygen saturation was >95%. The software automatically calculated these measures and CO using the indirect Fick equation and displayed them on screen.

A minimum of three measurements were performed. The wash out period between tests was at least three minutes. An average of these measurements were taken as the measure of CO_{rest}.

Figure 2.9 Subject performing resting CO_2 rebreathing maneuver

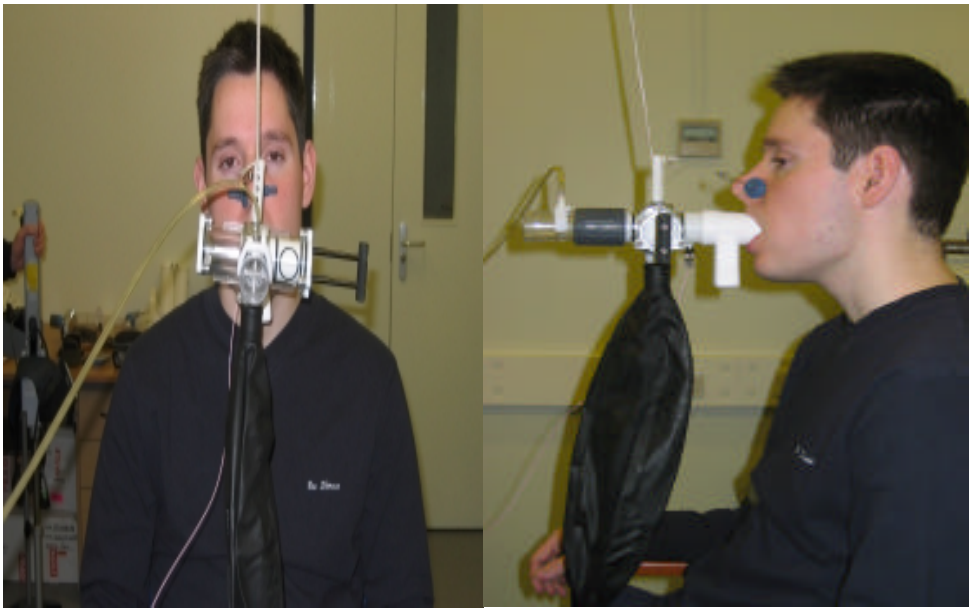
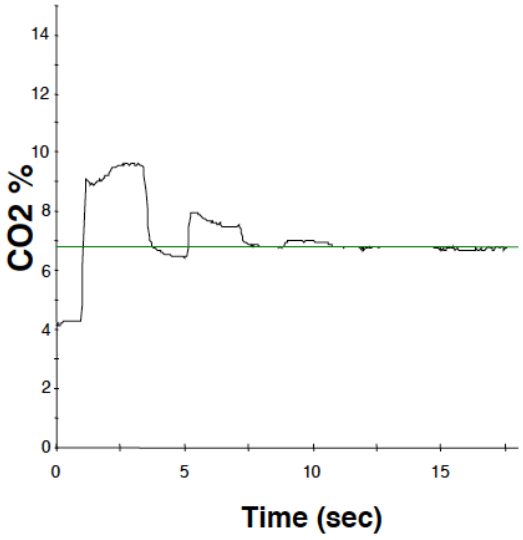


Figure 2.10 Capnograph of the CO_2 concentration reaching equilibrium during the rebreathing maneuver

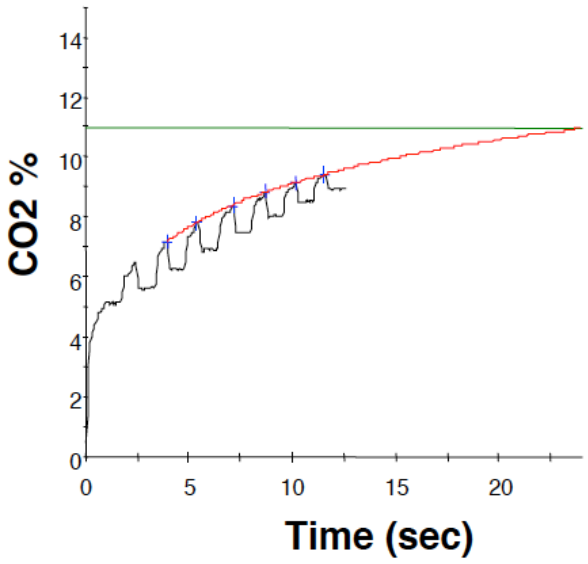


2.6.4 Stage 3 - Cardiac output measurement at maximal exercise

The Defares' exponential CO_2 rebreathing method was used to determine cardiac output at maximal exercise (CO_{max}) [Defares 1958]. The Defares' method has shown to be more accurate and reliable with exercise stress [Ferguson *et al* 1968, Cade *et al* 2004, Vanhees *et al* 2000]. In addition it is better tolerated at maximal exertion [Jones 1997].

The subject inserted the mouth piece, attached to the three way valve, as in the resting test described above (4.2.3.3.4). The subject then performed a constant maximum workload exercise test for at least 5 minutes to the same VCO_2 as achieved in the incremental test, as it was found that this achieved a peak VO_2 of at least that obtained during the maximal standardized incremental test. The anaesthesia bag was then filled with a gas mixture of 4% CO_2, 35% O_2 and balance N_2 to a volume of 1 to 1.5 litres greater than the subject's maximal V_T, determined in the incremental test. At the peak of the exercise, the plunger was pushed in at the end of expiration and the subject then rebreathed the gas mixture for 10 to 15 seconds, whilst continuing exercise. The 4% CO_2 was lower than the subject's $pvCO_2$ and resulted in an exponential rise in $ETpCO_2$. A complete equilibrium was never attained and $pvCO_2$ was mathematically calculated from the rise in $ETpCO_2$. The plunger was then retracted and the treadmill gradient and speed were briefly reduced to ensure subject comfort, obtain a peak blood pressure measurement and change the contents of the bag. The subject then exercised back to their peak again and the measurement was repeated. The Breeze software automatically displayed and applied a best fit exponential curve to the points, rejecting the first point and using eight seconds of rebreathing to create the exponential curve (Figure 2.11) [Heigenhauser & Jones 1979]. End tidal points were manually adjusted to obtain the most accurate exponential curve. The Breeze software again automatically calculated CO using the indirect Fick equation and then displayed it on screen.

Figure 2.11 Exponential curve at peak exercise using the Defares' method



2.6.3 Cardiac output measurement using inert gas rebreathing technique

2.6.3.1 Innocor

Innocor (Figure 2.12: Innovision, Odense, Denmark) is a relatively new compact device that was primarily designed to non-invasively measure CO, but has the option to also measure cardiopulmonary parameters. CO is measured by an inert rebreathing technique using nitrous oxide (N_2O) and 1% sulphur hexafluoride (SF_6).

Breath by breath gas data analysis is performed and presented by the Innocor software (version 5.05). Monitoring and presentation of the data is via the Innocor integrated computer with an embedded Pentium processor and Windows XP operating system. Airflow is measured by means of a differential pressure flowmeter (pneumotachometer). CO_2 gas analysis is performed by the photo acoustic gas analyser which uses the principle of Photo Acoustic Spectroscopy (PAS). O_2 is analysed using an oxygen sensor (Oxigraf Inc., USA) based on the principle of laser diode absorption spectroscopy.

Figure 2.12 Innocor

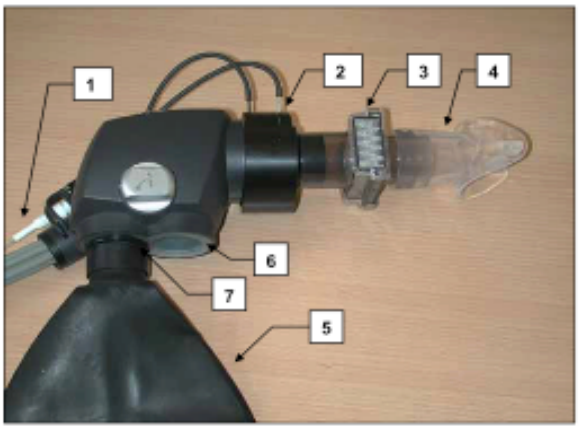
Image of Innocor device and touch screen operating system, Innovision 2005a.

2.6.3.2 Preparation for use

It was necessary to ensure the six-tube connector and the gas analyser sampling tube was connected to the rebreathing valve unit (RVU) and the Innocor (Figure 2.12). The Innocor has the option of using a pulse oximeter finger probe and non-invasive blood pressure cuff, however these were not used due to the inherent inaccuracies with exercise. An 18 liters gas cylinder, containing 5% N_2O and 1% SF_6, 94% O_2 (Innovision, Odense, Denmark) was also connected and the bottle pressure was checked on the Innocor to ensure it was adequate (>10 bar).

Figure 2.13 Rebreathing valve unit and Gas cylinder attachment

A



B

A: Respiratory valve unit (RVU): 1- Gas sampling line, 2- Flowmeter, 3- Bacterial filter, 4- Mouth piece, 5- Rebreathing bag, 6- BBB port, 7- Rebreath port. B: Back of Innocor device and attachment of gas cyclinder.

2.6.3.3 Calibration of Innocor

Calibration of the flowmeter and the flow-gas delay was performed initially on the each day of testing. Calibration was also performed every time the gas sample line or the flowmeter was replaced. To calibrate the flowmeter, it was necessary to select 'Setup', and then select 'Calibration- Adjust Flowmeter' on the Innocor. A certified 3-litre syringe (MedGraphics, St Paul, Minnesota, USA) was then attached to the RVU and as instructed by the Innocor software the syringe was emptied and filled 5 times. 2 of the 5 strokes were faster to cover the physiological test range.

A flow-gas delay calibration was also performed initially on each day of testing. Again 'Setup' was selected on the Innocor, followed by 'Calibration- Calculate gas delay'. The operator then started breathing in and out of the RVU, initially making slow expirations followed by fast inspirations until the 'OK' button was highlighted. The delays should not vary more than 20-40 ms from day to day, as an error of 25 ms can give a 5% error on the VO_2 and VCO_2 results.

The oxygen sensor underwent a 1-point calibration on a monthly basis by the investigator, while both oxygen sensor and photoacoustic gas analyser required multi-point calibration performed by manufacturer periodically every 6-12 months. Again this calibration was found under 'Setup", then 'Adjust O2'.

2.6.3.4 Cardiac output measurement using Innocor

Inert or "foreign" Gas Rebreathing is a well established technique introduced in 1912 by Krogh and Lindhard [Krogh and Lindhard 1912]. It is known that pulmonary blood flow (PBF) generally reflects left ventricular cardiac output as long as no shunt is present. Pulmonary blood flow is that which perfuses the ventilated alveoli.

Calculations are based on a single alveolar lung model with the following assumptions [Innovision 2005b]:

1. Complete and instantaneous mixing of all gases in the volume of alveolar, dead space and bag volume.

2. Instantaneous equilibrium of the soluble gas between alveoli and blood and between alveoli and tissue.

3. Constant pulmonary blood flow and volume of lung tissue

4. Negligible mixed venous concentration of soluble gas through the rebreathing period.

In order to measure CO, the Innocor had to determine both pulmonary blood flow and total systemic volume. This occurred through rebreathing small quantities of both a blood soluble, nitrous oxide (N_2O), and insoluble gas, 1% sulphur hexafluoride (SF_6), in a closed circuit.

During rebreathing, the insoluble gas (SF_6) decreased and reached equilibrium after a few breaths. The volume of the rebreathing bag was constant; therefore the total systemic volume could be determined from the dilution of SF_6. However the total systemic volume was not constant during rebreathing due to more forced ventilation and increased oxygen uptake and higher CO_2 production. The total systemic volume was defined as the middle of the first inspiration or time 0, which was difficult to measure due to incomplete mixing of SF_6. Therefore the Innocor back extrapolated by drawing a line from where complete mixing had taken place and then determined volume at time zero.

Formula to calculate total systemic volume at time zero:

$$V_{s.tot} = \frac{F_i^0}{F_{i,eq}} \cdot V_{rb}$$

$V_{s.tot}$ = Total systemic volume

F_i^0 = Initial concentration of insoluble gas in the rebreathing bag

$F_{i,eq}$ = Equilibrium concentration of insoluble gas (back extrapolated to t = 0)

V_{rb} = Volume of rebreathing bag

In the same rebreathing maneuver, there was an initial disappearance of the soluble gas (N_2O), attributed to absorption into lung tissue, followed by a slower absorption through alveola capillaries. The dissipation rate is proportional to pulmonary blood flow and can therefore be calculated. [Hoeper *et al* 1999]. Assuming pulmonary blood flow and total systemic volume are constant, the dissipation curve for N_2O describes a mono-exponentially decreasing function of time. The formula to calculate pulmonary blood flow is:

$$PBF = \frac{-\beta . V_{s.tot} . C_1 + C_2}{\alpha_b}$$

PBF = Pulmonary blood flow

$V_{s.tot}$ = Total systemic volume

$C_1 = 760/(P_B - 47)$

$C_2 = \alpha_t . V_t$, Constant to account for disappearance of soluble gas in lung tissue

α_b = Bunsen solubility coefficient in blood

α_t = Bunsen solubility coefficient in tissue

V_t = Lung tissue volume (default 600ml)

P_B = Ambient pressure in mmHg

As previously mentioned, there is initially incomplete mixing at the start of the rebreathing maneuver, therefore corrections of concentrations of soluble gas (N_2O) were made according to the change in concentration of the insoluble gas (SF_6).

2.6.3.5 Performing measurement of resting cardiac output using Innocor

The investigator pressed 'Test' on the Innocor to initiate a test. The subject's height (meters), and weight (kilograms) were measured and entered. The Haemoglobin (Hb) concentration was entered as 12 g/l, due to the majority of subjects not knowing their current haemoglobin level.

The subject was instructed to put on a nose clip and breathed normally in and out of the RVU via a mouthpiece with a bacterial filter attached. The following parameters were then continuously measured: VO_2, VCO_2, VE and $PETCO_2$.

When the investigator was ready to perform a cardiac output measurement, the Innocor device automatically prepared the rebreathing bag by emptying and filling it with the necessary volume of gas. The volume was calculated automatically as 40% of the predicted vital capacity at rest. The recommended mixture of gas at rest was 10% bolus of the gas container containing 94% O_2, 5% N_2O and 1% SF_6. The rest was filled with ambient air, giving a mixture of 28.3% O_2, 0.5% N_2O and 0.1% SF_6.

Once the bag was filled and the subject was ready, the investigator pressed 'Start'. At the end of the next expiration the valve switched, so that the subject then rebreathed the gas from the bag for a period of 10-15 seconds. During the rebreathing test, the subject was instructed to empty the bag during each inspiration at the speed indicated by the graphical tachymeter shown on Innocor (usually 20-30 breaths/min). The test automatically stopped once there were adequate numbers of

breaths (usually 4 or 5) and the valve switched back to ambient air. A minimum of three measurements were performed. At least 5 minutes delay was necessary for washout of the inert gases between tests. The Innocor software calculated CO automatically, based on a rebreathing model, and were then displayed on screen.

2.6.3.6 Performing measurement of cardiac output using Innocor during exercise

At the beginning of the exercise testing session the Innocor was prepared and calibrated. The investigator then pressed 'Test' on the Innocor to initiate a test. The subject's height (meters), and weight (kilograms) were measured and entered. The Haemoglobin (Hb) concentration was entered as 12 g/l. The exercise protocol was also entered with a planned sub-maximal CO in the protocol, although the Innocor was not used to drive the treadmill.

The subject was instructed to put on a nose clip and breathed normally in and out of the RVU via a mouthpiece with a bacterial filter attached. The following parameters were then continuously measured: VO_2, VCO_2, VE and $PETCO_2$. The investigator then started the exercise test and simultaneously started the exercise protocol on the Innocor. The subject then completed the exercise test, whilst continuously breathing through the RVU.

Once the subject completed the exercise protocol, the Innocor automatically prepared the rebreathing bag by emptying and filling it with the necessary volume of gas. Once the bag was filled and the subject was ready, the investigator pressed 'Start'. At the end of the next expiration the valve switched, so that the subject then rebreathed the gas from the bag for a period of 10-15 seconds. During the rebreathing test, the subject was instructed to empty the bag during each inspiration at the speed indicated by the graphical tachymeter shown on Innocor (usually 20-30 breaths/min). The test automatically stopped once there were adequate numbers of breaths (usually 4 or 5) and the valve switched back to ambient air. The innocor software calculated CO automatically, based on a rebreathing model, and was then displayed on screen.

2.7.4 Doppler Echocardiography

Transthoracic echocardiogram was used as a reference and alternative method to determine CO using the doppler echocardiography technique. All of the scans were performed on a GE Vingmed VIVID 7 (Horten – Norway) and images were post-processed on a dedicated Echopac PC. Imaging was performed by the same operator (the primary investigator) in a dedicated echocardiography room.

Stroke volume (SV) was calculated from the product of aortic blood velocity and the cross sectional area of the aorta. The aortic blood velocity was determined by taking a continuous wave (CW) doppler measurement parallel through the aortic valve in the standard apical five chamber view. The area underneath the curve or the velocity time integral (VTI) was calculated by tracing the CW envelope. 3 consecutive beats were averaged for each measurement. The diameter of the aortic orifice was then measured during systole in parasternal long axis view, by measuring from leading edge to leading edge of the anterior and posterior walls (as per BSE guidelines) [Wharton *et al* 2012] . Diameters of 3 consecutive beats were averaged and the cross sectional area (CSA) was then calculated:

$$CSA = \pi \times (D/2)^2, \text{ where } D = \text{mean aortic diameter}$$

A three lead ECG was attached at the start of the scan. Subjects then lay down in the left lateral, semi recumbent position. Diameter of the aortic orifice and doppler measurements thought the aortic valve were taken, as described above. Heart rate (HR) was determined from the RR interval on the ECG at the same time as the doppler measurement.

After completing the analysis to calculate SV, the cardiac output (CO) was then calculated

$$CO = SV \times HR$$

2.8 Quality of life and symptom assessment

The SF-36v2 health survey is a multipurpose short-form health survey with 36 questions that yield an eight scale profile of functional health and well being [Optum 2015] (Appendix C). It is the most frequently used measure of patient reported outcomes, often labeled as quality of life [Scoggins and Patrick 2009]. Its predecessor, the SF-36 survey, was developed as part of the Medical Outcomes Study (MOS) to assess physical and mental health [Ware and Sherbourne 1992]. The SF-36v2 came was a minor alteration of the original survey to address problems of meanings of some words [Optum.com 2015]. The eight domains are: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health The SF-36v2 is takes five to ten minutes to complete. Scaled scores on the SF-36 are derived by summing the items together within a scale, dividing by the range of scores and then transforming raw scores to a 0-100 scale. Higher scores in each scale indicate better functioning. Internal reliability of the SF-36 has been reported in 14 studies of more than 20,000 patients [Ware and Sherbourne 1992].

2.9 Data Analyses and calculations

Conventional equations were used to calculate the following parameters: respiratory exchange ratio ($RER=VCO_2/VO_2$), minute ventilation (V_E = product of tidal volume, V_t and respiratory rate, RR) and O_2 consumptions normalized by body mass (VO_2/kg). Cardiac output (CO in $L.min^{-1}$) was calculated using the indirect Fick method and two or more measurements were taken in order to calculate a mean value. Mean arterial pressure (MAP in mm Hg) was calculated using the standard equation, MAP = DBP + 0.412*(SBP–DBP) [Meaney 2000].

Cardiac power output (CPO in watts) was calculated using the following equation: CPO = cardiac work done per second = (CO x MAP) x K, where K is the conversion factor into watts (2.22×10^{-3}) [Tan 1986]. Cardiac reserve (CR in watts) is the difference between cardiac power output at peak exercise and rest and was calculated using the following equation, $CR = CPO_{max} – CPO_{rest}$ [Tan 1991].

The systemic vascular resistance (SVR in $dyne.sec.cm^{-5}$) was calculated as follows: SVR = (MAP/CO) x 80 [Klabunde 2011]; Circulatory Power (CircP in $mm\ Hg.ml.min^{-1}$), a surrogate index of cardiac power, was calculated as CircP = VO_2 x SBP [Cohen-Sohal 2002]. Stroke volume (SV in ml) was calculated from measurements

of cardiac output (CO) and heart rate (HR) using the standard equation]: SV = CO/ HR [Klabunde 2011. Stroke work (SW in g.m) was calculated using the product of stroke volume (SV) and mean arterial pressure (MAP): SW = SV x MAP [Klabunde 2011].

Chapter 3

Validation and reproducibility of cardiac output measurement

Chapter 3 Validation and reproducibility of cardiac output measurement

3.1 Introduction

Techniques to measure cardiac output have developed significantly over the last century. In clinical practice, measurement is primarily performed at rest, whereas measurement at peak exercise is only performed by the minority of physicians and researchers. Assessment of cardiac output via rebreathing techniques provides an accurate alternative to invasive methods (Fick, thermodilution and dye techniques) [Liu *et al* 1997,Triebwasser *et al* 1977, Muiesan *et al* 1968, Clausen *et al* 1970, Franciosa *et al* 1976, Gabrielsen *et al* 2002, Agastoni *et al* 2005], which are regarded as the most accurate way of measuring cardiac output [Nugent *et al* 1994]. It is also clear that reproducibility using rebreathing methods improves with increasing workloads [Liu *et al* 1997, Yeh *et al* 1987, Vanhees *et al* 2000].

The most commonly used rebreath techniques reported in the literature are using either an inert-gas rebreathing method or the CO_2 rebreathing method. One of the first inert gases introduced in the early 1900's was Acetylene, however with the advent of rapid gas analysers in the 1950's, the CO_2 rebreathing method grew in popularity due to it being a technically simple and easily repeatable method (Jones 1997), compared with mass spectrometers used in inert gas rebreathing methods, which were more expensive, unstable and complicated. More recently infrared photoacoustic spectroscopy analysers have been incorporated into a new Innocor device (Innovision, Denmark), which uses an inert gas (using a mixture of 0.5% nitrous oxide, 0.1% sulfurhexafluoride and 28% O_2) and is simple to use, mobile and less costly than mass spectrometers [Gabrielsen *et al* 2002].

Comparisons between non-invasive rebreathing techniques has not been widely reported. Jakovljevic *et al* [Jakovljevic *et al* 2008] compared the inert rebreathing technique, using Innocor, to the CO_2 rebreathing technique in 12 healthy subjects at rest and peak exercise using both the equilibrium and and exponential CO_2 rebreathing methods in comparison to the inert rebreathing method. He found that the equilibrium method produced significantly higher values at rest in comparison to the exponential and inert rebreathing methods. At peak exercise, there were no significant differences between the exponential and inert gas rebreathing methods

(P = 0.14). The mean difference and limits of agreement were 0.15 (-0.49 to 0.79) l min^{-1}.

Other studies have compared rebreathing methods to other non-invasive techniques, including impedance cardiography, echocardiography M-mode and Doppler techniques and cardiac magnetic resonance imaging [Tordi *et al* 2004, Julius 1990, Saur *et al* 2009a]. However, these were either performed at rest or using less accurate methods as a comparison and therefore do not help identify which rebreathing technique is the most reliable.

Therefore, in order to decide which rebreathing method to adopt, it was necessary to determine the validity and reproducibility of each method.

3.2 Study I: Validity and reproducibility of resting measurement of cardiac output using CO_2 and inert gas rebreathing methods and transthoracic echocardiography

3.2.1 Purpose and hypothesis of the study

The purpose of this study was to assess the repeatability and make a direct comparison of two commercially available systems that measure cardiac output (CO) using rebreathing techniques, with either carbon dioxide (CO_2 rebreathing) using Medgraphics Ultima (Medgraphics Corporation, St. Paul, Minnesota, USA), or inert gas (IGR), using Innocor (Innovision, Odense, Denmark). Both of these were also compared to the echocardiography doppler (Doppler) technique, as this was a more familiar and readily available technique and has been more widely used and published.

The hypotheses tested were

(i) Measurement of CO at rest would not be significantly different between 2 different rebreathing techniques (IGR and $CO_{2\ rebreathing}$) and Doppler.

(ii) Measurement of CO at rest using rebreathing techniques (IGR and CO_2 rebreathing) and Doppler is reproducible and reliable.

3.2.2 Methods

3.2.2.1 Study participants

Healthy volunteers were recruited from Leeds General Infirmary and The University of Leeds via personal invitation. They were all healthy and physically active. All subjects underwent screening with a medical history, physical examination and resting ECG to ensure they were in fact healthy.

Subjects were asked to abstain from any vigorous physical activity for 24 hours prior to testing. They were further instructed to have no food and caffeine for 3 hours and alcohol for 12 hours prior to their attendance.

3.2.2.2 Resting Doppler Echocardiography

Initially subjects underwent a transthoracic echocardiogram to determine their resting CO using the doppler echocardiography technique. All of the scans were performed on a GE Vingmed VIVID 7 (Horten – Norway) and images were post-processed on a dedicated Echopac PC. Imaging was performed by the same operator (the primary investigator) in a dedicated echocardiography room. The methods are described in detail in the Chapter 2. Two measurements of CO were taken 5 minutes apart, under the same conditions, to assess reproducibility and calculate a mean value for comparison with the other methods.

Following the echo, subjects then underwent seated resting assessment of their cardiac outputs using both the Medgraphics and Innocor systems. Subjects were randomized to undergo testing using each system, so that there was no bias.

3.2.2.3 Resting cardiac output measurement using CO_2 rebreathing technique (Medgraphics Ultima)

The Medgraphics Ultima cardio-pulmonary exercise (CPX) system (Medgraphics Corporation, St. Paul, Minnesota, USA) was used to measure resting CO using the Collier technique. The methods are described in detail in the Chapter 2. Two measurements of CO were measured after a 5 minutes wash out period, to assess reproducibility and calculate a mean value for comparison with the other methods.

3.2.2.4 Resting cardiac output measurement using inert gas rebreathing technique (Innocor)

Innocor (Innovision, Odense, Denmark) measured CO by an inert rebreathing technique using nitrous oxide (N_2O) and 1% sulphur hexafluoride (SF_6). The methods are described in detail in the Chapter 2. Two measurements of CO were measured after a 5 minutes wash out period, to assess reproducibility and calculate a mean value for comparison with the other methods.

3.2.3 Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 (SPSS Inc. Chicago, IL, USA). Descriptive statistics were performed to check data for parametric assumptions (normal distribution and homogeneity of variance). One way analysis of variance (ANOVA) was used to test differences between the three methods. Bland-Altman plots were constructed to assess agreement between different methods and duplicate measures of cardiac output using the same method [Bland and Altman 1986]. Intra class coefficients (ICC) and standard error of measurements (SEM) were calculated to establish within subject changes.

3.2.4 Results

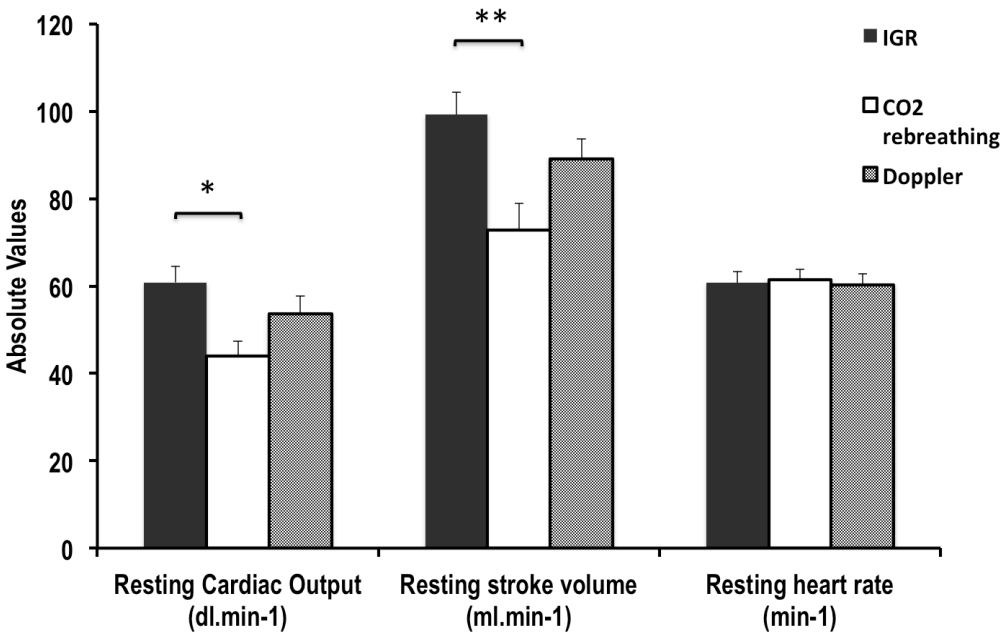
13 subjects were recruited and had normal findings on screening, however one individual was then found to have an incidental mildly dilated aortic root on echocardiography. He had no evidence of hypertension, structural heart disease or cardiac dysfunction and therefore was allowed to continue. The mean age of all subjects was 26 ± 3.6 years, BMI 23.6 ± 2.8, with 3 out of 13 being female. All 13 subjects completed all the resting without complications.

All 3 groups had similar homogeneity of variances. One-way ANOVA indicated that within groups there was a significant difference in CO (F=5.140, P=0.011, 22% of variation in CO caused by method of estimating cardiac output). Post Hoc testing with Bonferroni correction showed that mean CO measured by IGR (Innocor) was significantly larger than CO_2 rebreathing (Medgraphics) (mean difference 1.68 $l.min^{-1}$ higher, P=0.009). IGR was not significantly different from Doppler (mean difference 0.725 $l.min^{-1}$ higher, P=0.527) and CO_2 rebreathing was not significantly different from Doppler (mean difference 0.952 $l.min^{-1}$ lower, P=0.233). Heart rate did not significantly vary between tests, however stroke volume similarly was higher

with IGR than with CO_2 rebreathing (mean difference 26.3 ml, P=0.04) shown in Figure 3.1.

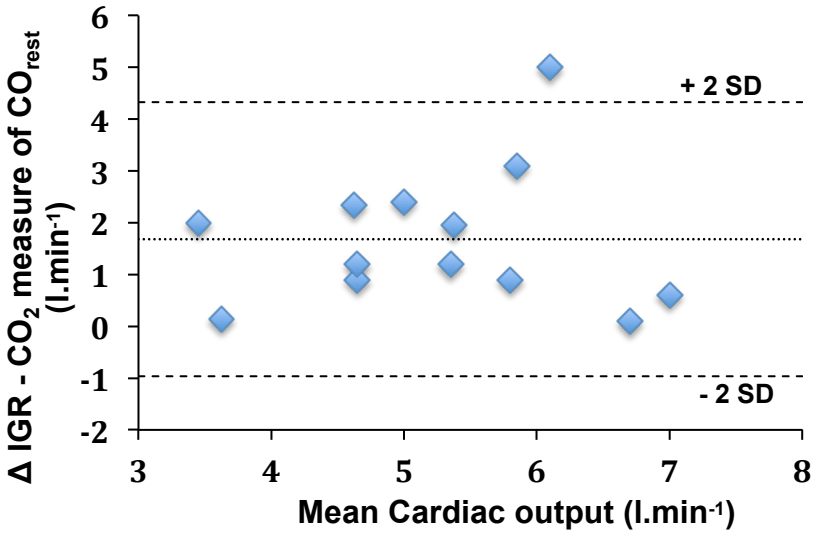
Bland-Altman analysis shows the mean difference in cardiac output and limits of agreement between methods. IGR - CO_2 rebreathing (1.68 ± 2.65 $l.min^{-1}$) (Figure 3.2); IGR – Doppler (1.17 ± 2.29 $l.min^{-1}$) (Figure 3.3); and CO_2 rebreathing – Doppler (-0.95 ± 3.16 $l.min^{-1}$) (Figure 3.4). There was more variation with CO_2 rebreathing compared to echo with higher cardiac output values, whereas IGR tended to be higher than Doppler at lower mean values of CO, but lower at higher mean values.

Figure 3.1 Comparison of resting cardiac output using different rebreath techniques and echocardiography



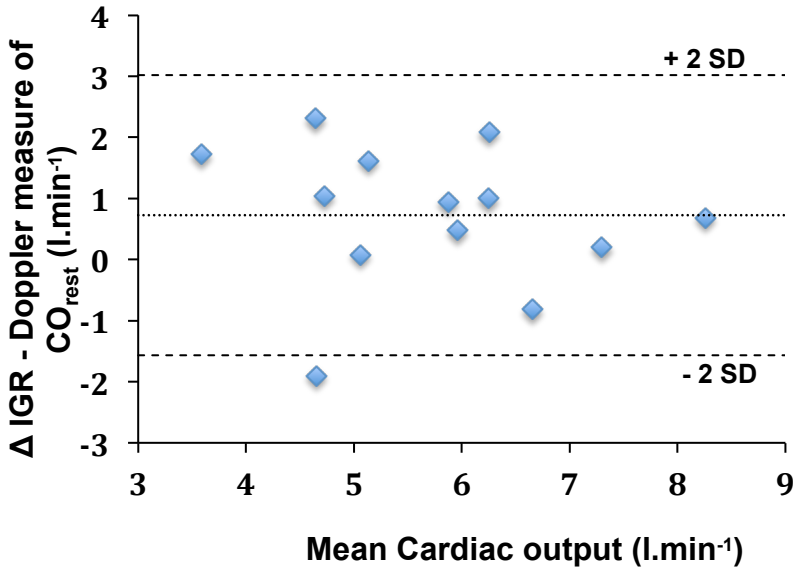
This graph shows the differences in mean resting cardiac output, stroke volume and heart rate between the three methods: CO_2 rebreathing (Medgraphics), inert rebreathing (Innocor) and echocardiography doppler technique (Echo). Innocor was found to have significantly higher resting cardiac output and stroke volume, in comparison to Medgraphics, however there was no difference in heart rate. Nor were there significant differences in any measurements between Medgraphics and Echo or Innocor and Echo.(*: p = 0.009; **: p = 0.04)

Figure 3.2 Bland-Altman plot to demonstrate mean difference and limits of agreement between inert gas rebreathing and CO_2 rebreathing



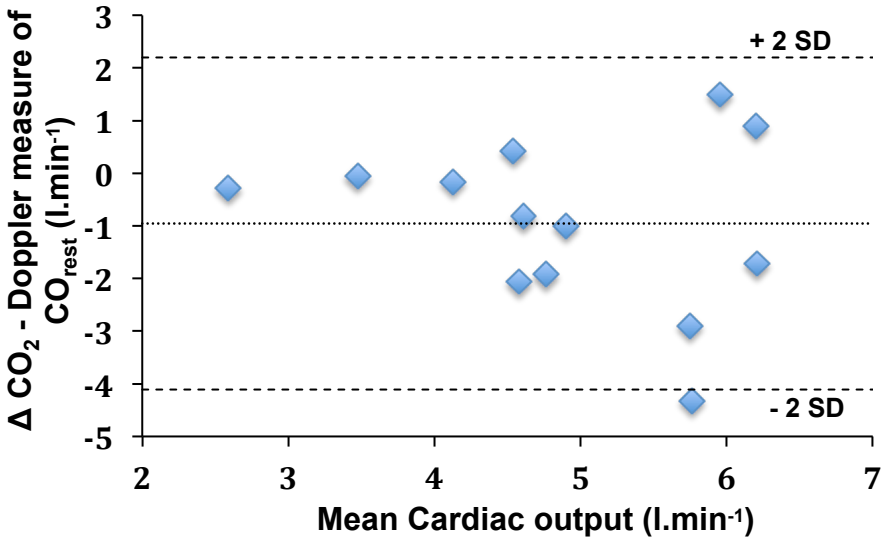
(CO: Cardiac output; IGR: inert gas rebreathe; SD: standard deviation)

Figure 3.3 Bland-Altman plot to demonstrate mean difference and limits of agreement between inert gas rebreathing and echocardiography doppler methods



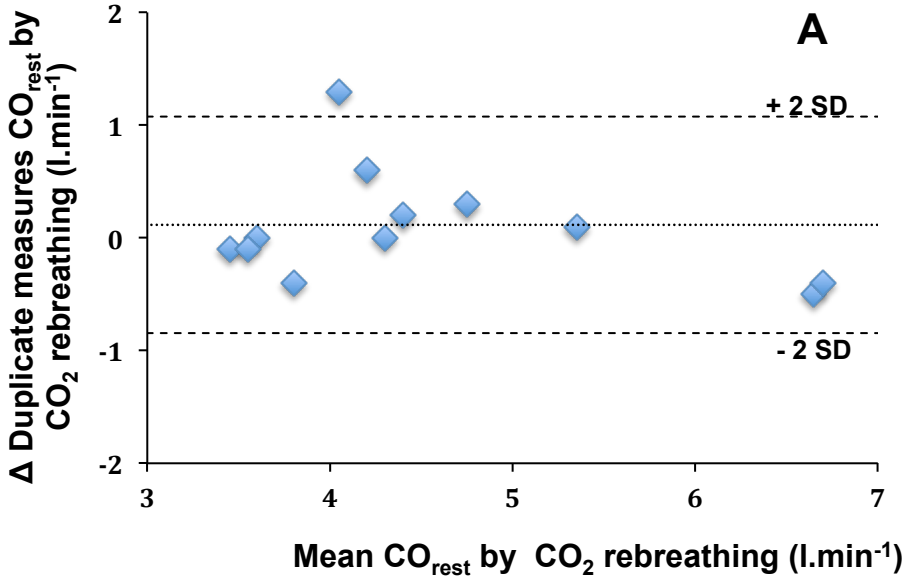
(CO: Cardiac output; IGR: inert gas rebreath; Doppler: Echocardiography doppler; SD: standard deviation)

Figure 3.4 Bland-Altman plot to demonstrate mean difference and limits of agreement between CO_2 rebreathing (Medgraphics) and echocardiography doppler methods



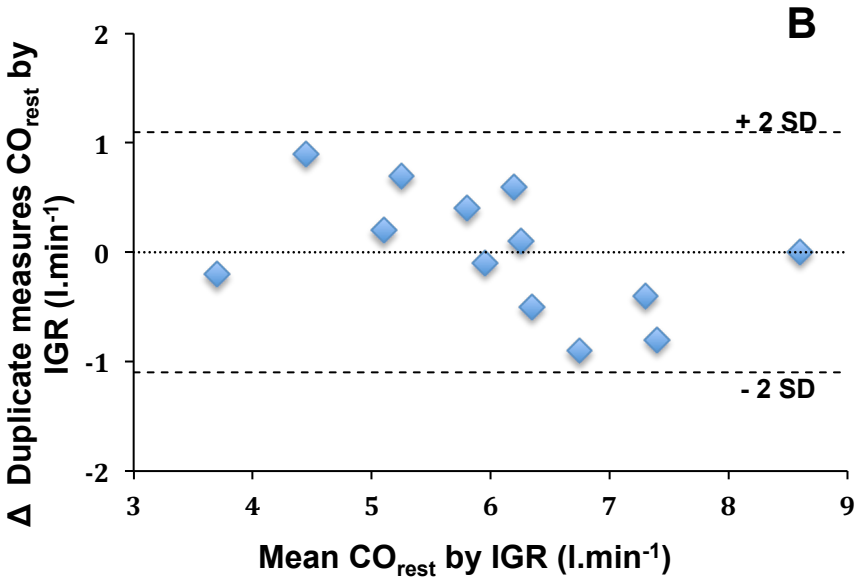
(CO: Cardiac output; Doppler: Echocardiography doppler; SD: standard deviation)

Figures 3.5 Bland-Altman plot to demonstrate mean differences and limits of agreement between duplicate measures of resting cardiac output determined by CO_2 rebreathing



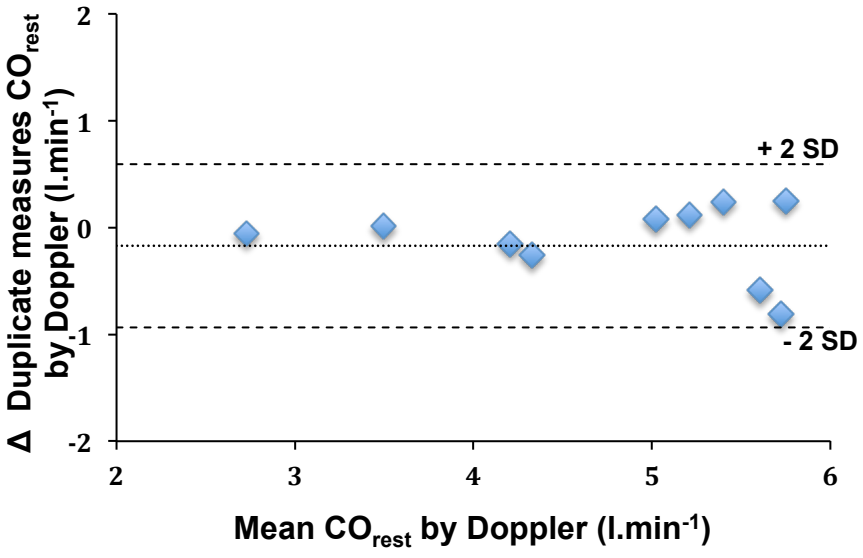
(CO: Cardiac output; SD: standard deviation)

Figures 3.6 Bland-Altman plot to demonstrate mean differences and limits of agreement between duplicate measures of resting cardiac output determined by Inert gas rebreathing



(CO: Cardiac output; IGR: inert gas rebreath; SD: standard deviation)

Figures 3.7 Bland-Altman plots to demonstrate mean differences and limits of agreement between duplicate measures of resting cardiac output determined by Doppler echocardiography



(CO: Cardiac output; Doppler: doppler echocardiography; SD: standard deviation)

3.2.5 Discussion

The purpose of this study was to make a direct comparison of two commercially available systems that measure CO using rebreathing techniques, and compare them to a well established technique using Doppler echocardiography. In addition, the study aimed to assess reproducibility of these 3 methods at rest.

The present study showed there was a distinct difference in measurements between the two techniques with those measures obtained by IGR (Innocor) being, on average, 1.7 $l.min^{-1}$ higher than CO_2 rebreathing (Medgraphics). One however cannot deduce from this which is the correct measure. When compared to Doppler, neither measure was significantly different, however Doppler measures on average were in between the two rebreathing measures and so one may assume that this figure may be more realistic.

The study by Jakovljevic et al [Jakovljevic *et al* 2008] also compared the equilibrium CO_2 rebreathing method, using the Medgraphics system, to the inert gas rebreathing method using Innocor, however found no significant difference between the two methods, although the actual measures of cardiac output were slightly higher using the CO_2 rebreathing method (6.6 ± 1.5 versus 5.1 ± 0.9 $l.min^{-1}$). It is difficult to explain why these results are very different and one can only assume different methods must be the main factor. Saur et al [Saur *et al* 2009] compared Innocor to Doppler echocardiography and also found a good correlation ($r = 0.53$, $P < 0.001$). They reported a mean difference of 0.4 ± 1.0 $l.min^{-1}$, with Innocor yielding higher values which are in keeping with the present study.

It is known that the CO_2 rebreathing equilibrium method tends to underestimate CO at rest [Franciosa *et al* 1977, Nugent *et al* 1994, Wilmore *et al* 1982, Muiesan *et al* 1968], and that both Innocor and Doppler echocardiography appear to closely correlate with invasive methods (Fick and thermodilution) [Agastoni *et al* 2005, Christie *et al* 1987, Bouchard *et al* 1987]. Saur et al [Saur *et al* 2009a] found that Innocor showed good agreement with MRI, which they felt to be the gold standard non-invasive method of assessment of CO at rest, but that it over-estimated CO in hyperdynamic circulations. Therefore, the closest measure of CO at rest, in young healthy female adults, may be best represented by Doppler echocardiography.

The present study further showed that all three methods were highly reproducible with low standard errors of measurement. This is in agreement with others who have shown these methods to be reproducible at rest [Jakovljevic *et al* 2008, Saur

et al 2009b, Vanhees *et al* 2000, Robson *et al* 1987b].

3.3 Study II: Comparison of two techniques to measure cardiac output during exercise, using CO_2 rebreath and inert gas rebreathing methods

3.3.1 Purpose and hypothesis of the study

The purpose of this study was to make a direct comparison of two systems that measure cardiac output (CO), using the CO_2 rebreathing method, using Medgraphics Ultima (Medgraphics Corporation, St. Paul, Minnesota, USA) and the inert gas rebreathing (IGR) method, using Innocor (Innovision, Odense, Denmark), during exercise.

The hypothesis tested was

(i) Measurement of CO at rest and during exercise would not be significantly different between IGR and CO_2 rebreathing and would have acceptable measures of agreement

3.3.2 Methods

3.3.2.1 Study participants

Healthy volunteers were recruited from Leeds General Infirmary and the University of Leeds via personal invitation. They were all healthy and physically active. All subjects underwent screening with a medical history, physical examination and resting ECG to ensure they were in fact healthy.

Subjects were asked to abstain from any vigorous physical activity for 24 hours prior to testing. They were further instructed to have no food and caffeine for 3 hours and alcohol for 12 hours prior to their attendance

3.3.2.2 Exercise protocol

Subjects were asked to perform 6 treadmill exercise tests during one visit. Subjects

initially performed stage I of the Bruce Protocol [Bruce *et al* 1971] (i.e. 3 minutes exercise at 1.7 mph and 10% gradient) twice, with 10 minutes recovery between tests. CO was measured at the end of each test using either the Innocor or Medgraphics Ultima. The order in which each test was done was randomised to exclude bias.

After a further 10 minutes recovery, subjects performed two further exercise tests up to and including stage II of the Bruce Protocol (i.e. a total of 6 minutes exercise, first 3 minutes stage I, second 3 minutes stage II at 2.5 mph and gradient 12%). CO was measured by both methods at the end of each test. In between tests there was 15 minutes recovery time.

Finally subjects performed the last two exercise tests up to and including stage III of the Bruce protocol (i.e. a total of 9 minutes of exercise, first 3 minutes stage I, second 3 minutes stage II and last 3 minutes stage III of the Bruce protocol at 3.5mph and 14%). CO was again measured at the end of each test by both methods. In between tests there was 20 minutes recovery.

3.3.2.3 Cardiac output measurement using Medgraphics Ultima

The Defares' exponential CO_2 rebreathing method was used to determine peak cardiac output (CO_{max}) [Defares 1958]. The methods are described in detail in the Chapter 2. Only a single measure of CO was performed at the end of each submaximal exercise test.

3.3.2.4 Cardiac output measurement using Innocor

A single measure of CO was performed by using the Innocor at the end of each submaximal exercise test. The methods are described in detail in the Chapter 2.

3.3.3 Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 (SPSS Inc. Chicago, IL, USA). Descriptive statistics were performed to check data for parametric assumptions (normal distribution and homogeneity of variance). One way analysis of variance (ANOVA) was used to test differences between the both methods. Correlation was established using the Pearson's correlation. A Bland-

Altman plot was constructed to assess agreement between methods [Bland and Altman 1986].

3.3.4 Results

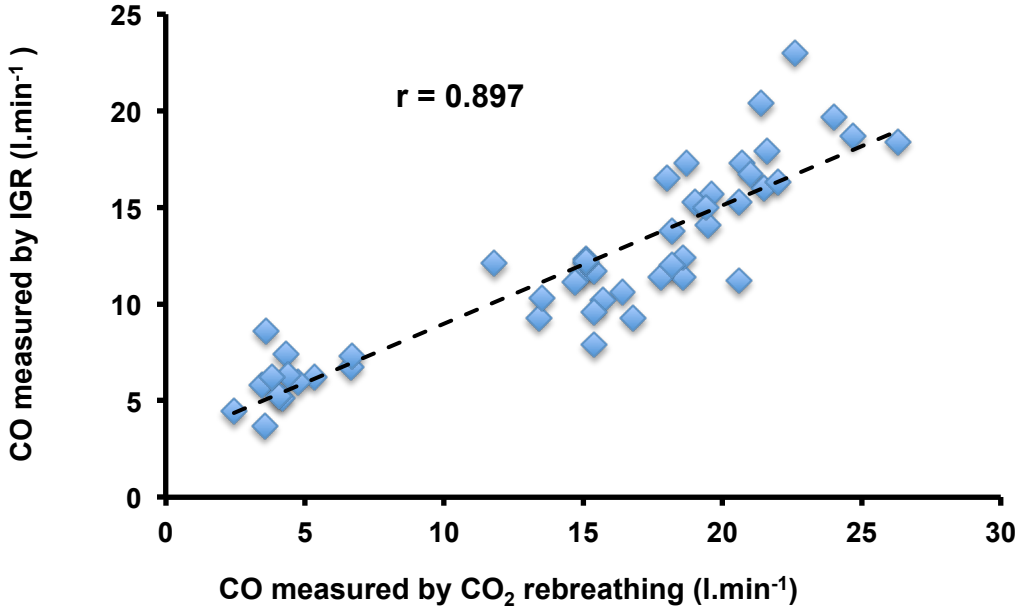
Both groups have similar homogeneity of variances. One-way ANOVA indicated that within groups there was a significant difference in CO at rest and during all stages of sub-maximal exercise ($F = 30.39$, $P < 0.0001$), (Table 3.1). However there was a good correlation between the two ($r = 0.897$, $P < 0.0001$) (Figure 3.8). The Bland-Altman plot shows that at rest, IGR has consistently higher values, where as at all stages of exercise CO_2 rebreathing has consistently higher values, with an overall bias of 2.98 ± 6.52 $l.min^{-1}$. (Figure 3.9)

Table 3.1. Difference in mean cardiac outputs between CO_2 rebreathing and IGR methods, at rest and during submaximal exercise.

	CO_2 rebreathing CO Mean (SD) ($l.min^{-1}$)	**IGR CO Mean (SD)** ($l.min^{-1}$)
Rest	4.40 (1.22)	6.08 (1.30)
3 min Bruce	15.41 (2.05)	10.84 (1.62)
6 min Bruce	18.22 (1.96)	13.71 (2.34)
9 min Bruce	21.88 (2.26)	17.56 (2.85)

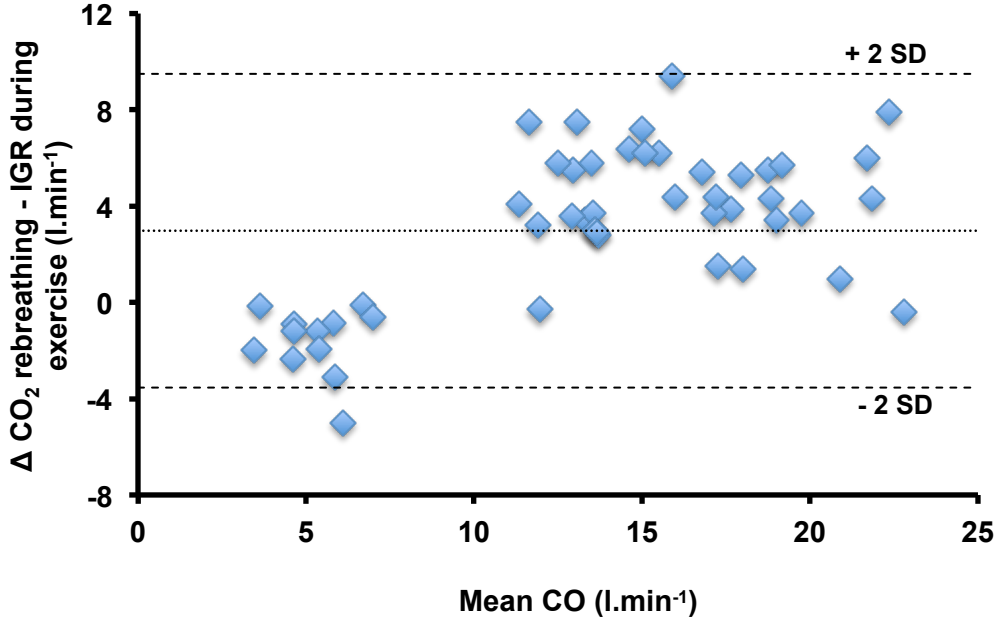
(CO: Cardiac output; IGR: innert gas rebreathing SD: standard deviation)

Figure 3.8 Correlation between IGR and CO_2 rebreathing methods at rest and during exercise



(CO: Cardiac output; IGR: innert gas rebreathing)

Figure 3.9 Bland-Altman plot to demonstrate mean difference and limits of agreement between IGR and CO_2 rebreathing methods at rest and sub-maximal exercise



(CO: Cardiac output; IGR: innert gas rebreathing)

3.3.5 Discussion

The purpose of this study was to make a direct comparison of two non-invasive systems that measure cardiac output during exercise using rebreathing techniques (CO_2 and inert gas).

The present study showed that both rebreath techniques are technically possible and easily performed at rest and during submaximal exercise. However although there appeared to be a linear correlation between measures, there were significant differences in values at rest and each submaximal stage of exercise. What was also clearly evident was that the pattern of agreement between measures changed if they were at rest (IGR 1.6 ± 1.4 $l.min^{-1}$ higher) or during exercise (CO_2 rebreathing 4.5 ± 2.2 $l.min^{-1}$ higher).

As previously mentioned, Jakovlejevic et al [Jakovlejevic *et al* 2008] found no difference in cardiac output between IGR and CO_2 rebreathing using the equilibrium method at rest. They also compared IGR and CO_2 rebreathing using the exponential method at peak exercise and found good agreement with a mean difference of 0.15 ± 0.64 $l.min^{-1}$. They however did not perform any values at sub-maximal exercise and so studies are not directly comparable.

It is generally accepted that CO_2 rebreathing by the equilibrium method underestimates cardiac output at rest in comparison to invasive methods of assessment [Nugent *et al* 1994, Wilmore *et al* 1982, Muiesan *et al* 1968]. Therefore, this helps explain the differences seen in the present study at rest, where measures of cardiac output at rest were significantly lower using CO_2 rebreathing, in comparison to IGR. However, it also known that variability with the CO_2 rebreathing method is larger at rest and improves with exercise [Reybrouck & Fagard 1990, Ferguson *et al* 1968, Clausen *et al* 1970]. Therefore, CO_2 rebreathing is considered a valid and reliable method of measuring cardiac output during exercise, and has acceptable limits of agreement with invasive methods [Espersen *et al* 1995].

Agastoni et al [Agastoni *et al* 2005] showed that Bland Altman plots confirmed no significant difference between IGR (using Innocor), Fick and thermodilution methods, cardiac output measured by IGR was less (95% of Fick and 78% of thermodilution). This helps explain why cardiac output by IGR was smaller than by CO_2 rebreathing in the present study.

A major limitation of the study was that there was no comparison between IGR and

CO_2 rebreathing at maximal exercise. Maximal testing was attempted with the Innocor during the pilot phase and it was found that the Innocor could not reliably measure cardiac output at peak exercise in all subjects, because of an error in the software. This appeared to be primarily associated with individuals who have higher rates of peak oxygen consumption. This has not been reported in the past, however the Innocor was designed and has primarily been used for measuring cardiac output in patients with heart failure, rather than athletic healthy subjects. This issue was also explored with the company who supplied the machine. They understood that there was a safety mechanism that created an error when the oxygen content in the rebreath bag become too low. An error message then presented on the software to prevent the subject from continuing the re-breath test with inadequate oxygen in the bag. The company recommended to use a larger volume of gas at the time of the rebreath test to try to overcome this, which worked in a few more tests, but not all tests where the peak oxygen consumption was high (i.e. over 5000 $ml.min^{-1}$). Due to the small number of subjects being tested, it was considered to be reliable enough to perform the comparison at maximal exercise. The same error was not seen at all during sub-maximal exercise testing.

3.4 Study III: Reproducibility of measurement of cardiac output at peak exercise using Medgraphics Ultima

3.4.1 Purpose and hypothesis of the study

Reproducibility of measurement of cardiac output at maximal treadmill exercise, on different days, in healthy subjects has not been reported. Therefore prior to embarking on studies to identify differences in cardiac outputs with different weight conditions, it was necessary to establish the reliability of the CO_2 rebreathing method used in the laboratory (using the Medgraphics Ultima system).

The hypothesis tested was

(i) Measurement of cardiac output at maximal treadmill exercise, using the exponential CO_2 rebreathing method, is reliable and will have acceptable measures of agreement and coefficient of variability.

3.4.2 Methods

3.4.2.1 Study participants

Healthy volunteers were recruited from Leeds General Infirmary and the University of Leeds via personal invitation. They were all healthy and physically active. All subjects underwent screening with a medical history, physical examination and resting ECG to ensure they were in fact healthy.

Subjects were asked to abstain from any vigorous physical activity for 24 hours prior to testing. They were further instructed to have no food and caffeine for 3 hours and alcohol for 12 hours prior to their attendance

3.4.2.2 Exercise testing protocols

Subjects were asked to attend the Leeds General Infirmary on three occasions to perform three separate cardiopulmonary exercise tests, during a two week period.

The first test was performed using a ramp treadmill protocol, based on the Bruce protocol [Bruce 1971], which I called the Liverpool protocol, shown below (Table 3.2). Subjects were asked to exercise to their peak volitional fatigue.

The next two visits and tests were performed in order to measure their peak cardiac output and peak cardiac power outputs. Both of these tests were performed using the same identical protocol and workload as that achieved during their first test.

The reason for choosing to use a ramp protocol with one minute increments was to obtain a more linear rise in VO_2 relative to the workload and avoid fluctuations apparent with the Bruce protocol. The reason for choosing peak work load as the constant measure was to limit the variability and potential fluctuations in cardiac output necessary to perform the peak test.

3.4.2.3 Initial maximal cardiopulmonary exercise test

The first test was a standard maximal cardiopulmonary exercise test. The methods are described in detail in the Chapter 2.

3.4.2.4 Measurement of cardiac output and cardiac power output at maximal exercise

The subject then went away and came back for two further visits within a 2 week period and where possible came at the same time of day. Identical procedures were used to measure cardiac output, using the Medgraphics Ultima, at maximal exercise determined by the workload and VO_{2max} achieved in the initial exercise test. MAP was measured at peak exercise and then CPO_{max} was calculated. The methods are described in detail in the Chapter 2.

Table 3.2 Liverpool protocol

Stage	Duration (min)	Speed (km/h)	Gradient (%)	Equivalent stage in Bruce
1	0-1	2.2	0	
2	1-2	2.2	0	
3	2-3	2.7	5	
4	3-4	2.7	10	I
5	4-5	3.3	11	
6	5-6	4	12	II
7	6-7	4.8	13	
8	7-8	5.5	14	III
9	8-9	6.2	15	
10	9-10	6.8	16	IV
11	10-11	7.4	17	
12	11-12	8	18	V
13	12-13	8.4	19	
14	13-14	8.8	20	VI
15	14-15	9.2	21	
16	15-16	9.6	22	VII

3.4.3 Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 (SPSS Inc. Chicago, IL, USA). Bland-Altman plots were constructed to assess agreement

between cardiac output and cardiac power output. Intra-class correlation coefficient (ICC) and coefficient of repeatability (CoR) were calculated to establish within subject change in performance and the 95% limits of agreement respectively. Standard Error of Measurement (SEM) was also reported.

3.4.4 Results

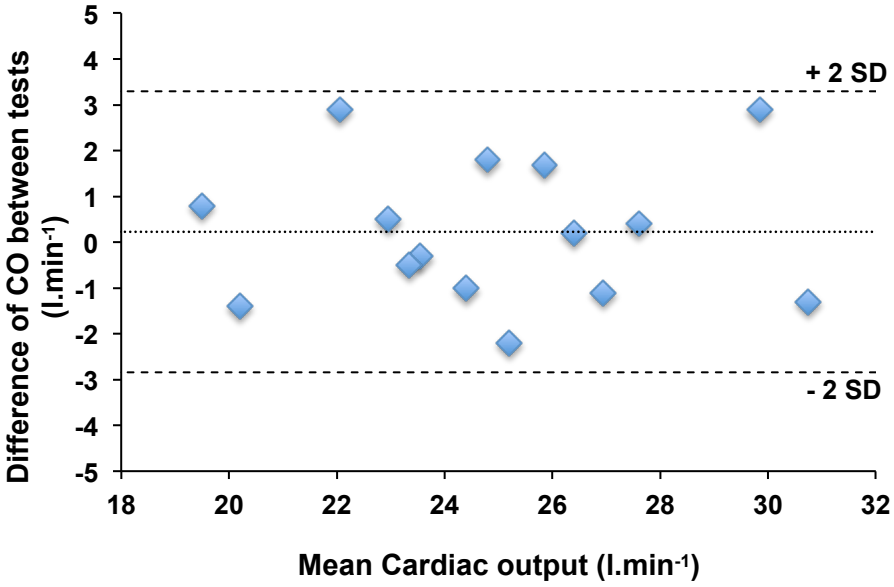
Duplicate mean and standard deviation values for both CO_{max} and CPO_{max} are displayed in Table 3.3. ICC for duplicate measures of CO_{max} and CPO_{max} showed the test to be reliable and consistent. Equally the SEM and CoR were low and again confirm acceptable reliability of the test. Bland-Altman analysis revealed that the mean difference between duplicate measures and limits of agreement of CO_{max} was 0.23 (-2.91 to 3.37) $l.min^{-1}$ (Figure 3.10), and 0.06 (-0.73 to 0.85) watts for CPO_{max} (Figure 3.11). The coefficient of variance for CO_{max} was 6.9%.

Table 3.3. Difference in duplicate measures of cardiac output, cardiac power output and oxygen consumption at maximal exercise.

	Test mean (SD)	**Re-test** mean (SD)	**ICC** (95% CI)	**CoR**	**SEM**
CO_{max} ($l.min^{-1}$)	25.01 (3.28)	24.78 (3.25)	0.942 (0.828, 0.980)	3.468	± 0.388
CPO_{max} (watts)	5.67 (1.12)	5.61 (1.15)	0.969 (0.904, 0.990)	1.765	± 0.239

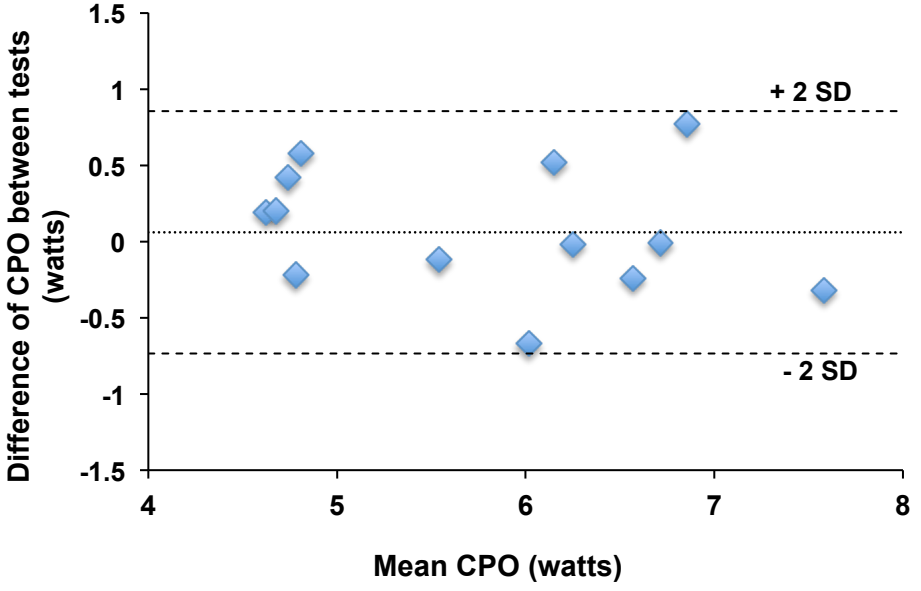
CI: confidence intervals; $CO_{:}$ cardiac output; CoR: coefficient of repeatability; $CPO_{:}$ cardiac power output; ICC =intra-class correlation; SD: standard deviation; SEM = standard error of measurement.

Figure 3.10 Bland-Altman plot to demonstrate limits of agreement between duplicate measures of maximal cardiac output



(CO: Cardiac output; SD: standard deviation)

Figure 3.11 Bland-Altman plot to demonstrate limits of agreement between duplicate measures of maximal cardiac power output



(CPO: Cardiac power output; SD: standard deviation)

3.4.5 Discussion

This is the first study to assess reproducibility of measurement of cardiac output and cardiac power output at maximal treadmill exercise, on different days, in healthy subjects, (using the CO_2 rebreathing method). This studied confirmed the test to be highly reproducible and consistent both within subjects and over time and with low measurement errors.

In previous studies done during submaximal exercise there has not been a significant difference between successive measurements of cardiac output using CO_2 rebreathing exponential method [Vanhees *et al* 2000, Da Silva *et al* 1985, Heigenhauser and Jones 1989]. Cooke *et al* and Hodges *et al* appear to be the only groups that have examined reproducibility using this method during maximal treadmill exercise [Cooke *et al* 1998, Hodges *et al* 2004]. Cooke *et al* repeated maximal exercise tests on 12 patients with heart failure 4 weeks apart and found a mean difference of -0.15 $l.min^{-1}$, CoR 1.13 $l.min^{-1}$, limits of agreement were -1.28 to 0.98 $l.min^{-1}$ and coefficient of variation was 7.08%. Hodges examined the differences in cardiac output at maximal exercise in 98 healthy males and females (equal ratio) during the same visit and exercise test. After completing the first rebreathe maneuver at maximal exercise, the patient partially recovered until the gases had been expired and then performed a second rebreathe maneuver. She found a mean difference of 0.34 $l.min^{-1}$, limits of agreement were -1.73 to 2.4 $l.min^{-1}$ and coefficient of variation was 6%.

3.5 Conclusions

Both CO_2 rebreathing and IGR are feasible and reproducible methods to measure resting CO and appear to be independently in agreement with doppler echocardiography, despite not agreeing with each other. Both were also highly reproducible, therefore if one were to consistently use either technique to compare longitudinal changes in resting CO, this would be acceptable.

However, measurement of cardiac output was significantly different using the IGR method (Innocor) and the CO_2 rebreathing method (Medgraphics) at both rest and exercise. Although there was a linear increase in CO with both methods, as workload increased, the relation between values using both methods changed from rest to exercise and so can not be used interchangeably or be corrected with a

simple formula.

Measurement of CO_{max} and CPO_{max} during maximal treadmill exercise using the CO_2 rebreathing method (Medgraphics) was shown to be reliable and consistent.

Therefore for the purposes of this thesis, I concluded that although different rebreathing methods were available, the most reliable, consistent and appropriate method to assess both resting and maximal CO and CPO was using the CO_2 rebreathing method.

Chapter 4

Cardiovascular physiological effects of weight carriage using a pregnancy simulator

Chapter 4

Study IV: Cardiovascular effects of weight carriage using a pregnancy simulator

4.1 Introduction

Changes in body mass during pregnancy can have a significant impact on patients with heart disease and, as such, pose significant challenges to clinicians in obstetrics, internal medicine, cardiology and anaesthesiology. Weight gain tends to precipitate or worsen symptoms of dyspnoea and fatigue [Milne 1978, Zib 1999], that may also mimic typical heart failure symptoms [Gei 2001]. When objectively tested, such as with symptom-limited treadmill exercise testing or submaximal walk tests (e.g. Shuttle or 6-minute walk tests), a reduction in exercise capacity would be noted. Formal cardiopulmonary exercise (CPX) testing is likely to show decreased peak O_2 consumption (VO_{2max}) [Artal 1986, Sady 1990], thus suggesting a new onset of or an exacerbation of pre-existing heart failure. It is often clinically difficult to differentiate whether the worsening symptoms and exercise intolerance are due to progressive cardiac impairment or merely secondary to weight gain. To resolve these issues, it is necessary to measure the overall function of the heart directly. Such a method of cardiac evaluation has become available and has been previously described [Tan 1986, Tan 1987], and can also be applied in the interdisciplinary field of maternal cardiology. The new conceptual basis is that each heart, whether normal, athletic or diseased, has its own ceiling performance above which it cannot exceed without intrinsic modification, such as through corrective surgery. The ceiling performance can be measured during maximum cardiac stimulation, however achieved. In clinical practice, a physiological, non-invasive means of maximally stimulating the heart is by conducting a symptom-limited exercise test. The haemodynamic variable that best represents overall organ function is cardiac power output (CPO) [Cotter 2003, Williams 2005], which when measured at peak exercise (CPO_{max}) has been shown to be the strongest predictor of prognosis in patients with heart failure [Williams 2001, Lang 2009].

The impact of weight gain in pregnancy on exercise ability and the reserve function of the cardiovascular system can be subdivided into three major components: (i) the effects of carrying increased inert mass, (ii) the effects of

perfusing the extra tissue mass, and (iii) the combined effects of other factors, including the musculoskeletal, metabolic, neurohormonal and psychological effects of weight gain. In this investigation, as a first step, we set out to investigate the effect of increased inert mass upon exercise ability and cardiac function independent of changes in vasculature, metabolic and neurohormonal changes. During pregnancy, the average weight gain from pre-conception to term is 13 kg (range 7–19 kg) [Ferrari 2014]. This amount of weight gain can be simulated with the use a device called the "*Empathy Belly*" (Figure 4.1).

4.2 Purpose and hypothesis of the study

The purpose of the study was to examine the effects of *"Empathy Belly"* on aerobic exercise capacity and cardiac function at maximal exercise in healthy pre-menopausal female subjects.

The hypotheses tested in this investigation were

(i) The carriage of *"Empathy Belly"*, simulating the extra weight gain at full term pregnancy, during maximal treadmill exercise, would result in a reduction in exercise duration and a concomitant decrease in VO_{2max}

(ii) Reductions in exercise duration and VO_{2max} are associated with a proportional reduction in peak cardiac performance as represent by CPO_{max}

(iii) Conventional indirect indicators of cardiac function are as reliable as direct measures of overall cardiac function during exercise stress testing with weight loading.

4.3 Ethical approval

Ethical approval was approved by the Leeds (West) Ethics Committee.

4.4 Methods

4.4.1 Study participants

Female volunteers were recruited by direct invitation from colleagues at the University of Leeds and Leeds General Infirmary and friends and family members. Subjects attended a dedicated cardiopulmonary exercise laboratory at the Leeds

General Infirmary, and were screened and assessed by the investigator to establish that they were healthy and had no physical disability that would prevent them from exercising fully or carrying weight. Only those free from cardio-respiratory and neuromuscular problems, who were normotensive, BMI < 30 $kg.m^{-2}$, and not taking medications proceeded to participate in the study. The first visit also allowed familiarization with the equipment and environment (treadmill, breathing equipment and maneuvers).

Cardiopulmonary exercise testing was then performed over 2 subsequent visits, initially at baseline and then whilst wearing a pregnancy simulator, in the form of an *"Empathy Belly"* (Birthways, Inc, Vashon Island, USA) (Figure 4.1) [http://www.empathybelly.org]. The *"Empathy Belly"* is a weighted cloth garment that simulates the latter stages of pregnancy, by allowing the subject to experience the effects and distribution of weight carriage. It has a number of weighted components, which enabled up to 14.5kg of external weight carriage. The amount of weight worn was guided by the maximum amount the subject was able to tolerate without discomfort.

4.4.2 Cardiopulmonary exercise tests

An initial symptom-limited, maximal treadmill exercise test was performed, using the Bruce protocol, with the Medgraphic Ultima metabolic cart (Medgraphics Corporation, St. Paul, Minnesota, USA) and continuous ECG monitoring to measure and monitor breath-by-breath rates of ventilation, O_2 consumption (VO_2), CO_2 production (VCO_2), beat-by-beat heart rate (HR) and exercise duration. Manual cuff sphygmomanometry was used to measure systolic and diastolic blood pressures (SBP and DBP) in mm Hg. A second peak single-stage exercise test was performed after 45 minutes rest, to target the peak workload attained during the prior incremental test and enable measurement of cardiac output using the CO_2 re-breathing technique [Vanhees *et al* 2000]. Detailed explanation of the testing procedure and equipment used is outlined in Chapter 2.

4.4.3 Statistics

All data were analysed using SPSS. Data are presented as mean ± standard deviation, or as counts with proportions. Statistical comparisons were made with Student's paired, two-tailed t test. A *P* value of < 0.05 was considered to be statistically significant.

Figure 4.1. A. Schematic diagram of an *"Empathy Belly"*

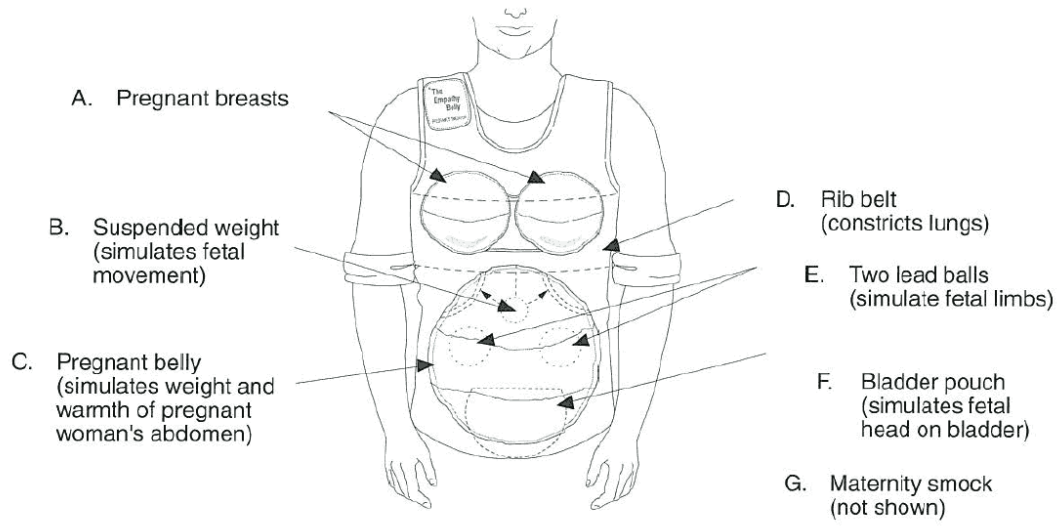
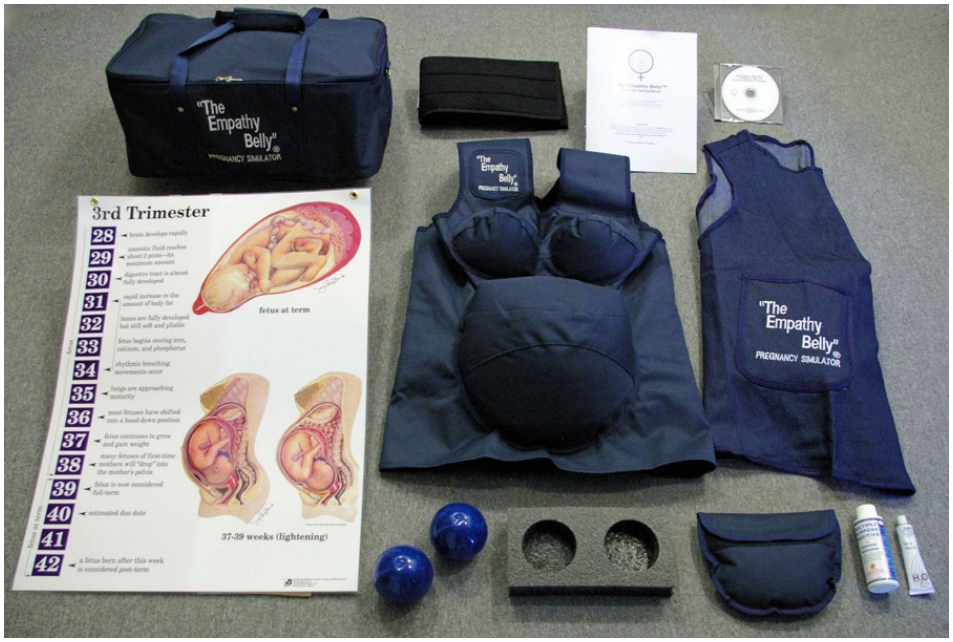


Diagram of the pregnancy simulator suit (*"Empathy Belly"*), showing the distribution of weight. http://www.empathybelly.org

Figure 4.1 B. Photographic image of *"Empathy Belly"* parts



Simulator pregnancy suit (*"Empathy Belly"*), round weighted walls, smock and comparison to diagram of anatomical changes in pregnancy. http://www.empathybelly.org

Figure 4.1 C. A volunteer wearing an *"Empathy Belly"*

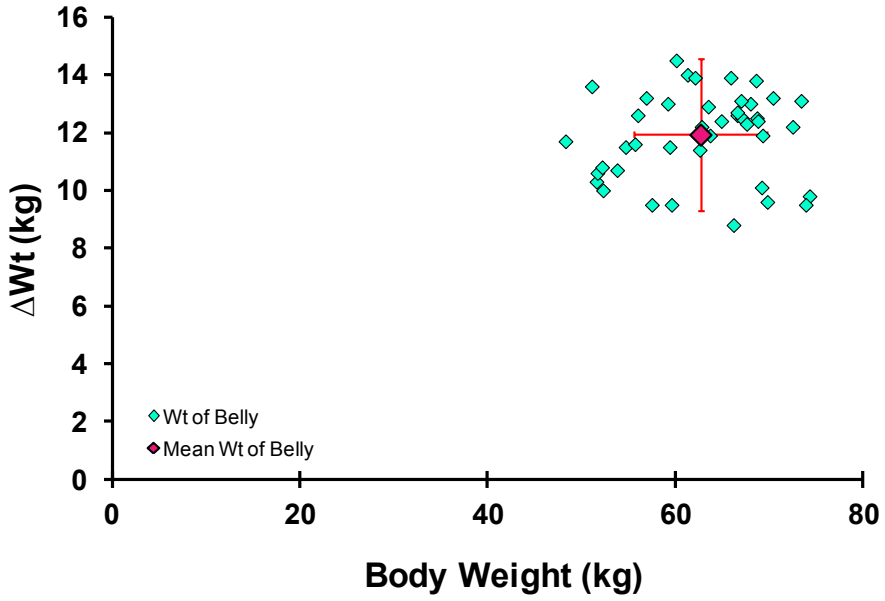
Front and side view of a volunteer performing a cardiopulmonary exercise test, whilst wearing the pregnancy simulator suit (*"Empathy Belly"*).

4.5 Results

4.5.1 Study population baseline characteristics

A total of 45 female volunteers were screened and 42 eligible participants were recruited, all of whom completed the study without any complication. All subjects were healthy and active, taking no regular medication, and had no impediment to exercise. The mean age was 26.2 ± 7.4 years, mean baseline body mass (BM) was 62.7±7.1 kg, and mean BMI was 22.4 ± 1.9 $kg.m^{-2}$. Load carriage in the form of the *"Empathy Belly"* garment (Belly) averaged 11.9 ± 1.5kg, which was equivalent to 19.2 ± 3.0% of the subjects' body weight (Figure 4.2). Since wearing the Belly is considered to be a simulation of the extra body mass gained at full-term pregnancy, in this investigation the combined inert mass of the Belly and the body mass of each subject will be supposed to be equivalent to the total body mass (74.7 ± 7.4 kg) at full-term pregnancy.

Figure 4.2: Graph of individual and mean Belly weights relative to the body weights of participants.



4.5.2 Gaseous exchanges and central haemodynamics during peak exercise

During exercise testing, there were no adverse events and all subjects exercised to their volitional exhaustion, above a minimum respiratory exchange ratio (RER) of 1.1. At peak exercise, there was a small difference between RER_{max} for the control (C, without loading) and weighted (B, *"Empathy Belly"*) tests (RER_{max} C: 1.23 ± 0.08, B: 1.20 ± 0.07; P = 0.042). During control tests, 15 stopped exercise due to leg fatigue, 12 due to breathlessness, 5 to general fatigue, 1 due to dizziness and 8 were hot or had a dry mouth. With Belly loading, 20 stopped due to leg fatigue, 8 due to breathlessness, 7 due to general fatigue, 2 were dizzy, 3 had back pain and 2 struggled to run with the belly. As shown in Figures 4.4, 4.6 and Table 4.1, 39 of 42 participants exercised for a shorter duration when wearing the Belly. Thus, the average duration using the Bruce protocol was 13.5 ± 2.6 min during control exercise, and this decreased significantly with Belly to 11.8 ± 1.9 min (P < 0.001). In Figure 4.5 A, the down-sloping trend of data points showed a tendency for lower exercise duration with higher total weight carriage (body mass and inert mass). Figure 4.5 B shows that while carrying the Belly garment of 9-15 kg some participants managed to maintain the same exercise duration as without extra weight, while others decreased by as much as 5 minutes of the Bruce protocol treadmill exercise, with no obvious relationship between the actual weights carried

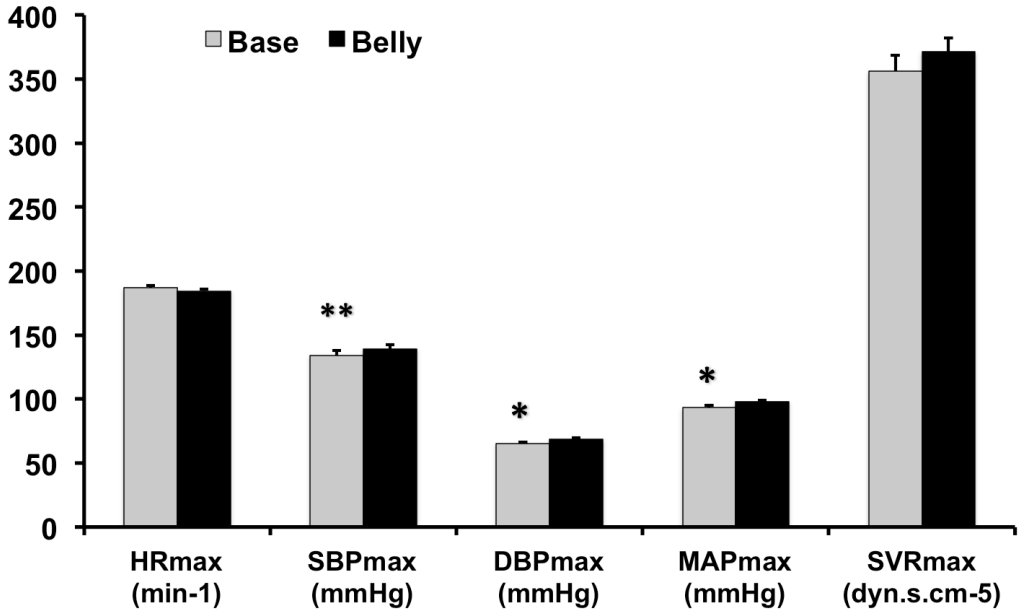
and exercise diminution. The VO_{2max} was also significantly decreased (Figure 4.5 C, C: 2.78 ± 0.47, Belly, B: 2.67 ± 0.45 $L.min^{-1}$, P = 0.012), but the reduction was even more marked when the O_2 uptake was corrected for body mass VO_{2max}/kg (C: 44.57 ± 7.47, B: 35.92 ± 5.38, $P < 10^{-12}$) as shown in Figure 4.5 D. The peak minute ventilation (VE_{max}) was significantly lower during Belly loading (C: 99.4 ± 21.5, B: 94.8 ± 21.4 $L.min^{-1}$, P = 0.007), whereas end-tidal pCO_{2max} ($ETpCO_{2max}$) were not significantly different (C: 37.1 ± 4.9, Belly; 37.8 ± 4.7 mm Hg, P = 0.53).

At peak exercise, the heart rate (HR_{max}), was slightly but significantly lower with Belly loading (C: 186.8 ± 11.0, B: 184.4 ± 11.2 min^{-1}, P = 0.00144). The peak stroke volumes were not significantly different (SV_{max}, C: 119.8 ± 16.3, B: 120.9 ± 18.7 ml, P = 0.679). The product of these two factors, cardiac output, was not significantly altered by the inert mass loading (CO_{max}, C: 21.4 ± 2.8, B: 21.6 ± 3.2 $l.min^{-1}$, p = 0.626). In contrast, the heart generated greater systemic arterial pressures with physical loading, with increases in both systolic (ΔSBP_{B-C} = 5.1 mm Hg [Confidence Interval, CI: 1.2, 9.1]) and diastolic (ΔDBP_{B-C} = 3.5 mm Hg [CI: 1.2, 5.7]) pressures with Belly loading during peak exercise. The mean arterial pressure at peak exercise (MAP_{max}) was significantly higher during loading (C: 93.3 ± 11.3, B; 97.7 ± 9.5 mm Hg, P < 0.001). These occurred in the absence of significant difference in systemic vascular resistance (SVR) at peak exercise (C: 356 ± 79, B: 371 ± 71 $dyn.s.cm^{-5}$, P = 0.104). When subjects were loaded with the Belly during peak treadmill exercise, the heart generated and imparted significantly greater rates of cardiac hydraulic energy (C: 4.40 ± 0.68, B: 4.66 ± 0.73 W, P = 0.015), mainly through producing significantly greater work at each stroke (C: 151.3 ± 24.2, B: 160.2 ± 25.8 g.m, P = 0.025). As shown in Figure 4.5 E, the up-sloping trend of datapoints suggest that there was a tendency of greater cardiac power output with increasing total weight (weight of body+Belly). The percentage increase in peak cardiac power was significant at 6.8% (95% CI: 2.4%, 11.2%). However, the surrogate index of cardiac power, $CircP_{max}$ (C: 372 ± 91, B: 372 ± 88 mmHg.ml $O_2.min^{-1}$, P = 0.95) was not significantly altered by the Belly loading during peak exercise (Figure 4.5F).

The impact of the inert mass carriage (Belly) on physical functional reserve, as measured by aerobic exercise capacity, is significantly reduced and associated with the significant reduction in treadmill exercise duration, as shown in Figure 4.6 A. If the VO_{2max} were to be expressed with correction for body mass, then the reduction appears even more marked (Figure 4.6 B). In contrast, when cardiac function was directly measured and represented as peak exercise cardiac power, then despite reduced exercise capacity, cardiac performance was nevertheless

higher with load bearing on treadmill (Figure 4.6 C). The relative mean changes of various physical and cardiac variables after Belly loading during peak treadmill CPX are shown in Figure 4.7. The most marked decrease with loaded exercise was in exercise duration followed by VO_{2max}, while the most marked increase was in CPO_{max} followed by SW_{max}. The flow generating capacities of the heart (CO_{max} and SV_{max}) were not significantly changed with loaded exercise, as was a surrogate ($CircP_{max}$) for peak cardiac power.

Figure 4.3 Maximal exercise variables at baseline and with *"Empathy Belly"*.



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. *: $p<0.01$; **: $p<0.05$

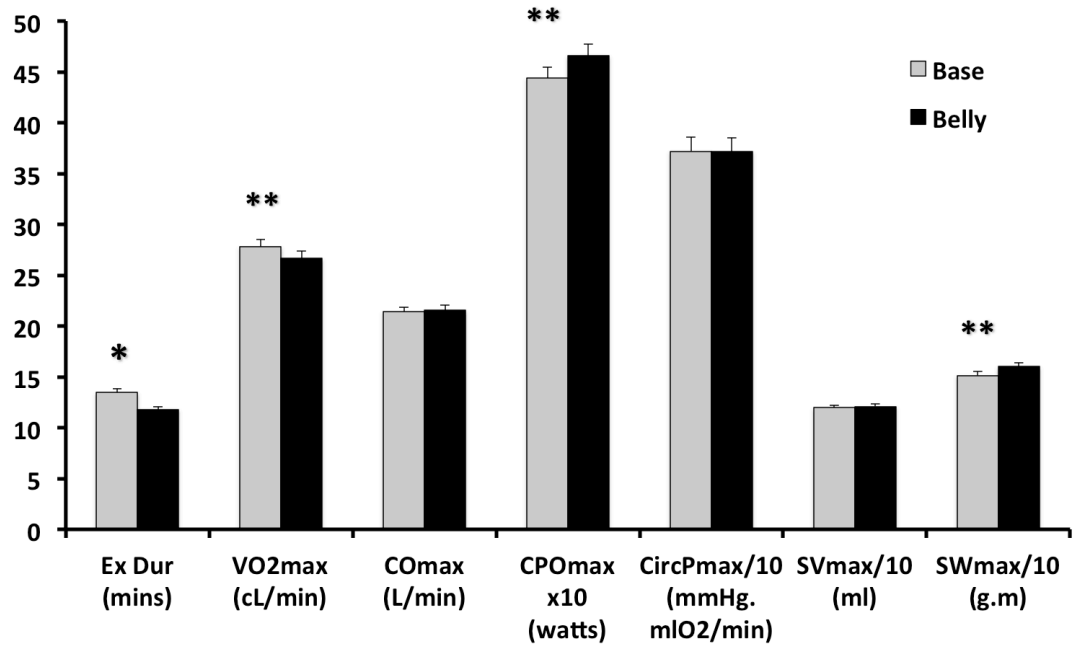
Differences in mean exercise variables between an unloaded (Base) test and test with the *"Empathy Belly"* (Belly) are displayed. The y axis shows absolute values. There is a significantly higher SBP ($p = 0.014$), DBP ($p = 0.002$) and MAP ($p = 0.001$) at maximal exercise when wearing the *"Empathy Belly"*, but no significant difference in HR or SVR.

Table 4.1 Maximal exercise variables at baseline and with *"Empathy Belly"*.

Variables	Base	Belly	P value	Δ	Δ%
	Mean (SD)	Mean (SD)		Mean (95% CI)	Mean (95% CI)
ExDur (mins)	13.5 (2.6)	11.8 (1.9)	<0.001	-1.7 (-2.1, -1.3)	-11.6 (-14.1, -9.2)
VO_{2max} ($ml.min^{-1}$)	2781 (465)	2665 (453)	0.012	-115 (-196, -35)	-3.7 (-6.5, -0.9)
VO_{2max}/kg ($ml.kg.min^{-1}$)	44.6 (7.5)	35.7 (5.2)	<0.001	-8.8 (-10.3, -7.4)	-19.2 (-21.7, -16.6)
VCO_{2max} ($ml.min^{-1}$)	3400 (585)	3151 (573)	0.002	-250 (-398, -101)	-6.3 (-10.6, -2.0)
HR_{max} (min^{-1})	186.8 (11.0)	184.4 (11.2)	<0.01	-2.4 (-3.8, -1.4)	-1.3 (-2.0, -0.5)
SV_{max} (ml)	119.8 (16.3)	120.9 (18.7)	0.679	1.0 (-3.9, 5.9)	1.4 (-2.4, 5.3)
CO_{max} ($l.min^{-1}$)	21.4 (2.8)	21.6 (3.2)	0.626	0.2 (-0.6, 0.9)	1.1 (-2.0, 4.2)
SBP_{max} (mmHg)	134.1 (24.9)	139.2 (20.4)	0.014	5.1 (1.2, 9.1)	5.0 (1.9, 8.1)
DBP_{max} (mmHg)	65.3 (8.2)	68.8 (7.8)	0.002	3.5 (1.2, 5.7)	6.1 (2.7, 9.5)
MAP_{max} (mmHg)	93.3 (11.3)	97.7 (9.5)	0.001	4.6 (2.3, 6.9)	5.6 (2.9, 8.2)
SVR_{max} ($dyn.s.cm^{-5}$)	356.4 (79.2)	371.3 (70.5)	0.032	14.9 (1.8, 28.1)	5.5 (1.4, 9.6)
SW_{max} (g.m)	151.3 (24.2)	160.2 (25.8)	0.025	8.9 (1.4, 16.4)	7.1 (2.1, 12.2)
CPO_{max} (watts)	4.40 (0.68)	4.66 (0.73)	0.015	0.26 (0.07, 0.45)	6.8 (2.4, 11.2)
$CircP_{max}$ ($mmHg.ml.O_2.min^{-1}$)	372 (91)	372 (88)	0.95	-0.5 (-15.9, 14.9)	0.9 (-3.3, 5.0)

Data presented as mean (SD, standard deviation). CI: confidence intervals; CO: cardiac output; CircP: circulatory power; CPO: cardiac power output; DBP: Diastolic blood pressure; Ex Dur: exercise duration; HR: heart rate; MAP: mean arterial blood pressure; max: values at peak exercise; SBP: systolic blood pressure; SV: stroke volume; SVR: systemic vascular resistance; SW: stroke work; VO_2: oxygen consumption; VCO_2: carbon dioxide production

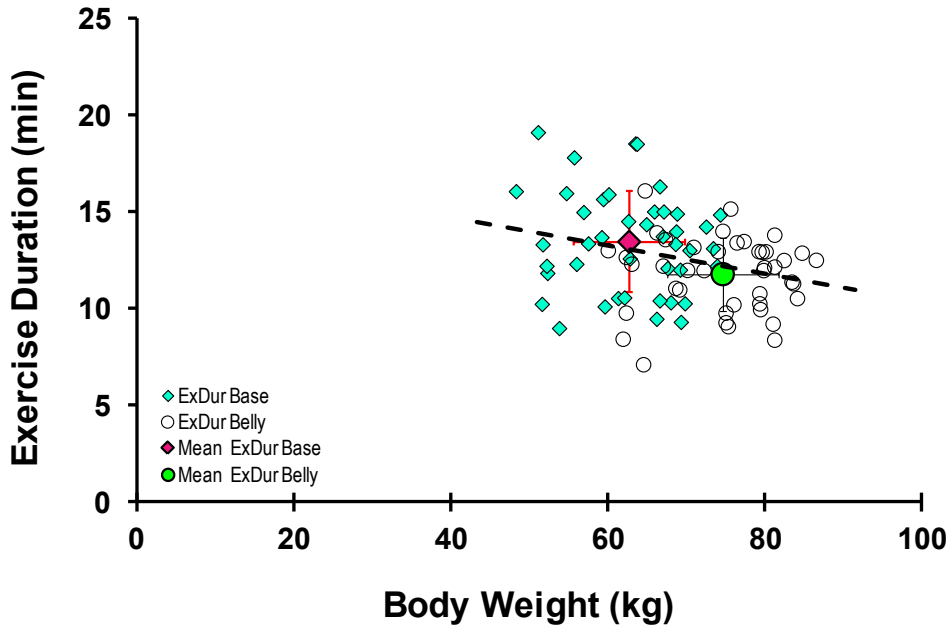
Figure 4.4 Maximal exercise variables at baseline and with *"Empathy Belly"*.



Ex Dur: exercise duration; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: Circulatory power; SV: stroke volume; SW: stroke work. *: $p<0.01$; **: $p<0.05$

Differences in mean exercise variables between an unloaded (Base) test and test with the *"Empathy Belly"* (Belly) are displayed. The y axis shows absolute values. There is a significantly lower exercise duration ($p < 0.001$) and VO_{2max} ($p= 0.012$) at maximal exercise when wearing the *"Empathy Belly"*, however both CPO_{max} ($p= 0.015$) and SW_{max} ($p = 0.025$) were significantly higher.

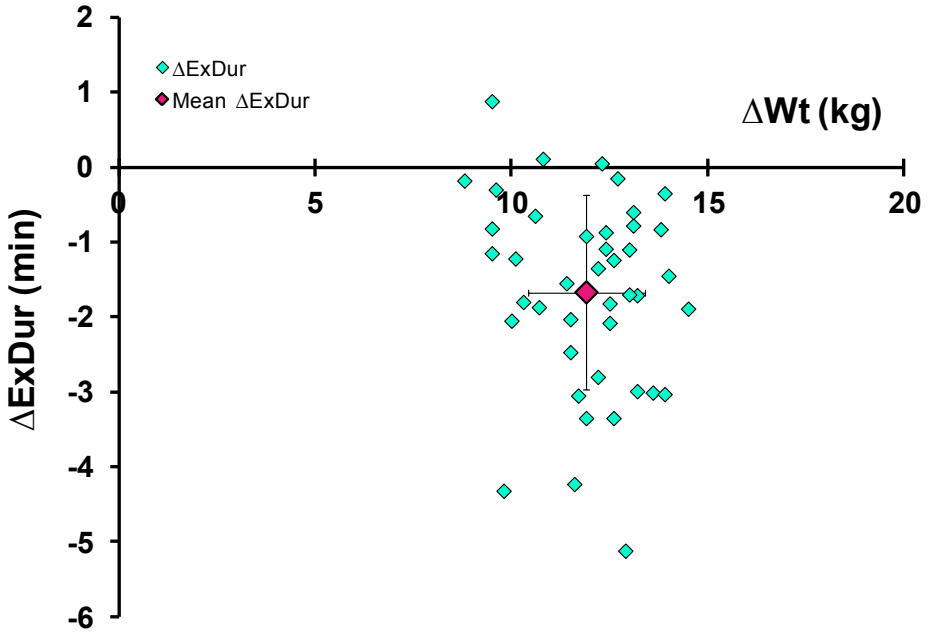
Figure 4.5 A. Comparison of exercise duration with and without *"Empathy Belly"*



Ex Dur: exercise duration; Base: unloaded test; Belly: test wearing pregnancy simulator suit

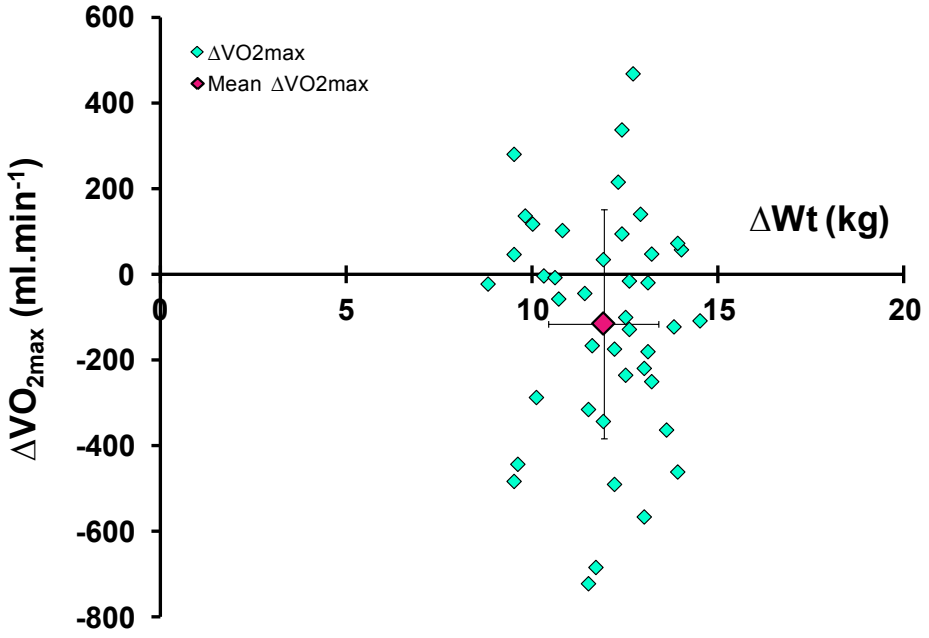
The figure shows a comparison of exercise duration in minutes, whilst performing treadmill exercise using the Bruce protocol, between a baseline unloaded test (blue diamonds) and when wearing the *"Empathy Belly"* (clear circles). The red diamond shows mean baseline test and green circle the mean loaded test exercise duration. The down-sloping dashed regression line for all the data points suggests that there was a tendency towards greater exercise intolerance with higher total weights.

Figure 4.5 B. Change in exercise duration with load carriage wearing the *"Empathy Belly"*



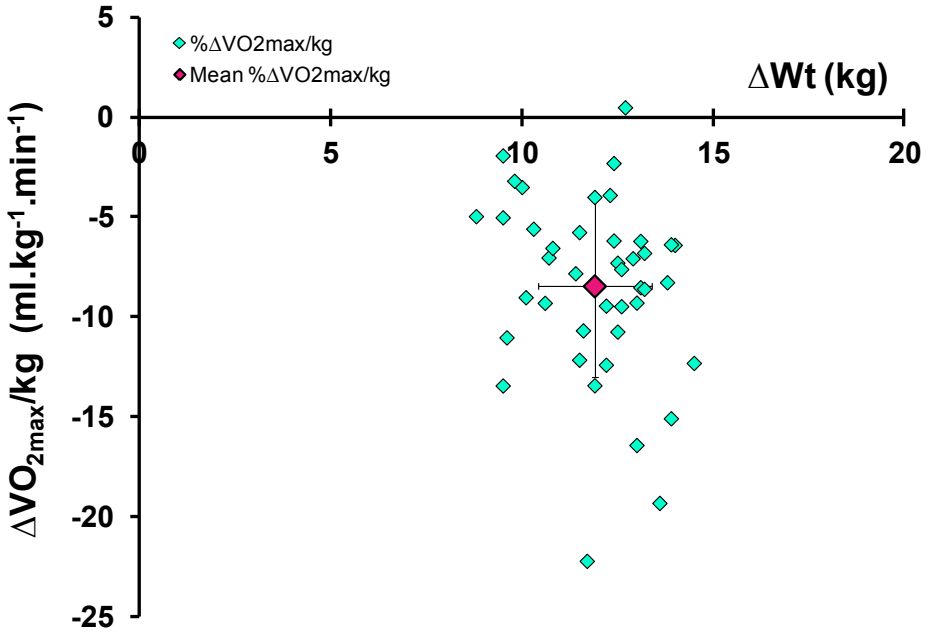
The figure shows the change in treadmill exercise durations (ΔExDur in minutes) from baseline (zero-weight carriage) to carriage of the *"Empathy Belly"* (ΔWt, kg). This showed that while carrying the *"Empathy Belly"*, some participants managed to maintain the same exercise duration as without extra weight, while others decreased by as much as 5 mins with no clear relationship between the actual weight carried and exercise diminution.

Figure 4.5 C. The change in peak oxygen consumption (ΔVO_{2max}) with load carriage wearing the *"Empathy Belly"*



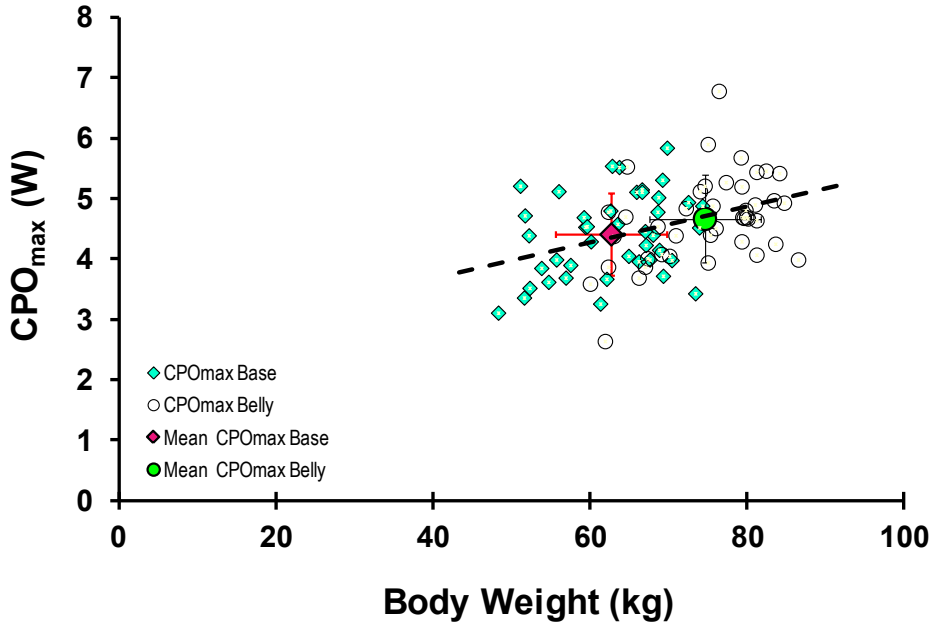
The figure shows the change in VO_{2max} (Δ VO_{2max}) from baseline (zero-weight carriage) to carriage of the *"Empathy Belly"* (ΔWt, kg). The VO_{2max} was significantly decreased when wearing the *"Empathy Belly"* (Base: 2.78 ± 0.47, Belly: 2.67 ± 0.45 $L.min^{-1}$, P = 0.012).

Figure 4.5 D. The change in peak oxygen consumptions corrected for body weight (ΔVO_{2max}/kg) with load carriage wearing the *"Empathy Belly"*.



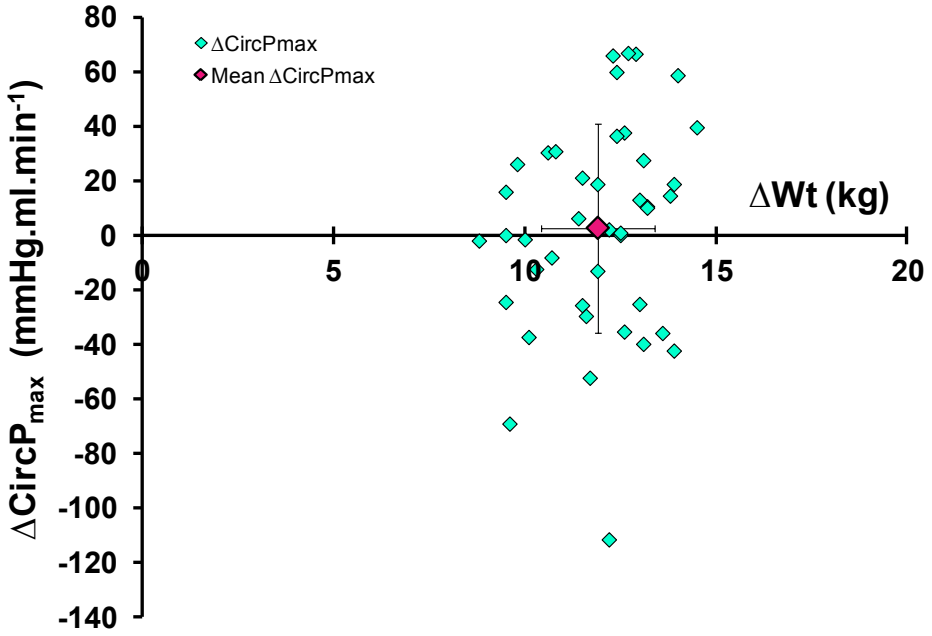
The figure shows the change in VO_{2max}/kg (Δ $VO_{2max/kg}$) from baseline (zero-weight carriage) to carriage of the *"Empathy Belly"* garment (ΔWt, kg). There was a more marked reduction in O_2 uptake wearing the pregnancy simulator suit when VO_{2max} was corrected for body mass VO_{2max}/kg (Base: 44.57 ± 7.47, Belly: 35.92 ± 5.38, $P < 10^{-12}$).

Figure 4.5 E. Comparison of peak cardiac power outputs (CPO_{max} in watts) with and without *"Empathy Belly"*



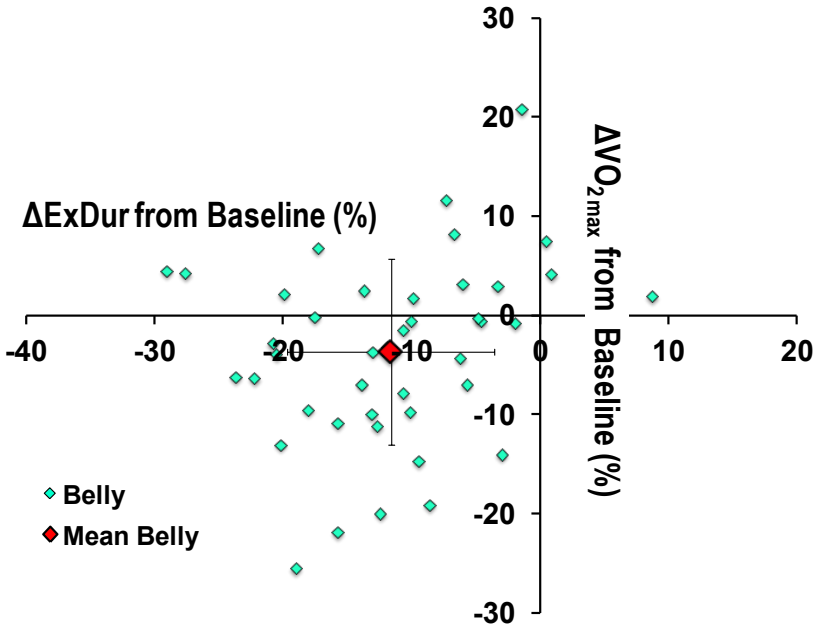
The figure shows a comparison of peak cardiac power outputs, whilst performing treadmill exercise, between a baseline unloaded test (blue diamonds) and when wearing the *"Empathy Belly"* garment (clear circles). The up-sloping dashed regression line for all the data points suggests there was a tendency towards higher peak cardiac power with higher total weight carriage. The mean differences were (Base (Red diamond): 4.40 ± 0.68, Belly (Green circle): 4.66 ± 0.73 W, P = 0.015)

Figure 4.5 F. The change in peak circulatory power with load carriage wearing the *"Empathy Belly"*.



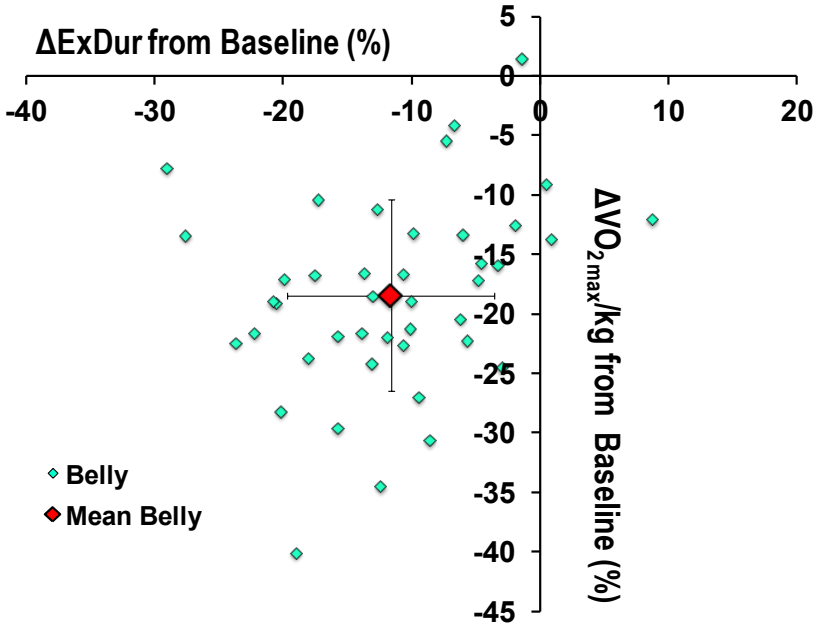
The figure shows the change in peak circulatory power ($\Delta CircP_{max}$, a surrogate indicator of cardiac power) from baseline (zero-weight carriage) to carriage of the *"Empathy Belly"* (ΔWt, kg). $CircP_{max}$ was not significantly altered by the Belly loading during peak exercise (Base: 372 ± 91, Belly: 372 ± 88 mmHg.ml O_2.min^{-1}, P = 0.95).

Figure 4.6. A. The relationship between change in peak O_2 consumption and change in exercise duration with weight loading wearing the Empathy belly.



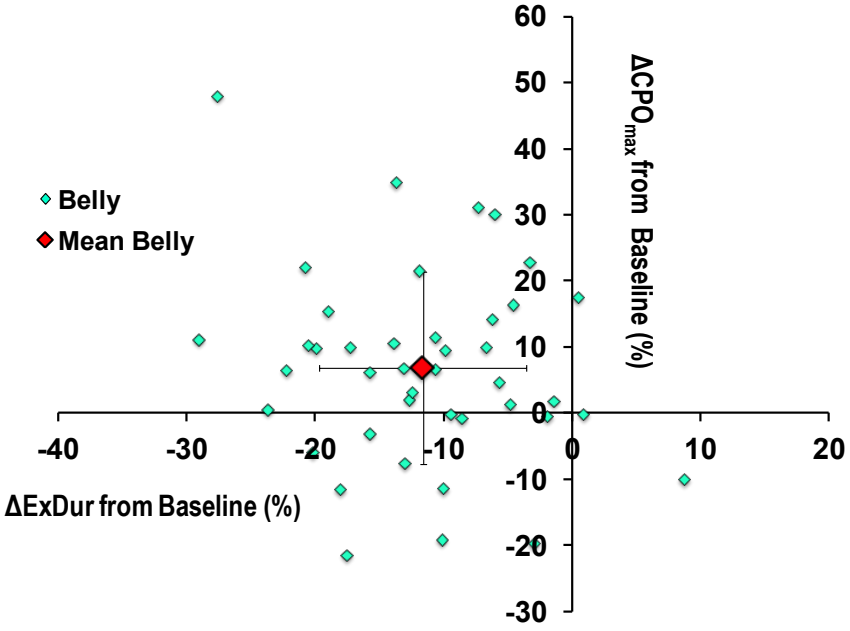
The figure shows a concomitant reduction in peak O_2 consumption (ΔVO_{2max}) and exercise duration (ΔExDur) during maximal treadmill exercise, from baseline when weight loaded with the *"Empathy Belly"*.

Figure 4.6 B. The relationship between change in peak O_2 consumption per kilogram and change in exercise duration with weight loading wearing the Empathy belly.



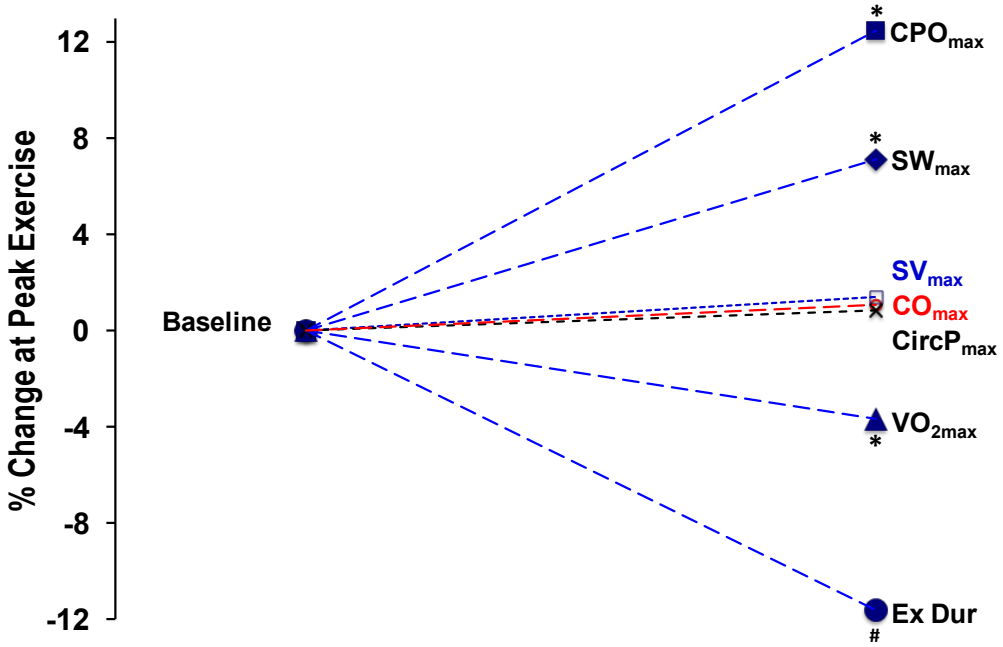
The figure shows a more marked concomitant reduction in peak O_2 consumption per kilogram (ΔVO_{2max}/kg) and exercise duration (ΔExDur) during maximal treadmill exercise, from baseline when weight loaded with the *"Empathy Belly"*.

Figure 4.6 C. The relationship between change in peak Cardiac power output and change in exercise duration with weight loading wearing the Empathy belly.



The figure shows an increase in peak cardiac power output (ΔCPO_{max}) with a divergent reduction in and exercise duration (ΔExDur) during maximal treadmill exercise, from baseline when weight loaded with the *"Empathy Belly"*.

Figure 4.7 Delta maximal exercise variables with *"Empathy Belly"*.



$CircP_{max}$: peak circulatory power; CPO_{max}: cardiac power output; SW_{max}: peak stroke work. SV_{max}: peak stroke volume; CO_{max}: peak cardiac output; VO_{2max}: oxygen consumption; Ex Dur: exercise duration. *P<0.05, #P<0.001.

The figure shows the changes in exercise variables with weight loading wearing the *"Empathy Belly"*. The most marked decrease was in exercise duration followed by VO_{2max}, while the most marked increase was in CPO_{max} followed by SW_{max}. The flow generating capacities of the heart (CO_{max} and SV_{max}) were not significantly changed with loaded exercise, as was a surrogate ($CircP_{max}$) for peak cardiac power.

Table 4.2 Markers of exercise effort between baseline and *"Empathy Belly"*

	Weight Mean (SD)	**Peak RER** Mean (SD)	**Peak VE** Mean (SD)	**$ETpCO_2$ Peak** Mean (SD)
Base	62.7 (7.1)	1.23 (0.08)	99.4 (21.5)	37.1 (4.9)
Belly	74.7 (7.4)	1.20 (0.07)	94.8 (21.4)	37.8 (4.7)
P value		0.042	0.007	0.525

RER: respiratory exchange ratio; VE: minute ventilation; $ETpCO_2$: end-tidal partial pressure of carbon dioxide.

4.5.3 Resting central haemodynamics and gas exchange

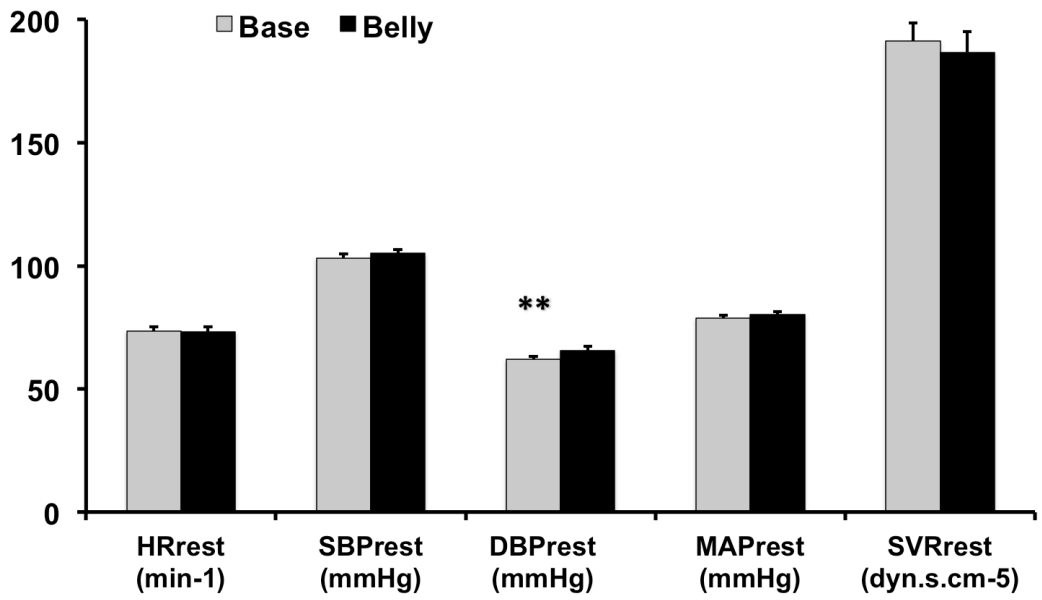
The only resting variables that significantly changed were diastolic blood pressure, which increased by 6.5% with weight carriage ($p = 0.03$), and VCO_{2rest}, which increased by 23.8%. Heart rate, systolic blood pressure, mean arterial blood pressure and SVR did not significantly change, as shown in Table 4.3. Resting indicators of cardiac function including cardiac output, cardiac power output, stroke volume and stroke work all showed some increase but none significantly.

Table 4.3 Resting variables at baseline and with *"Empathy Belly"*.

Variables	Base	Belly	P value	Δ	Δ%
	Mean (SD)	Mean (SD)		Mean (95% CI)	Mean (95% CI)
VO_{2rest} ($ml.min^{-1}$)	218 (70)	239 (88)	0.180	20 (-9.8, 50.1)	18.1 (1.6, 34.7)
VO_{2rest}/kg ($ml.kg.min^{-1}$)	3.5 (1.3)	3.2 (1.2)	0.192	-0.3 (-0.8, 0.2)	-0.5 (-14.9, 14.0)
VCO_{2rest} ($ml.min^{-1}$)	181 (57)	207 (75)	0.043	26 (1.5, 50.2)	23.8 (5.0, 42.5)
HR_{rest} (min^{-1})	73.5 (10.3)	73.3 (12.8)	0.781	-0.3 (-3.5, 3.0)	0.3 (-4.5, 5.1)
SV_{rest} (ml)	47.9 (12.5)	52.1 (18.6)	0.067	4.2 (-0.2, 8.6)	9.8 (1.4, 18.2)
CO_{rest} ($l.min^{-1}$)	3.5 (0.9)	3.8 (1.3)	0.076	0.3 (-0.03, 0.6)	9.2 (0.3, 18.0)
SBP_{rest} (mmHg)	103.2 (11.2)	105.1 (10.6)	0.154	1.9 (-0.7, 4.5)	2.3 (-0.4, 5.0)
DBP_{rest} (mmHg)	62.0 (7.6)	65.5 (10.8)	0.030	3.5 (0.2, 6.8)	6.5 (1.1, 11.9)
MAP_{rest} (mmHg)	78.8 (8.1)	80.2 (8.1)	0.417	1.4 (-1.2, 4.1)	2.4 (-1.0, 5.8)
SVR_{rest} ($dyn.s.cm^{-5}$)	1912 (477)	1868 (551)	0.506	-44 (-182, 94)	-1.1 (-8.1, 5.8)
SW_{rest} (g.m)	51.4 (14.6)	56.5 (20.4)	0.058	5.1 (-0.02, 10.2)	12.5 (3.0, 22.1)
CPO_{rest} (watts)	0.62 (0.18)	0.68 (0.24)	0.125	0.06 (0.0, 0.12)	12.5 (2.1, 22.9)

Data presented as mean (SD, standard deviation); CI: confidence intervals; CO: cardiac output; CPO: cardiac power output; DBP: Diastolic blood pressure; HR: heart rate; MAP: mean arterial blood pressure; rest: values at rest; SBP: systolic blood pressure; SV: stroke volume; SVR: systemic vascular resistance; SW: stroke work; VO_2: oxygen consumption; VCO_2: carbon dioxide production

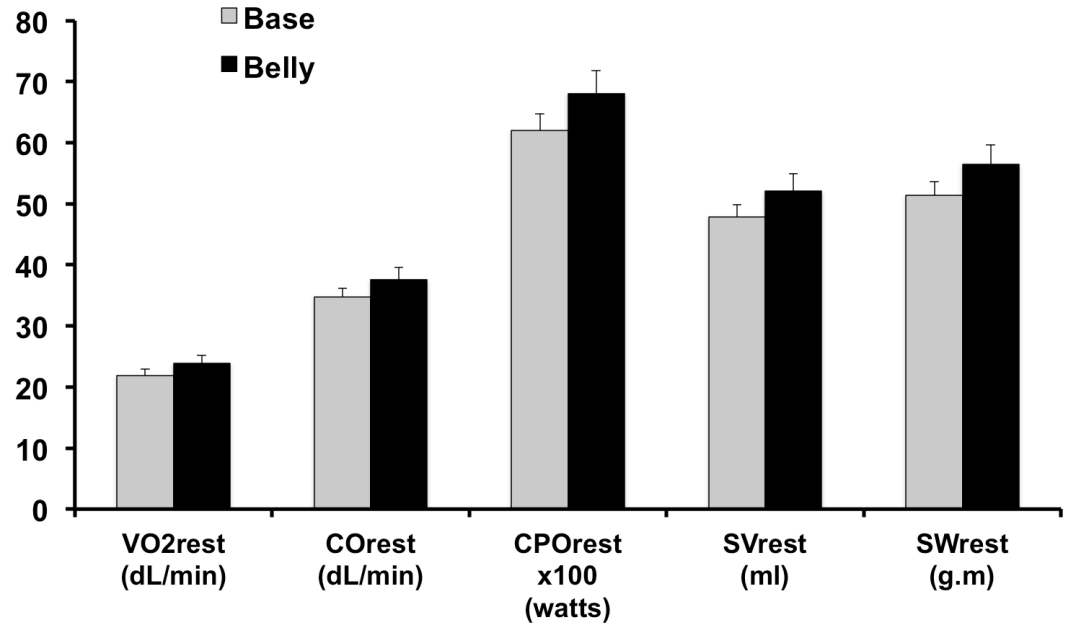
Figure 4.8 Resting variables at baseline and with "*Empathy Belly"*



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. **: $p<0.05$

Differences in mean resting variables between an unloaded (Base) test and loaded test with the *"Empathy Belly"* (Belly) are displayed. The y axis shows absolute values. There was a significantly higher diastolic blood pressure ($p = 0.03$) when wearing the *"Empathy Belly"*, however there were no significant difference in heart rate, systolic or mean arterial pressure or systemic vascular resistance.

Figure 4.9 Resting cardiac variables at baseline and with *"Empathy Belly"*.



VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Differences in mean resting cardiac variables between an unloaded (Base) test and loaded test with the *"Empathy Belly"* (Belly) are displayed. The y axis shows absolute values. There were no significantly differences in cardiac variables when wearing the *"Empathy Belly"*, although there appeared to be a trend to higher measures of resting cardiac function.

4.5.4 Reserve haemodynamics

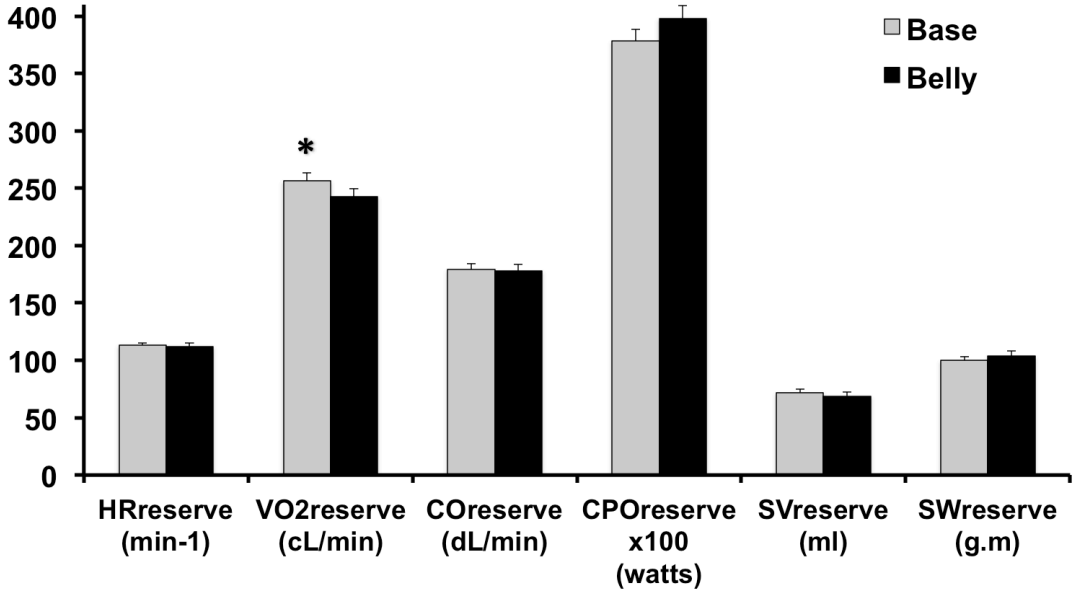
There was a significant reduction in reserve oxygen consumption with weight carriage (p = 0.005) and no significant changes in heart rate reserve, cardiac output reserve, cardiac power output reserve, stroke volume reserve or stroke work reserve, as shown in Figure 4.6. However reserve cardiac power output significantly increased by 6%, when expressed as a percentage change from baseline, shown in Table 4.4.

Table 4.4 Reserve variables at baseline and with *"Empathy Belly"*.

Variables	Base	Belly	P value	Δ	Δ%
	Mean (SD)	Mean (SD)		Mean (95% CI)	Mean (95% CI)
$VO_{2reserve}$ ($ml.min^{-1}$)	2562 (464)	2427 (455)	0.005	-136 (-221, -51)	-4.7 (-8.1, -1.3)
$VO_{2reserve}$/kg ($ml.kg.min^{-1}$)	41.0 (7.3)	32.5 (5.3)	<0.001	-8.5 (-10.0, -7.0)	-20.0 (-23.0, -17.1)
$HR_{reserve}$ (min^{-1})	113.3 (11.8)	112.1 (18.3)	0.894	-1.2 (-7.3, 4.9)	-0.2 (-5.8, 5.4)
$SV_{reserve}$ (ml)	71.9 (20.5)	68.8 (25.2)	0.323	-3.2 (-9.4, 3.0)	-3.4 (-11.9, 5.2)
$CO_{reserve}$ ($l.min^{-1}$)	17.9 (3.1)	17.8 (3.5)	0.808	-0.1 (-0.9, 0.7)	-0.2 (-4.2, 3.9)
SW_{rest} (g.m)	99.9 (23.3)	103.7 (29.9)	0.408	3.8 (-5.1, 12.8)	6.2 (-2.3, 14.6)
CPO_{rest} (watts)	3.78 (0.65)	3.98 (0.74)	0.076	0.20 (-0.01, 0.4)	6.4 (1.1, 11.7)

Data presented as mean (SD, standard deviation); CI: confidence intervals; CO: cardiac output; CPO: cardiac power output; HR: heart rate; SV: stroke volume; SW: stroke work; VO_2: oxygen consumption.

Figure 4.10 Reserve variables at baseline and with *"Empathy Belly"*



HR: heart rate; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work. *****: $p<0.01$.

Differences in mean reserve variables between an unloaded (Base) test and loaded test with the *"Empathy Belly"* (Belly) are displayed. The y axis shows absolute values. There was only a significant reduction in reserve oxygen consumption (VO2resreve) seen with weight loading with the *"Empathy Belly"* ($P < 0.001$). However there appeared to be a trend to higher cardiac power output reserve ($CPO_{reserve}$) with weight loading with the Belly.

4.6 Discussion

This study is the first to utilize a direct and comprehensive measure of cardiac function to test acute effects of weight changes to evaluate cardiac pumping capability in the absence of direct changes in vasculature, metabolic and neurohormonal status. The results show that the carriage of an inert weight in the form of an *"Empathy Belly"* (Figure 1) to simulate the net weight gained by women during the third trimester of pregnancy result in a significant 11.6% (95% CI: 9.2%, 14.1%) reduction in exercise duration during standard Bruce protocol treadmill exercise testing, accompanied by a significant reduction in peak oxygen consumption (VO_{2max}, P = 0.012). These observations supported our first hypothesis that the carriage of inert weight *per se* simulating the extra weight gain at full term pregnancy would result in a reduction in exercise capacity.

The effects of gestational weight gain on physical and functional reserves have previously been investigated using *submaximal* bicycle ergometric exercise testing, but such non-weight bearing type of exercise is rather unrepresentative of what pregnant women experience during a common activity, like walking or climbing stairs, which are weight-bearing. It is during these activities that the pregnant mothers experience breathlessness and fatigue that overlap with symptoms which heart failure patients complain. For clinicians caring for pregnant cardiac patients, it is essential to delineate whether these symptoms represent true development or exacerbation of HF or whether they occur as a result of sheer weight gain by directly measuring cardiac function. Moreover, to gauge whether the heart can cope with labour, a maximal instead of submaximal exercise test would be more informative, such as the methodology employed in our current study.

The rate of oxygen consumption at peak exercise (VO_{2max}) is most commonly expressed per kilogram of body weight, VO_{2max}/kg, and, as such, there was an even greater reduction of 18.8% (CI: 16.2%, 21.3%) with Belly carriage during peak treadmill exercise. According to conventional concepts in cardiological practice [Weber 1982, Myers 1998], these reductions suggest a reduction in cardiac pumping performance during peak exercise with extra-load carriage. However, the rate of hydraulic energy generated and imparted into the circulation by the heart did not decrease with the extra weight carriage of the *"Empathy Belly"*. Instead, we observed a significant peak cardiac power increase of 6.8% (P = 0.015), indicating that our second hypothesis (that peak cardiac performance would follow the diminution in Belly-loaded exercise capacity) was not supported by experimental evidence. Of all the available variables, since peak cardiac power (CPO_{max}) is the most direct representation of overall cardiac function [Tan 2010], our results

therefore show that some conventionally utilized indirect indicators of cardiac performance are not reliable when used in assessing cardiac function in states of weight changes such as during pregnancy. This experimental result therefore does not support our third hypothesis, thereby questioning the reliability of conventional indirect indicators of cardiac function in traditional cardiological practice, such as VO_{2max}/kg [Mancini 1991], during states of weight gain.

The net effects of carrying the weight of an *"Empathy Belly"* are equivalent to the inert component of weight gain during third-trimester or full-term gestation. As shown in Figure 2 and Table 1, with increased body weight carriage, there was an increase in cardiac pumping performance at peak exercise despite diminution of exercise tolerance and aerobic metabolism. Exercise duration and oxygen consumption both fell significantly with weight carriage. In contrast, both cardiac power output and stroke work both significantly increased. One important inference we can draw is that, in the context of weight gain, a diminution of exercise tolerance (represented by exercise duration in this study) or aerobic capacity (VO_{2max}) can no longer be assumed to represent a reduction in cardiac pumping capability. It is also interesting to note that, unlike cardiac power, the often-used surrogate index of cardiac power, circulatory power, did not show any significant difference with versus without Belly loading, suggesting that it may not be a fully reliable surrogate.

This is the first study examining the physiological responses to weight loading using the *"Empathy Belly"* type of pregnancy simulator. Published studies examining the effects of weight loading have primarily focused on assessing indirect measures, including oxygen consumption during submaximal exercise in a predominantly male military population wearing a range of rucksack designs and weights [Soule 1969, Soule 1978]. So far, it is not known how much weight carriage alone contributes to changes in peak oxygen consumption and cardiac function. However it has been shown that oxygen consumption during load carriage is directly dependent upon factors such as amount of exercise, body weight and weight of load carriage [Haisman 1988]. It has been estimated that for each kilogram of weight carried, the VO_2 increases by 33.5ml/min [Borghols 1978]. Moreover in the latter stages of pregnancy oxygen consumption increases during weight bearing submaximal exercise, but does not change with non-weight bearing exercise (cycling) [Knuttgen 1974, Ueland 1973]. Hence there appears to be a close relationship between increase in body weight and the additional oxygen consumption [Hutchinson 1981].

The fact that extra weight carriage produces dichotomous outcomes of lower exercise capacity, but higher peak cardiac performance would require further discussion. Previous studies reported that at the same submaximal level of exercise on a treadmill, load carriage compared to unloaded exercise has been shown to be

accompanied with higher heart rates and oxygen consumption [Soule *et al* 1969]. Two studies by Sagiv *et al* in 1994 and 2002, compared the differences in submaximal haemodynamics between two different loads after a period of fixed rate walking in healthy males [Sagiv *et al* 1994] and healthy elderly subjects [Sagiv *et al* 1995]. Unfortunately, the studies by Sagiv and colleagues did not measure cardiac output in the unloaded state to compare to the loaded state. Bhambhani's studies in 1997 compared the physiological responses during submaximal treadmill exercise with graded loads (15 and 20kg) and showed significant differences in HR, VO_2, CO, and MAP during both load carriage tests compared to the unloaded tests [Bhambhani *et al* 1997]. Our study at maximal exercise showed a similar increase in MAP, but did not show significant differences in heart rate or CO and inversely showed a significant reduction in VO_2 at peak exercise with loading.

If the heart is required to perform at a higher level (by a ΔIncrement) at a selected submaximal level of exercise, in order to reach the same peak level of exercise (be it measured by the same stage of Bruce protocol, or the same VO_{2max}), the heart will be required to perform above the previous peak by the same Δ Increment. For example, at a submaximal level of exercise, the cardiac output without loading is CO_{submax}, and with weight loading it is increased to CO_{submax}+ ΔCO. In order to support the same peak exercise level with weight loading as without loading, the CO_{max} will need to be increased by a similar amount of ΔCO to give a higher CO_{max} = (CO_{max}+ ΔCO). Interestingly, as shown in Table 4.2, this was not attained as there was no significant change in CO_{max} ($P = 0.626$). However, from physics and fluid dynamics, we know that the entity that maintains the continuous circulation is not flow, but hydraulic energy imparted by the heart [Tan 2010]. There was a corresponding and significant 6.8% ($P = 0.015$) increase in CPO_{max} with Belly, but this was presumably insufficient to prevent a significant fall in exercise capacity, as measured by exercise duration ($P < 0.001$) and VO_{2max} ($P = 0.012$).

Our investigation is the first to report the cardiovascular hydraulic impacts of extra load carriage on treadmills at maximal exertion. From the mechanistic viewpoint, performing treadmill exercise, whilst carrying weight, is a combination of both isometric and isotonic exercise. Cardiovascular responses during isotonic exercises consist of volume loading to the left ventricle, and the response is proportional to the amount of active skeletal muscles and intensity of exercise. There is an increase in cardiac output, heart rate and stroke volume with a decrease in SVR and less increase in blood pressure [Fletcher 1995, Vella 2005]. Cardiovascular responses during isometric exercises such as hand grip or weight-lifting, consist more of a pressure loading effect on the left ventricle than isotonic exercise, with a greater rise in arterial pressure, a smaller increase in cardiac output, primarily

through an increase in heart rate and no change in stroke volume and usually no significant change in systemic vascular resistance [Laird *et al* 1979]. The carriage of the extra Belly load during weight-bearing treadmill exercise is sustained by additional isometric muscle contractions, and this demands a greater hydraulic pressure to perfuse the recruited isometrically contracting postural muscles. This necessitates a higher pressure generating capacity by the cardiac pump without compromising its flow generation, both of which are supplied by the greater hydraulic energy imparted by the heart [Tan 1987, Chantler 2006].

All subjects on both occasions exercised to RER_{max} above 1.1, which is conventionally accepted as adequate efforts for peak exercise (Table 4.2) [Milani 2004]. It was noteworthy that no significant change in $ETpCO_{2max}$ between control and weight-loaded tests was observed. Knowing that the participants do not have hyperventilatory syndrome and were highly motivated individuals who performed each CPX test to their true volitional exhaustion irrespective of load carriage, it is reasonable to infer that the similar $ETpCO_{2max}$ values represent attainment of equivalent exercise limits during the unloaded and loaded exercise tests.

4.61 Study Limitations

The study was limited by the inability to measure flow (cardiac output) and blood pressure continuously non-invasively during peak exercise. This is not technically possible with the methods used, and can only be more accurately done with invasive measurements, which were felt not to be ethically appropriate. Equally we did not use any sophisticated scaling methods via measurements of body compositions using DEXA or whole body MRI scanning. This was felt not necessary, as individuals did not have a broad range of body sizes and they were used as their own controls and so had no change in body mass between tests. The effects of *"Empathy Belly"* on physical and cardiac performances in this investigation were acute effects, whereas during pregnancy, the weight gains are gradual and only reach the equivalent of the *"Empathy Belly"* mass at full term or during the third trimester. The difference between the total weight carrying the *"Empathy Belly"* and the unloaded weight was temporally more akin to the difference between the full-term versus post-partum weights. Equally it was not possible to simulate all the areas of weight change, particularly around the lower limbs or account for the musculoskeletal and respiratory changes that occur due to the enlarged uterus that occur in the latter stages of pregnancy. These issues would beneficially be addressed in future studies, and the adoption of the method of directly measuring cardiac reserve would also help in elucidating other component

impacts of pregnancy on the cardiovascular system other than from inert weight gain.

4.7 Conclusion

At peak exercise, weight loading using a pregnancy simulator resulted in a significant reduction in exercise duration and O_2 consumption. Opposed to this, the hearts of healthy volunteers responded with significantly enhanced performance. Therefore, there was a divergent response in physical versus cardiac performances from wearing an inert mass equivalent to a standard weight gain at full-term pregnancy. When evaluating cardiac function in states of body weight alterations such as during pregnancy, it is no longer safe to assume that changes in VO_{2max} would represent similar changes in cardiac functional reserve. One useful clinical practice point to draw from this investigation is that, to resolve any uncertainty about whether cardiac function has deteriorated or not during pregnancy, it would seem prudent to assess cardiac functional reserve directly, instead of indirectly.

Chapter 5

Cardiovascular physiological effects of additional weight loading using a pregnancy simulator and rucksack

Chapter 5

Study V: Cardiovascular effects of additional weight loading using a pregnancy simulator and rucksack

5.1 Introduction

Obesity epidemic is an established and burgeoning health issue in industrialized societies [WHO 2000; Caballero 2007]. The risks are exacerbated in obese pregnant mothers, as at least two lives are involved in every pregnancy. The CEMACH 2007 Report has highlighted that “obese pregnant women with a body mass index (BMI) > 30 are far more likely to die”, necessitating guidelines on ideal weight gains during pregnancy to be drawn [Rasmussen *et al* 2009; Siega-Riz *et al* 2013; CMACE/RCOG 2010]. The Institute of Medicine guidelines recommend a total weight gain throughout pregnancy to be between 5 and 18 kg, depending on the pre-pregnancy weight category, recommending most weight gain for those underweight and least for obese women [Institute of Medicine 2009]. Approximately 40% of normal weight and 60% of overweight women gain more weight than the recommended guidelines [Chu 2009].

In cardiology, the issue of obesity is further complicated by the puzzle termed “obesity paradox” [Lavie *et al* 2013; Clark *et al* 2014; Padwal *et al* 2014], partly because cardiac functional responses to weight gains have been under investigated and poorly understood. Obesity and pregnancy can be viewed as different modes of body weight gain, and the impacts of extra tissue masses on the diseased hearts of cardiac patients pose significant challenges to practitioners in specialties including anaesthesiology, bariatric surgery, cardiology, midwifery and obstetrics. However, in cardiological practice, there is considerable uncertainty about the best ways of evaluating cardiac function in the context of significant weight gains. The carriage of excess body masses often results in the precipitation or worsening of symptoms of exertional dyspnoea and fatigue in both pregnancy and obesity [Gibson 2000; Jensen *et al* 2009; Bernhardt & Babb 2014]. This was confirmed in study IV (Chapter 4), where weight carriage caused significant reductions in both exercise duration and VO_{2max}. It has also been reported that scaling VO_{2max} by body mass highlights these differences further in both pregnancy and obesity [Wolfe 2005; Sady et al 1990; Hothi *et al* 2015]. Decrease in $VO_{2max/kg}$ is often interpreted as an

indirect evidence of progressive cardiac dysfunction and can often lead to introduction of heart failure therapies at one end, to exclusion from bariatric surgery and even termination of pregnancy at the other end. However, we now know from study IV (Chapter 4) that there were divergent responses in physical versus cardiac performances, wearing an inert mass equivalent to a standard weight gain at full-term pregnancy. As a second step, it was necessary to establish if the same principle held true with a further increase in weight carriage. Moreover, are incremental deterioration and improvements seen in physical and cardiac performances respectively?

5.2 Purpose and hypothesis of the study

The purpose of this study was to examine the effects incremental weight carriage, using the *"Empathy Belly"* and a rucksack together, on aerobic exercise capacity and cardiac function at maximal exercise in healthy pre-menopausal female subjects.

The hypotheses tested in this investigation were

(i) The carriage of *"Empathy Belly"* and a rucksack, simulating the excessive weight gain at full term pregnancy, during maximal treadmill exercise, would result in a further reduction in exercise duration and a concomitant decrease in VO_{2max}.

(ii) There will be an incremental increase in peak cardiac performance with further weight loading.

(iii) Conventional indirect indicators of cardiac function remain unreliable as measures of overall cardiac function, during exercise testing with increased weight loading.

5.3 Ethical approval

Ethical approval was approved by the Leeds (West) Ethics Committee.

5.4 Methods

Female subjects were recruited by direct invitation from colleagues at the University of Leeds, Leeds General Infirmary and friends and family members. Subjects attended a dedicated cardiopulmonary exercise laboratory at the Leeds General

Infirmary, and were screened and assessed by the investigator to establish that they were healthy and had no physical disability that would prevent them from exercising fully or carrying weight. Only those free from cardio-respiratory and neuromuscular problems, who were normotensive, BMI < 30 $kg.m^{-2}$, and not taking medications proceeded to participate in the study. The first visit also allowed familiarization with the equipment and environment (treadmill, breathing equipment and maneuvers).

Cardiopulmonary exercise testing was then performed over 3 subsequent visits. Test 1; baseline test; Test 2: wearing the *"Empathy Belly"* (Birthways, Inc, Vashon Island, USA) and Test 3: wearing the *"Empathy Belly"* and a weighted rucksack. In this study subjects were randomised to perform the tests in different orders (either A: Test 1, Test 2, Test 3; B: Test 2, Test 3, Test 1; C: Test 3, Test 1, Test 2).

In Test 2, the *"Empathy Belly"* weight was fixed at 12.5Kg for all subjects. In Test 3, the total weight of the *"Empathy Belly"* and weighted rucksack was estimated to be 35% of the subject's body weight. The weight used in the rucksack was in the form of dumbbell weights to the nearest 1kg. The weight carried was distributed more evenly to enable subject comfort and prevent injury during exercise.

Prior to visits, participants were instructed to refrain from vigorous physical activity for 24 hours prior to testing and to abstain from alcohol for 12 hours and have no food or caffeine for at least 3 hours beforehand.

5.4.2 Cardiopulmonary exercise tests

An initial symptom-limited, maximal treadmill exercise test was performed, using the Bruce protocol, with the Medgraphic Ultima metabolic cart (Medgraphics Corporation, St. Paul, Minnesota, USA) and continuous ECG monitoring to measure and monitor breath-by-breath rates of ventilation, O_2 consumption (VO_2), CO_2 production (VCO_2), beat-by-beat heart rate (HR) and exercise duration. Manual cuff sphygmomanometry was used to measure systolic and diastolic blood pressures (SBP and DBP) in mm Hg. A second peak single-stage exercise test was performed after 45 minutes rest, to target the peak workload attained during the prior incremental test and enable measurement of cardiac output using the CO_2 re-breathing technique [Vanhees *et al* 2000]. Detailed explanation of the testing procedure and equipment used is outlined in the methods chapter (Chapter 2).

5.4.3 Statistics

All data were analysed using SPSS. Data are presented as mean ± standard deviation, or as counts with proportions. Statistical comparisons were made with Student's paired, two-tailed t test. A *P* value of < 0.05 was considered to be statistically significant.

5.5 Results

5.5.1 Study population baseline characteristics

A total of 26 female volunteers were screened and 25 eligible participants were recruited, all of whom completed the study without any complication. All subjects were healthy and active, taking no regular medication, and had no impediment to exercise. The mean age was 22.7 ± 3.4 years, mean baseline body mass (BM) was 63.1 ± 6.1kg and mean BMI was 22.2 ± 1.7kg.m^{-2}. Load carriage in the form of the *"Empathy Belly"* (Belly) averaged 12.8 ± 0.8kg, which was 20.5 ± 2.4% of the subjects' baseline BM. Load carriage wearing the Belly and rucksack (Sack) averaged 22.1 ± 2.3kg, which was 35 ± 2% of the subjects' baseline BM (Figure 5.1).

Since wearing the Belly is considered to be a simulation of the extra body mass gained at full-term pregnancy, in this investigation the combined inert mass of the Belly and the body mass of each subject will be supposed to be equivalent to the total body mass (74.7±7.4 kg) at full-term pregnancy. Similarly, the combination of bearing the Belly and the rucksack is regarded as a simulation of weight gain due to full-term pregnancy and obesity, giving the equivalent combined body mass of 85.2 ± 8.2 kg.

5.5.2 Gaseous exchanges and central haemodynamics during peak exercise

During exercise testing, there were no adverse events and all subjects exercised to their volitional exhaustion, above a minimum respiratory exchange ratio (RER) of 1.1. At peak exercise, there was a small stepwise decrease in peak RER from baseline control CPX (C, without loading, 1.23 ± 0.09), to loading with *"Empathy Belly"* during CPX (B: 1.20 ± 0.07; P=0.132), and to Rucksack + Belly loading CPX (R: 1.18 ± 0.06; P=0.012 vs C, and P = 0.424 vs B), shown in Table 5.1. Similarly,

there was a small stepwise decrease in peak minute ventilation, (VE_{max}) from baseline control load-free CPX (C: 103.5 ± 17.0), to belly-loaded CPX (B: 97.4 ± 20.2; P=0.106), and to CPX with rucksack + belly loading (R: 93.1 ± 20.0; P = 0.015 vs C, and P = 0.093 vs B). However, the end-tidal pCO_{2max} ($ETpCO_{2max}$) were neither significantly altered with belly loading (C: 38.3 ± 5.3, B: 37.8 ± 4.8 mm Hg, P = 0.468), nor with rucksack + belly loading (R: 38.0 ± 4.5 mm Hg, P = 0.422).

As shown in Figure 5.2A and Table 5.2, there was a stepwise progressive significant reduction in Bruce protocol exercise duration with each incremental inert mass loading during maximal CPX. Compared to control exercise (C: 14.5 ± 2.6 min), all participants but one exercised for a shorter duration when wearing the Belly (B: 12.5 ± 1.7 min, P < 0.001), and every subject reduced exercise duration with the combined inert masses (R: 11.9 ± 2.0 min (P < 0.001). In Figure 5.2B, there was a downward trend of decline in exercise duration with higher combined body and load carriage. Figure 5.3 shows that load carriage during CPX reduced the exercise duration from zero to over 5mins of the Bruce protocol, but there was no apparent relationship between the mass carried and the extent of reduction. The VO_{2max} was also significantly decreased with every increment of load carriage during CPX (Figure 5.3A, C: 2.90 ± 0.39, B: 2.76 ± 0.37, R: 2.65 ± 0.42 $L.min^{-1}$, all P = 0.02), but the reduction was even more marked when the O_2 uptake was corrected for the combined body and inert weight, VO_{2max}/kg (C: 46.4 ± 7.9, B: 36.5 ± 4.9, R: 31.3 ± 5.2, all P < 0.001) as shown in Figure 5.3B and 5.3C.

At peak exercise, the heart rate (HR_{max}), was slightly but significantly lower with Belly loading (C: 189.8 ± 9.4 min^{-1}, B: 187.7 ± 9.4 min^{-1}, P = 0.037), with a further fall with addition of the rucksack but not significantly (R: 186.4 ± 10.4 min^{-1}, P = 0.084), although the amplitudes of decrease were small (ΔHR_{max}, B: -1.1%, and R: -1.8%). The peak stroke volumes were not significantly different with either weight loading (SV_{max}, C: 123.9 ± 16.5 ml, B: 126.0 ± 20.8 ml, R: 125.9 ± 16.7 ml, all P > 0.5). The product of these two factors, cardiac output, was not significantly altered by the inert mass loading either (CO_{max}, C: 22.4 ± 2.2 $l.min^{-1}$, B: 22.9 ± 2.9 $l.min^{-1}$, R: 22.8 ± 2.5 $l.min^{-1}$, all P > 0.3). In contrast, with Belly loading during peak exercise, the systemic mean arterial pressures was significantly higher (C: 88.0 ± 9.5 mm Hg, B: 94.9 ± 9.0 mm Hg, P < 0.001), with a further rise with addition of the rucksack but incrementally not significantly (R: ΔMAP_{max}, 1.3 ± 7.5 mm Hg, P = 0.412). Compared to baseline systemic vascular resistance (SVR) during peak unloaded CPX (C: 316 ± 42 $dyn.s.cm^{-5}$), the SVR was slightly but significantly greater by 6.83 ± 13.56% (P = 0.019) with Belly loading and by 8.25 ± 14.61% (P = 0.011) with combined belly and rucksack loading. With Belly loading at peak CPX,

the heart imparted significantly greater rates of cardiac hydraulic energy (C: 4.38 ± 0.70 W, B: 4.81 ± 0.73 W, P = 0.001), but with addition of rucksack the further increment in CPO_{max} was not significant as shown in Figures 5.4A and 5.4B. Similarly, the heart produced significantly greater work at each stroke with Belly loading (C: 148.6 ± 26.6, B: 162.3 ± 28.8 g.m, P = 0.01) and with addition of rucksack (R: 164.7 ± 27.8, P = 0.002). However, the surrogate index of cardiac power, $CircP_{max}$ (C: 349 ± 73, B: 359 ± 73 mmHg.ml $O_2.min^{-1}$, P = 0.291) was neither significantly altered by the Belly loading during peak exercise, nor with additional rucksack loading (R: 357 ± 71 mmHg.ml $O_2.min^{-1}$, P = 0.59).

The relative mean changes of various physical and cardiac variables after loading with both Belly and Belly and Sack, during peak treadmill CPX are shown in Figures 5.5 and 5.6. The most marked decrease with loaded exercise was in exercise duration carrying the Belly and Sack, while the most marked increase was in CPO_{max} carrying the Belly and Sack. Additional reduction was seen in exercise duration and both VO_{2max} and $VO_{2max/kg}$ when more weight was carried. However there were no increases in CPO_{max} and its surrogates with additional weight carriage on top of the Belly.

The impact of additional load carriage (Belly and Sack) on aerobic exercise capacity is reduced further and associated with a more significant reduction in treadmill exercise duration (Figure 5.7). However cardiac power output at peak exercise appears to linearly increase, despite reduced exercise capacity, with increased load carriage (Figure 5.8). The dichotomous response of increasing CPO_{max} and decreasing VO_{2max} is more evident with increased load carriage (Figure 5.9). The pressure generating response also appears to be greater with increased load carriage (Figure 5.10).

Table 5.1 Markers of exercise effort between tests at baseline and with differential weight carriage.

	Weight Mean (SD)	Peak RER Mean (SD)	Peak VE Mean (SD)	$ETpCO_{2\ Peak}$ Mean (SD)
Base	63.1 (6.1)	1.23 (0.09)	103.5 (17.0)	38.3 (5.3)
Belly	75.8 (6.4)	1.20 (0.07)	97.4 (20.2)	37.8 (4.8)
Sack	85.1 (8.2)	1.18 (0.06)	93.1 (20.0)	38.0 (4.5)
Base vs Belly P value		0.132	0.106	0.468
Base vs Sack P value		0.012	0.015	0.422
Belly vs Sack P value		0.424	0.093	0.868

RER: respiratory exchange ratio; VE: minute ventilation; $ETpCO_2$: end-tidal partial pressure of carbon dioxide.

Figure 5.1. Weight loading with the *"Empathy Belly"* and *"Empathy Belly* & rucksack"

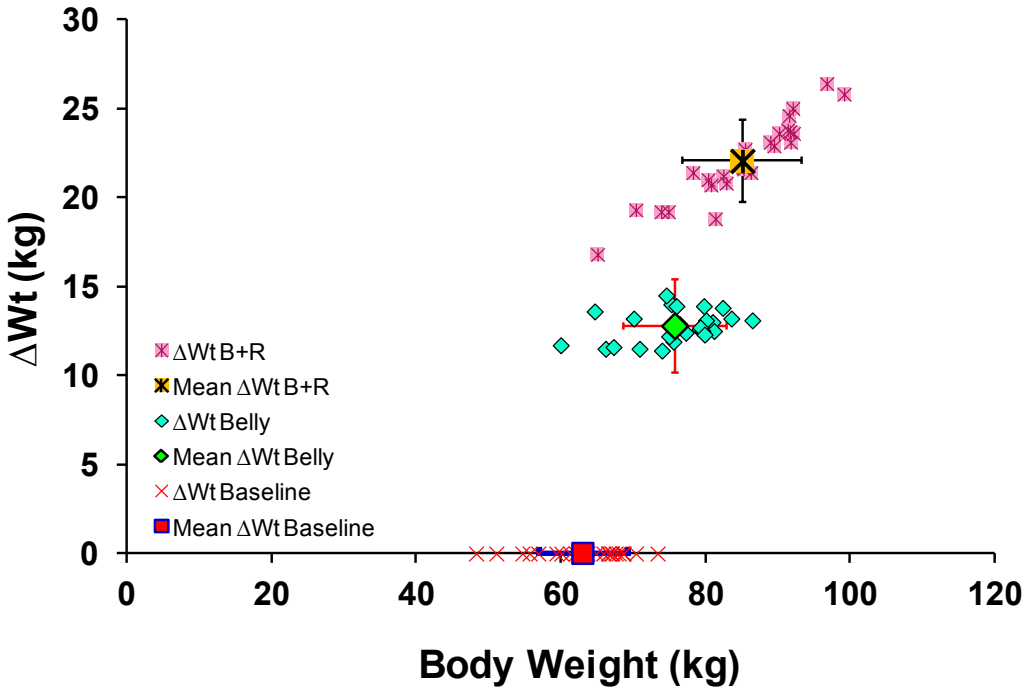


Table 5.2 A. Maximal exercise variables at baseline and with differential weight carriage.

Variables	Base	Belly	Sack	Base vs Belly	Base vs Sack	Belly vs Sack
	Mean (SD)	Mean (SD)	Mean (SD)	P value	P value	P value
Ex Dur (mins)	14.5±2.6	12.5±1.7	11.9±2.0	<0.001	<0.001	0.001
VO_{2max} ($ml.min^{-1}$)	2897±394	2756±372	2648±415	0.023	<0.001	0.013
VO_{2max}/kg ($ml.kg^{-1}.min^{-1}$)	46.4±7.9	36.5±4.9	31.3±5.2	<0.001	<0.001	<0.001
HR_{max} (min^{-1})	189.8±9.4)	187.7±9.4	186.4±10.4	0.037	0.002	0.084
SV_{max} (ml)	123.9±16.5	126.0±20.8	125.9±16.7	0.57	0.54	0.984
CO_{max} ($l.min^{-1}$)	22.4±2.2	22.9±2.9	22.8±2.5	0.321	0.372	0.927
SBP_{max} (mmHg)	120.4±17.1	130.0±16.8	134.2±14.8	<0.001	<0.001	0.172
DBP_{max} (mmHg)	63.4±8.4	69.4±9.4	71.5±10.4	<0.001	0.001	0.180
MAP_{max} (mmHg)	88.0±9.5	94.9±9.0	96.2±10.4	<0.001	<0.001	0.412
SVR_{max} ($dyn.s.cm^{-5}$)	316±42	337±52	341±50	0.019	0.011	0.712
SW_{max} (g.m)	148.6±26.6	162.3±28.8	164.7±27.8	0.01	0.002	0.561
CPO_{max} (watts)	4.38±0.70	4.81±0.73	4.87±0.7	0.001	<0.001	0.626
$CircP_{max}$ ($mmHg.ml.min^{-1}$)	349±73	359±73	357±71	0.291	0.59	0.566

Data presented as mean (SD, standard deviation). CI: confidence intervals; CO: cardiac output; CircP: circulatory power; CPO: cardiac power output; DBP: Diastolic blood pressure; Ex Dur: exercise duration; HR: heart rate; MAP: mean arterial blood pressure; max: values at peak exercise; SBP: systolic blood pressure; SV: stroke volume; SVR: systemic vascular resistance; SW: stroke work; VO_2: oxygen consumption.

Table 5.2 B. Delta changes between maximal exercise variables at baseline and with differential weight carriage.

Variables	Δ Base vs Belly Mean (SD) 95% CI	%Δ Base vs Belly Mean (SD) 95% CI	Δ Base vs Sack Mean (SD) 95% CI	%Δ Base vs Sack Mean (SD) 95% CI	Δ Belly vs Sack Mean (SD) 95% CI	%Δ Belly vs Sack Mean (SD) 95% CI
Ex Dur (mins)	-2.0 (1.3) -2.5, -1.5	-13.2 (7.3) -16.0, -10.3	-2.6 (1.3) -3.1, -2.1	-17.4 (7.9) -20.5, -14.4	-0.6 (0.7) -0.9, -0.3	-4.8 (6.2) -7.2, -2.4
$VO_{2\,max}$ ($ml.min^{-1}$)	-141 (264) -245, -38	-4.4 (9.3) -8.1, -0.8	-249 (228) -338, -159	-8.6 (7.9) -11.6, -5.5	-107 (189) -181, -33	-4.0 (7.0) -6.7, -1.2
VO_{2max}/kg ($ml.kg^{-1}.min^{-1}$)	-9.9 (5.1) -11.9, -7.9	-20.6 (8.2) -23.8, -17.4	-15.1 (4.5) -16.8, -13.3	-32.2 (6.3) -34.7, -29.8	-5.2 (2.3) -6.0, -4.3	-14.3 (6.3) -16.8, -11.9
HR_{max} (min^{-1})	-2.1 (4.8) -4.0, -0.2	-1.1 (2.6) -2.1, -0.1	-3.5 (5.1) -5.5, -1.5	-1.8 (2.7) -2.9, -0.8	-1.4 (3.8) -2.8, 0.1	0.7 (2.0) -0.1, 1.5
SV_{max} (ml)	2.0 (17.7) -4.9, 9.0	2.1 (13.4) -3.2, 7.3	2.0 (15.9) -4.3, 8.2	2.4 (12.0) -2.3, 7.1	-0.1 (14.8) -5.9, 5.8	1.0 (11.5) -3.5, 5.5
CO_{max} ($l.min^{-1}$)	0.48 (2.35) -0.45, 1.40	2.3 (9.8) -1.5, 6.1	0.43 (2.36) -0.50, 1.36	2.4 (10.3) -1.7, 6.4	-0.05 (2.50) -1.02, 0.93	0.54 (10.9) -3.7, 4.8
SBP_{max} (mmHg)	9.6 (11.0) 5.3, 13.9	8.5 (9.4) 4.9, 12.2	13.8 (13.9) 8.4, 19.3	12.7 (13.0) 7.6, 17.8	4.2 (15.1) -1.7, 10.1	4.2 (12.6) -0.7, 9.2
DBP_{max} (mmHg)	6.0 (6.0) 3.7, 8.3	9.8 (9.4) 6.1, 13.5	8.1 (7.3) 5.3, 11.0	13.2 (11.5) 8.7, 17.7	2.1 (7.7) -0.9. 5.1	3.6 (10.9) -0.7, 7.8
MAP_{max} (mmHg)	6.9 (6.9) 4.2, 9.6	8.3 (8.5) 5.0, 11.6	8.2 (7.1) 5.4, 11.0	9.6 (8.6) 6.3, 13.0	1.3 (7.5) -1.7, 4.2	1.5 (7.8) -1.6, 4.6
SVR_{max} ($dyn.s.cm^{-5}$)	20.3 (40.4) 4.4, 36.1	6.8 (13.6) 1.5, 12.1	24.0 (43.3) 7.0, 40.9	8.3 (14.6) 2.5, 14.0	3.7 (49.8) -15.8, 23.2	2.3 (14.7) -3.5, 8.0
SW_{max} (g.m)	13.7 (24.5) 4.1, 23.3	10.5 (16.9) 3.9, 17.1	16.1 (23.2) 7.0, 25.2	12.2 (16.1) 5.9, 18.5	2.1 (20.5) -5.6, 10.5	2.4 (13.4) -2.9, 7.6
CPO_{max} (watts)	0.43 (0.58) 0.20, 0.66	10.8 (13.5) 5.5, 16.1	0.49 (0.59) 0.26, 0.72	12.2 (14.1) 6.6, 17.7	0.06 (0.58) -0.17, 0.29	1.9 (13.1) -3.2, 7.0
$CircP_{max}$ (mmHg.ml $O_2.min^{-1}$)	10.2 (47.2) -8.3, 28.7	-4.4 (14.9) -10.2, 1.5	8.1 (73.6) -20.8, 36.9	4.9 (24.8) -4.9, 14.6	-3.1 (51.4) -23.3, 17.1	1.4 (23.4) -7.8, 10.5

Data presented as mean (SD, standard deviation). CI: confidence intervals; CO: cardiac output; CircP: circulatory power; CPO: cardiac power output; DBP: Diastolic blood pressure; Ex Dur: exercise duration; HR: heart rate; MAP: mean arterial blood pressure; max: values at peak exercise; SBP: systolic blood pressure; SV: stroke volume; SVR: systemic vascular resistance; SW: stroke work; VO_2: oxygen consumption.

Figure 5.2 A. Effect of loading with the *"Empathy Belly"* and *"Empathy Belly* & rucksack" on peak exercise capacity

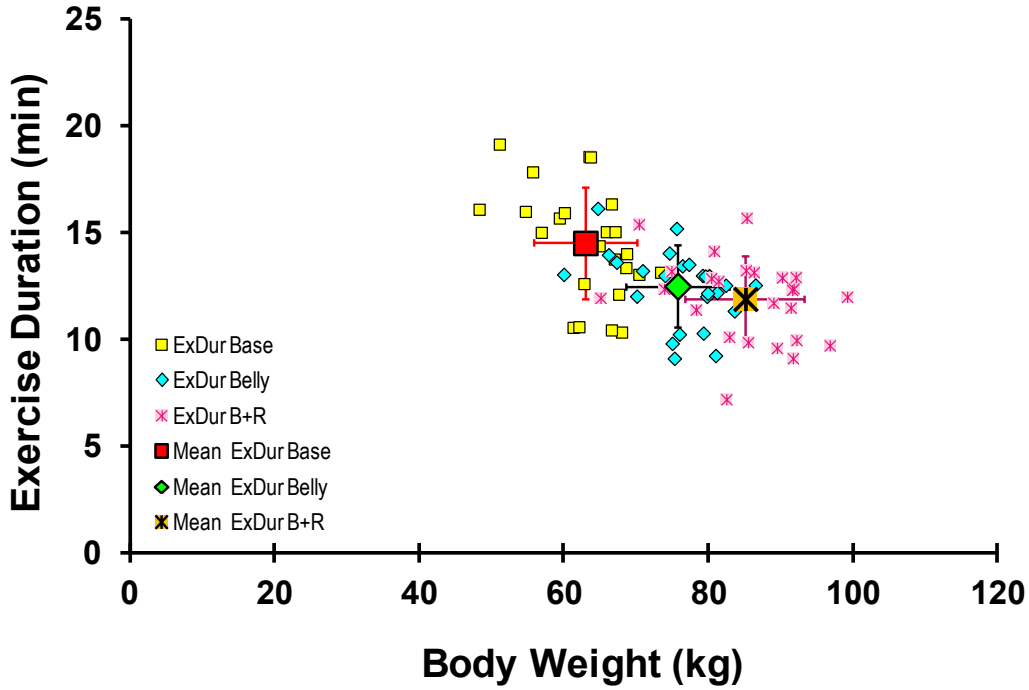


Figure 5.2 B. Effect of inert weight carriage on peak exercise capacity

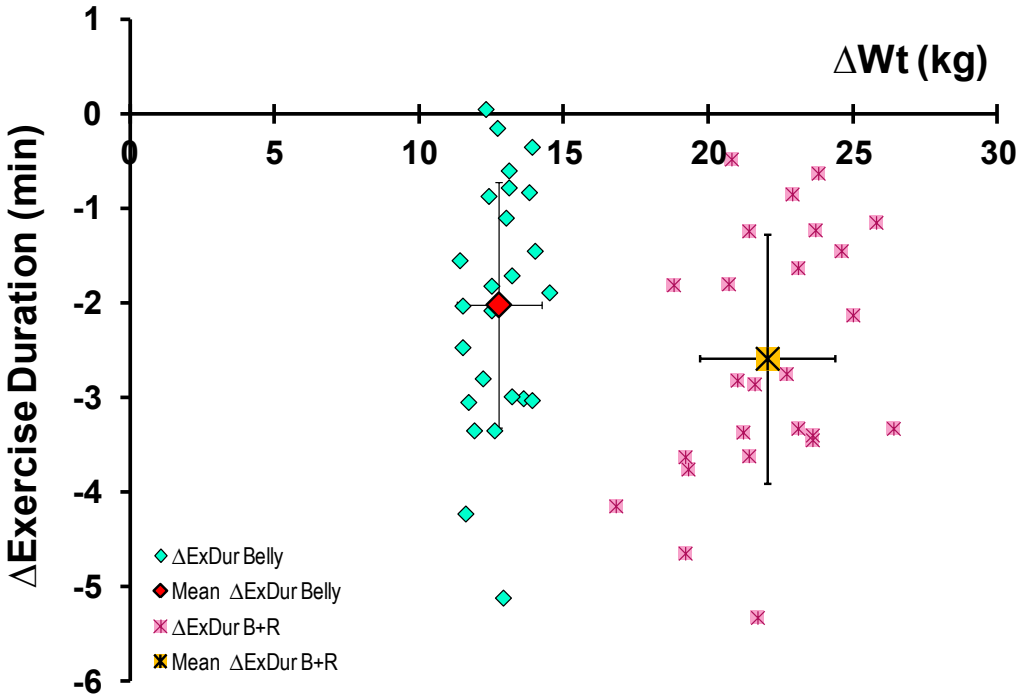


Figure 5.3 A. Effect of loading with the *"Empathy Belly"* and *"Empathy Belly* & rucksack" on peak oxygen consumption

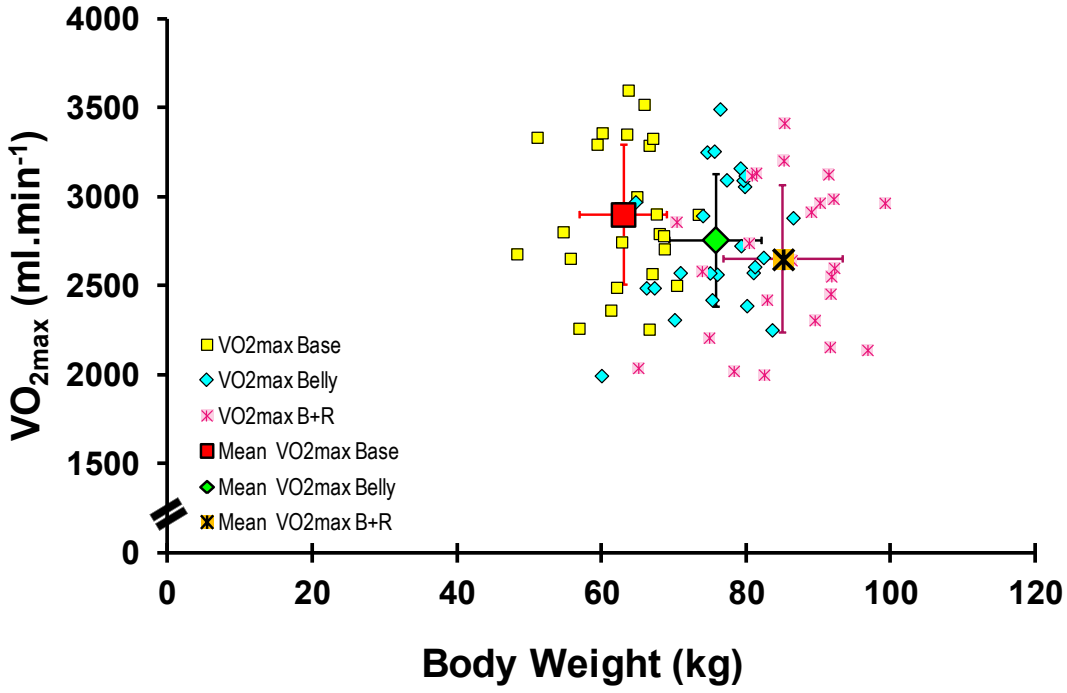


Figure 5.3 B. Effect of inert weight carriage on peak oxygen consumption

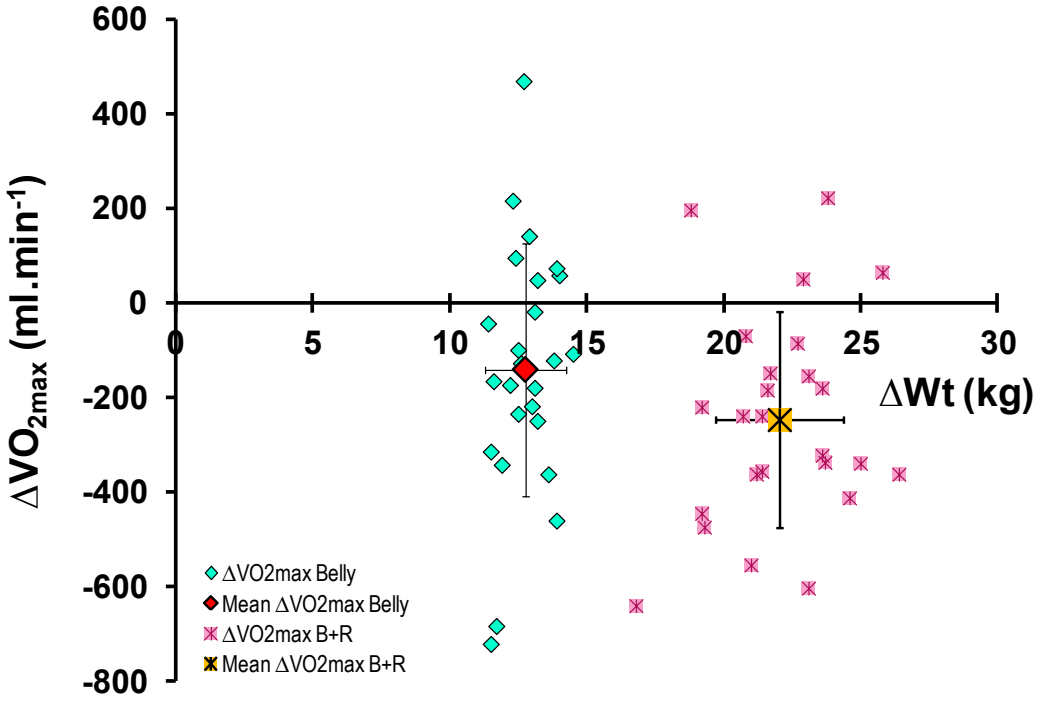


Figure 5.3 C. Effect of inert weight carriage on peak oxygen consumption scaled by body mass (per kilogram)

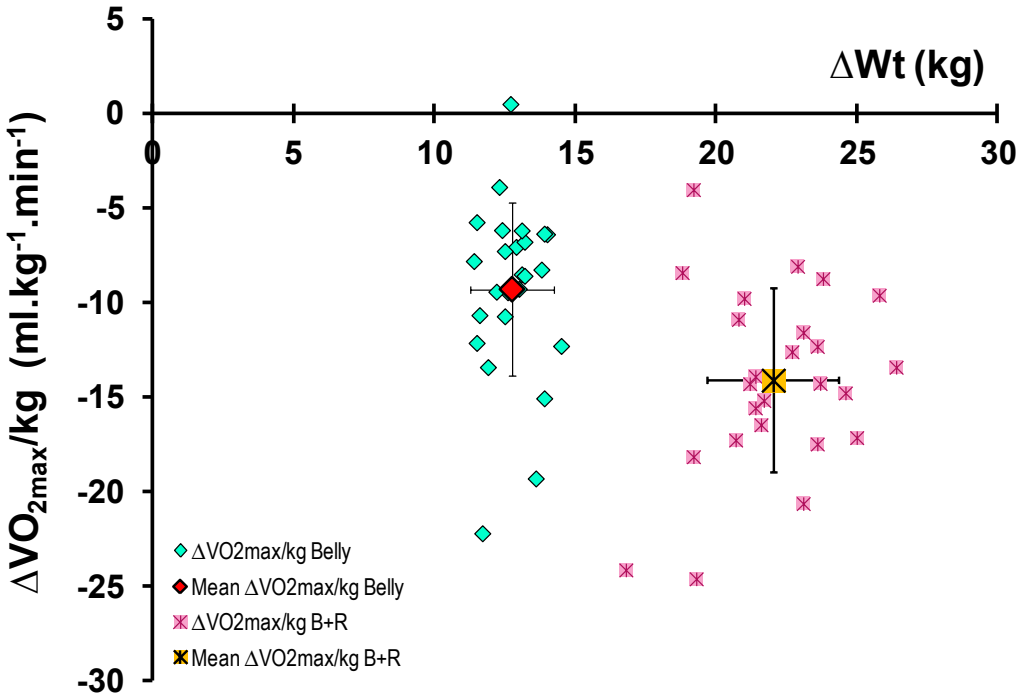


Figure 5.4 A. Effect of loading with the *"Empathy Belly"* and *"Empathy Belly* & rucksack" on peak cardiac power output

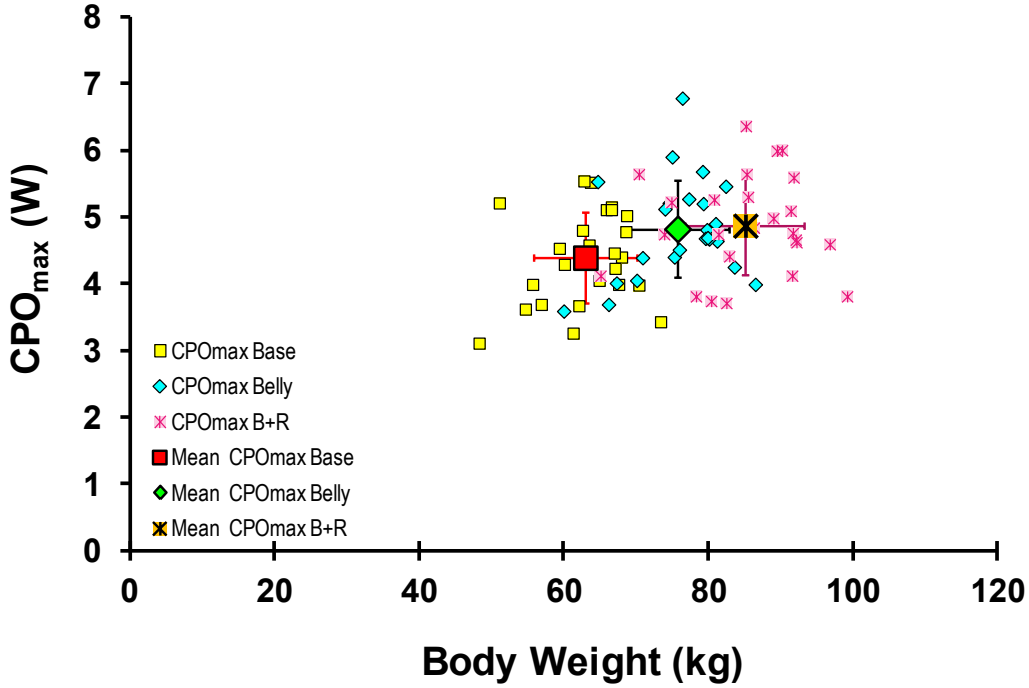


Figure 5.4 B. Effect of inert weight carriage on peak cardiac power output

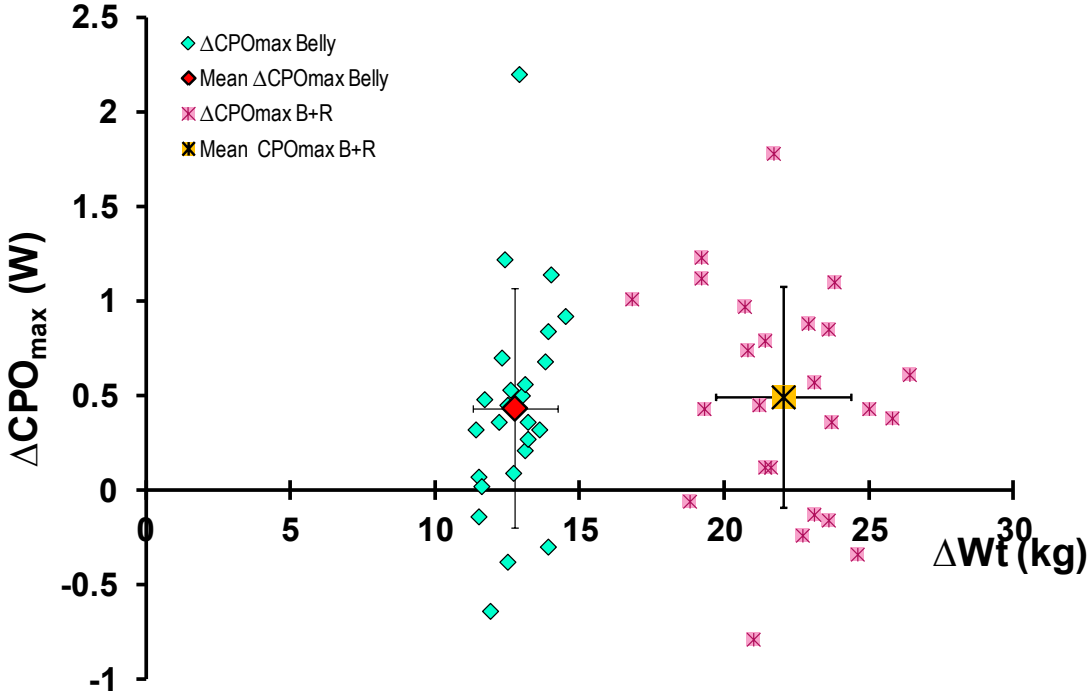


Figure 5.5 A. Maximal exercise haemodynamics at baseline and with differential inert weight carriage.

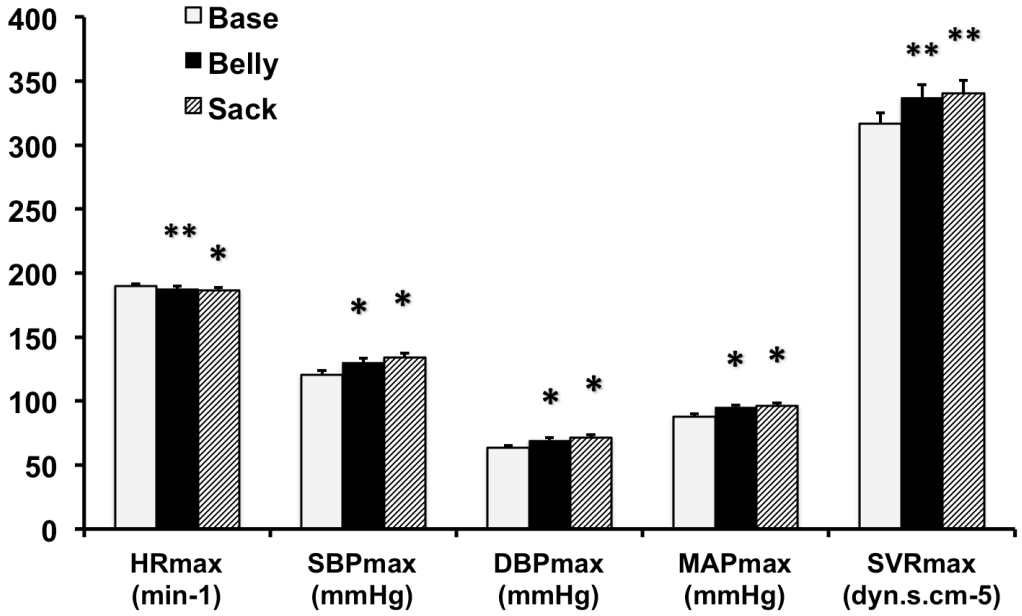
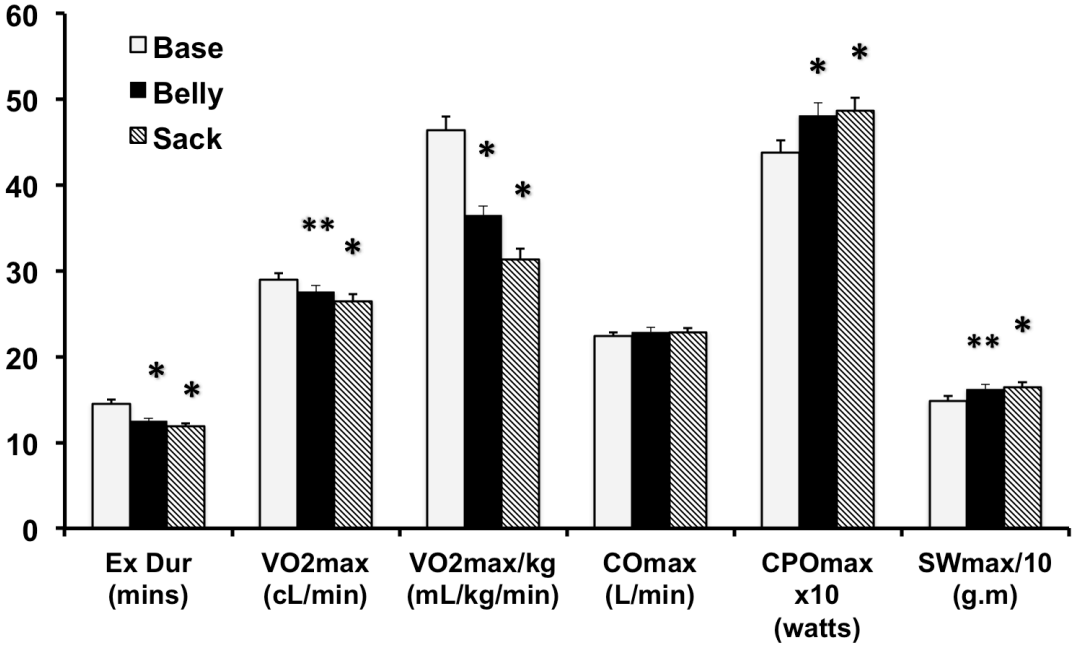
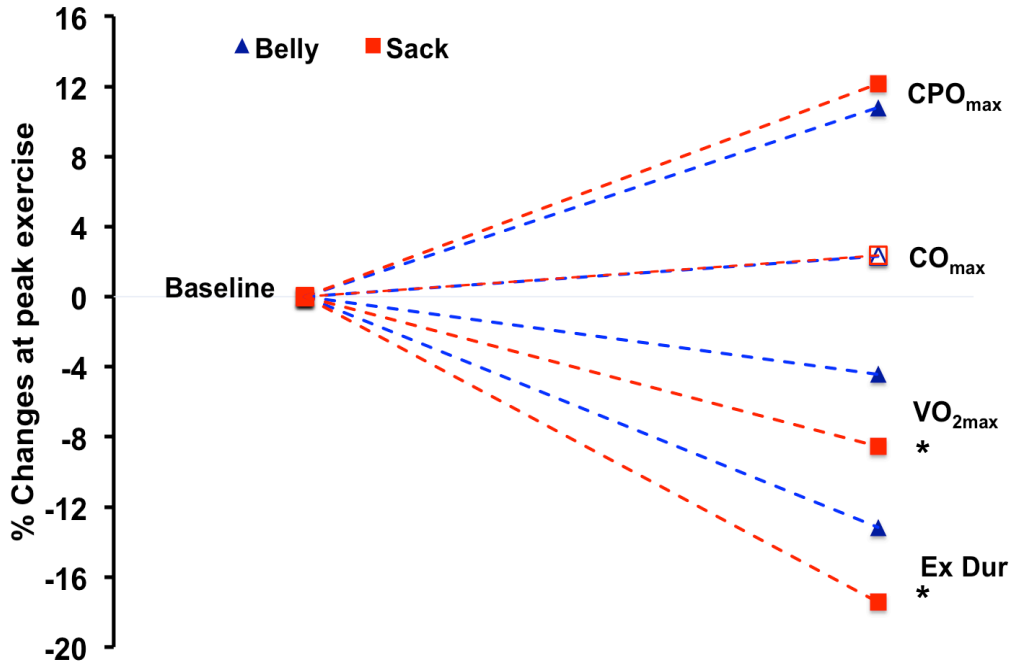


Figure 5.5 B. Maximal exercise variables at baseline and with differential inert weight carriage.



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work. **Significance in comparison to baseline test. *: p<0.01; **: p<0.05**

Figure 5.6 Delta maximal exercise variables with differential inert weight carriage.



CPO: cardiac power output; CO: cardiac output; VO_2: oxygen consumption; Ex Dur: exercise duration;

Significance between Baseline and Sack tests. *: p<0.01

The relative mean changes of physical and cardiac variables after loading with both Belly and Sack (Belly & Sack) during peak treadmill CPX. The most marked decrease with loaded exercise was seen in exercise duration carrying the Belly and Sack, while the most marked increase was in CPO_{max} carrying the Belly and Sack. Additional reduction was seen in exercise duration and both VO_{2max} and $VO_{2max/kg}$ when more weight was carried, however no improvement in cardiac performance was seen with additional weight carriage.

Figure 5.7 Relationship between the change in VO_{2max} and change in exercise duration with differential inert weight carriage.

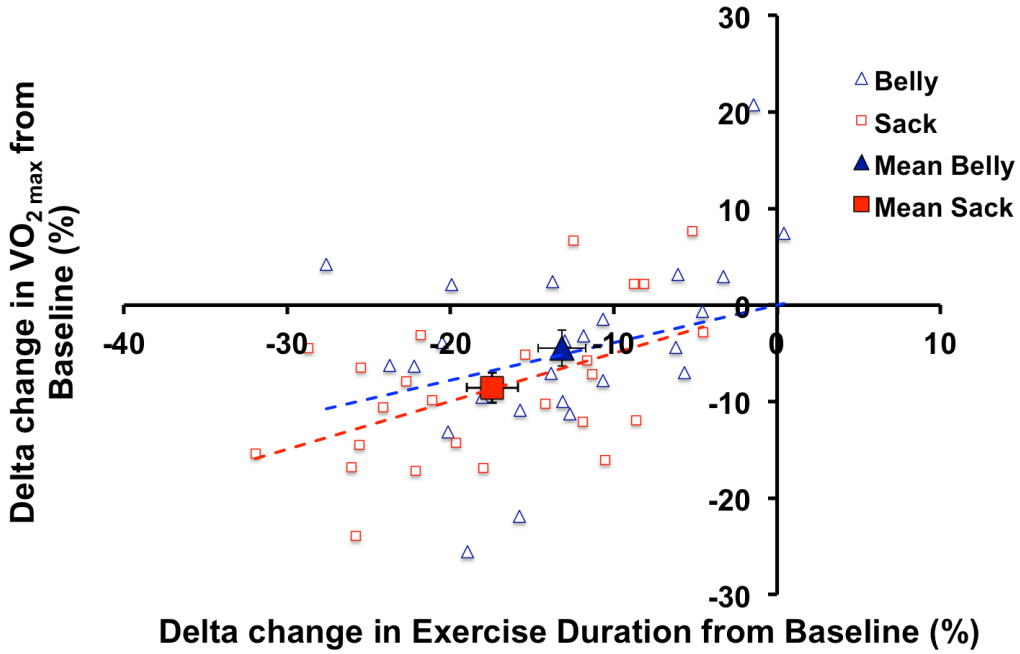


Figure 5.8 Relationship between the change in CPO_{max} and change in exercise duration with differential inert weight carriage.

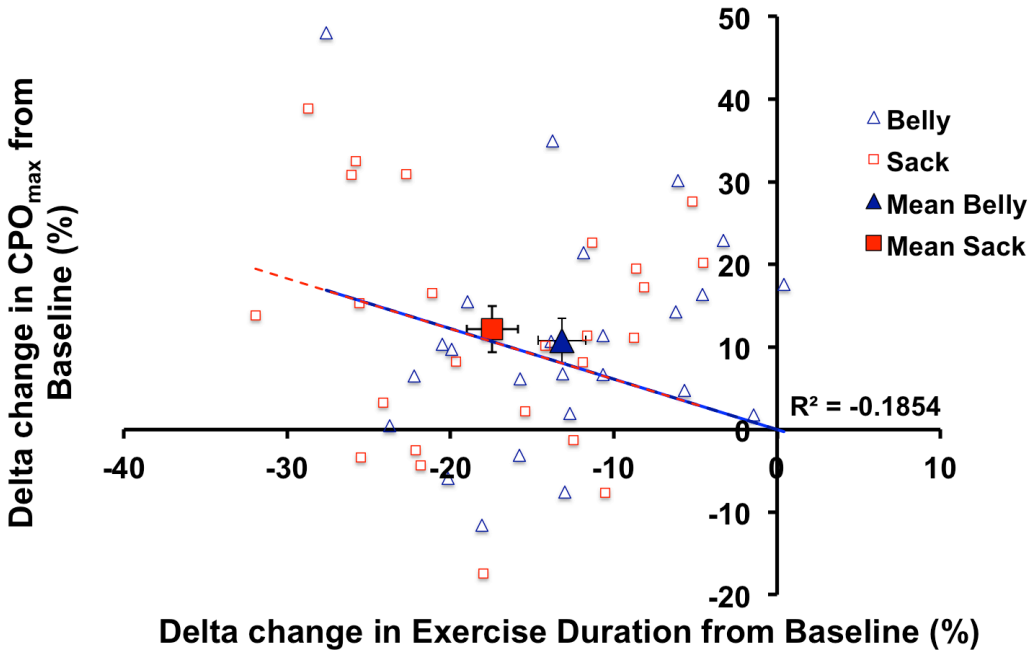


Figure 5.9 Relationship between the change in VO_{2max} and change in CPO_{max} with differential inert weight carriage.

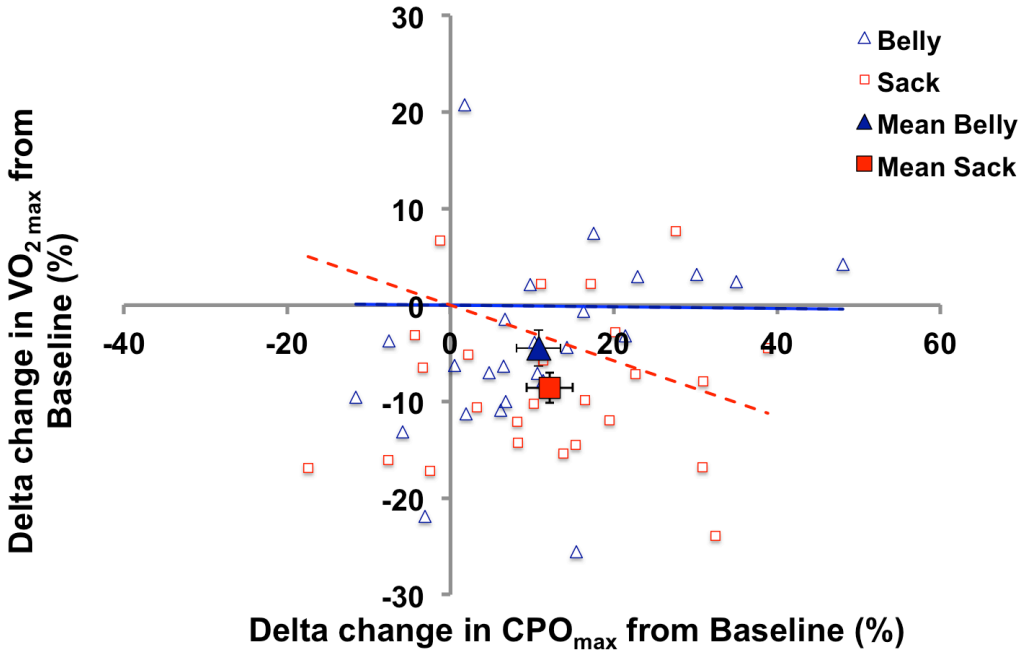
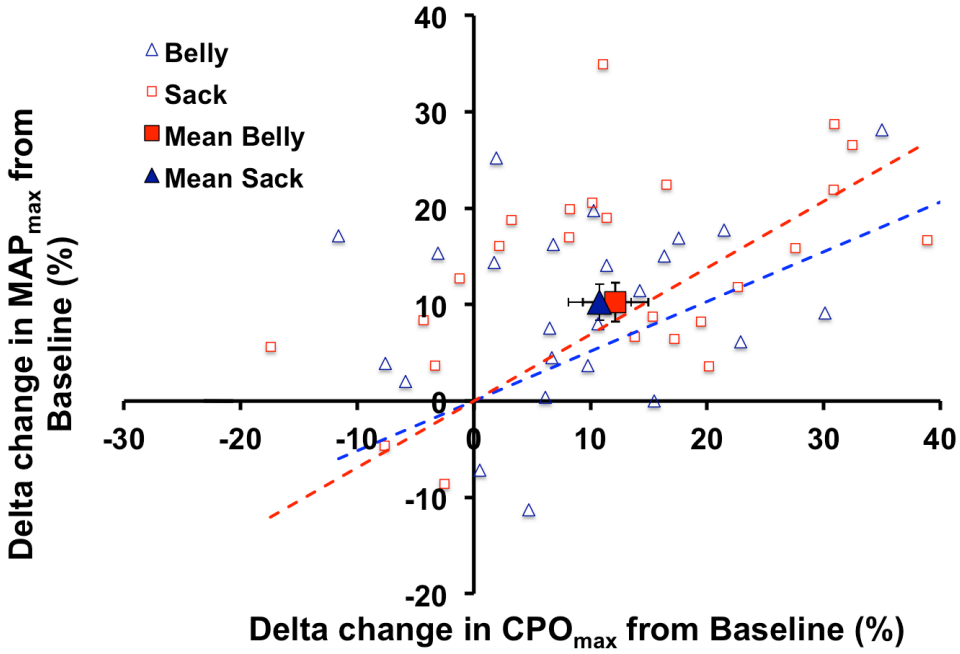


Figure 5.10 Relationship between the change in MAP_{max} and change in CPO_{max} with differential inert weight carriage.



5.5.2 Resting measures

With combined loading of the *"Empathy Belly and rucksack"*, the only resting variables that significantly changed were systolic arterial pressure (C: 102.1±11.8, R: 107.1±14.6 mm Hg, P=0.031), diastolic arterial pressures (C: 62.2±7.8, R: 68.8±11.8 mm Hg, P=0.001) and mean arterial pressure (C: 78.7±8.8, R: 84.6±12.4 mm Hg, P=0.002), as shown in Table 5.3A. SVR at rest did not change significantly. Other resting indicators of cardiac function including heart rate, stroke volume, cardiac output, and stroke work all showed no significant change, except cardiac power (p = 0.022, increase of 12%), while standing and carrying the combined weight of *"Empathy Belly"* and rucksack.

Table 5.3 A. Resting variables at baseline and with differential weight carriage.

Variables	Base	Belly	Sack	Base vs Belly	Base vs Sack	Belly vs Sack
	Mean (SD)	Mean (SD)	Mean (SD)	P value	P value	P value
$VO_{2\ rest}$ ($ml.min^{-1}$)	196±40	202±33	214±56	0.609	0.16	0.301
VO_{2rest}/kg ($ml.kg^{-1}.min^{-1}$)	3.14 (0.72)	2.69 (0.50)	2.52 (0.60)	0.013	0.001	0.214
HR_{rest} (min^{-1})	74.4±11.4	73.4±12.7	74.2±13.7	0.665	0.928	0.734
SV_{rest} (ml)	43.7±10.4	45.5±11.4	43.2±10.3	0.408	0.826	0.073
CO_{rest} ($ml.min^{-1}$)	3.22±0.69	3.33±0.65	3.38±0.67	0.41	0.148	0.763
SBP_{rest} (mmHg)	102.1±11.8	105.1±12.1	107.1±14.6	0.069	0.031	0.418
DBP_{rest} (mmHg)	62.2±7.8	67.9±11.2	68.8±11.8	0.013	0.001	0.714
MAP_{rest} (mmHg)	78.7±8.8	83.3±10.8	84.6±12.4	0.009	0.002	0.539
SVR_{rest} ($dyn.s.cm^{-5}$)	2026±428	2020±459	2010±423	0.945	0.874	0.934
SW_{rest} (g.m)	47.1±13.8	49.7±12.4	48.5±13.5	0.294	0.622	0.423
CPO_{rest} (watts)	0.58±0.17	0.62±0.15	0.64±0.19	0.174	0.022	0.575

Data presented as mean (SD, standard deviation); CO: cardiac output; CPO: cardiac power output; DBP: Diastolic blood pressure; HR: heart rate; MAP: mean arterial blood pressure; rest: values at rest; SBP: systolic blood pressure; SV: stroke volume; SVR: systemic vascular resistance; SW: stroke work; VO_2: oxygen consumption.

Table 5.3 B. Delta changes between resting variables at baseline and with differential weight carriage.

Variables	Δ Base vs Belly Mean (SD) 95% CI	% Δ Base vs Belly Mean (SD) 95% CI	Δ Base vs Sack Mean (SD) 95% CI	% Δ Base vs Sack Mean (SD) 95% CI	Δ Belly vs Sack Mean (SD) 95% CI	% Δ Belly vs Sack Mean (SD) 95% CI
$VO_{2\,rest}$	5.9 (57.2)	7.5 (28.2)	17.9 (61.7)	11.9 (30.5)	12.0 (30.5)	7.5 (27.4)
($ml.min^{-1}$)	-16.5, 28.3	-3.6, 18.6	-6.3, 42.1	-0.04, 23.9	-0.04, 23.9	-3.3, 18.2
VO_{2rest}/kg	-0.45 (0.84)	-10.7 (23.4)	-0.62 (0.82)	-17.1 (22.6)	-0.17 (0.65)	-4.4 (23.4)
($ml.kg.min^{-1}$)	-0.78, -0.12	-19.9, -1.5	-0.94, -0.30	-26.0, -8.2	-0.42, 0.09	-13.5, 4.8
HR_{rest}	-0.9 (10.5)	-0.4 (16.5)	-0.2 (8.7)	0.05 (11.8)	0.8 (11.1)	1.9 (15.1)
(min^{-1})	-5.0, 3.2	-6.8, 6.1	-3.6, 3.3	-4.6, 4.7	-3.6, 5.1	-4.0, 7.9
SV_{rest}	1.8 (10.4)	5.8 (21.9)	-0.52 (11.8)	1.5 (24.0)	-2.3 (6.1)	-9.1 (40.6)
(ml)	-2.3, 5.8	-2.8, 14.4	-5.1, 4.1	-7.9, 10.9	-4.6, 0.1	-25.0, 6.8
CO_{rest}	0.11 (0.67)	5.8 (21.0)	0.16 (0.53)	6.5 (17.5)	0.04 (0.72)	3.44 (22.4)
($l.min^{-1}$)	-0.15, 0.38	-2.5, 14.0	-0.05, 0.36	-0.3, 13.4	-0.24, 0.33	-5.5, 12.3
SBP_{rest}	3.0 (7.9)	3.2 (8.1)	5.0 (10.9)	5.1 (10.8)	2.0 (12.1)	2.3 (12.7)
(mmHg)	-0.1, 6.1	0.1, 6.4	0.7, 9.3	0.9, 9.4	-2.8, 6.8	-2.6, 7.3
DBP_{rest}	5.7 (10.7)	9.9 (17.2)	6.6 (8.4)	10.7 (13.7)	0.9 (11.9)	2.9 (19.1)
(mmHg)	1.5, 9.9	3.2, 16.7	3.3, 9.9	5.3, 16.0	-3.8, 5.5	-4.5, 10.4
MAP_{rest}	4.6 (8.1)	6.1 (10.7)	5.9 (8.4)	7.6 (11.0)	1.3 (10.8)	2.2 (13.7)
(mmHg)	1.4, 7.8	1.9, 10.3	2.7, 9.2	3.3, 11.9	-2.9, 5.6	-3.2, 7.6
SVR_{rest}	-6.5 (465)	1.5 (21.3)	-15.8 (495)	1.7 (22.7)	-9.3 (559)	3.7 (27.8)
($dyn.s.cm^{-5}$)	-189, 176	-6.8, 9.8	-210, 178	-7.3, 10.6	-229, 210	-7.2, 14.6
SW_{rest}	2.6 (12.2)	9.6 (25.3)	1.4 (13.8)	6.6 (29.8)	-1.2 (7.6)	-2.4 (14.4)
(g.m)	-2.2, 7.4	-0.3, 19.6	-4.0, 6.8	-5.1, 18.3	-4.2, 1.7	-8.0, 3.3
CPO_{rest}	0.04 (0.14)	10.7 (25.8)	0.06 (0.12)	11.7 (20.2)	0.02 (0.18)	5.72 (31.7)
(watts)	-0.02, 0.09	0.63, 20.9	0.01, 0.11	3.8, 19.7	-0.05, 0.09	-6.7, 18.2

Data presented as mean (SD, standard deviation); CI: confidence intervals; CO: cardiac output; CPO: cardiac power output; DBP: Diastolic blood pressure; HR: heart rate; MAP: mean arterial blood pressure; rest: values at rest; SBP: systolic blood pressure; SV: stroke volume; SVR: systemic vascular resistance; SW: stroke work; VO_2: oxygen consumption.

Figure 5.11 A. Resting variables at baseline and with differential inert weight carriage.

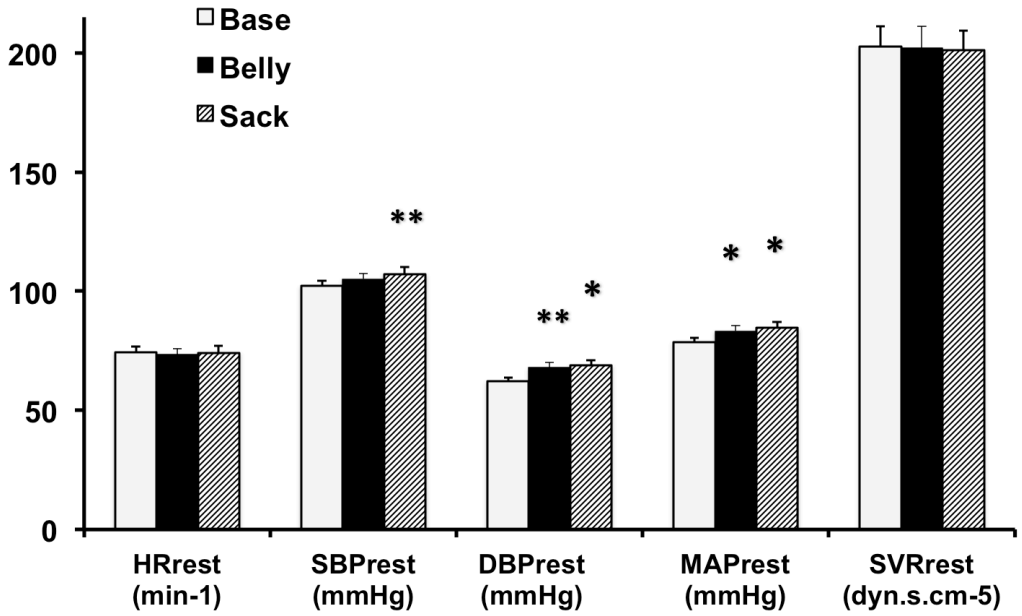
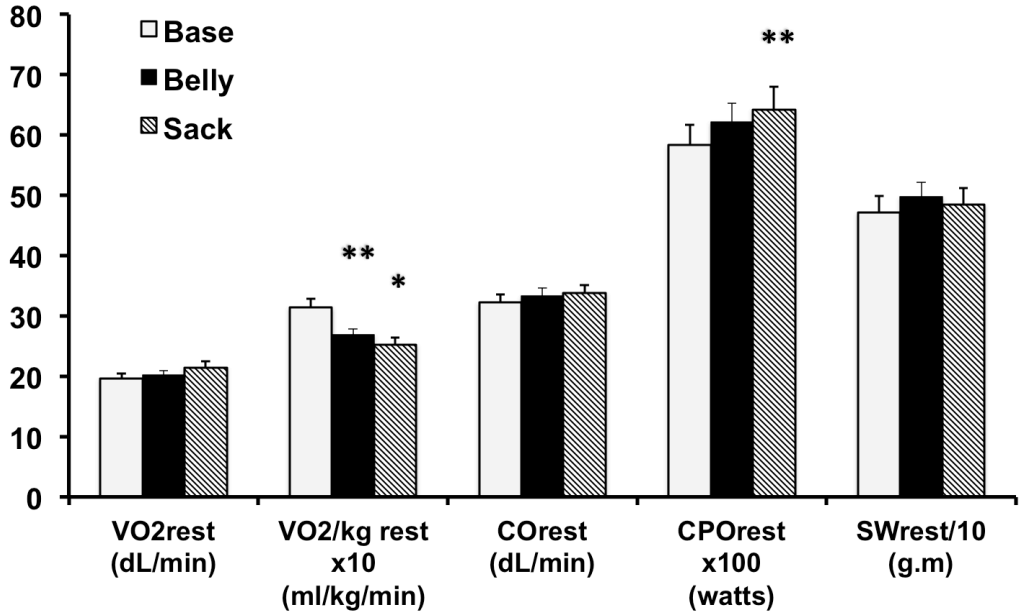


Figure 5.11 B. Resting cardiac variables at baseline and with differential inert weight carriage.



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SW: stroke work. **Significance in comparison to baseline test. *: p<0.01; **: p<0.05***

5.5.4 Reserve haemodynamics

There was a significant and incremental decrease in reserve oxygen consumption ($VO_{2\ reserve}$) (B: decrease 5%, p = 0.016; R: decrease 10%, p < 0.001; Belly versus Sack: p = 0.007). Significant increases were seen in both reserve cardiac power output (B: increase 12%, p = 0.002; Sack: increase 13%, p = 0.001) and reserve stroke work (B: increase 14%, p = 0.033; R: increase 18%, p = 0.011), however neither were significantly incremental. There were no significant changes in reserve cardiac output or reserve stroke volume, as shown in Tables 5.4A and B and Figure 5.12.

Table 5.4 A. Reserve variables at baseline and with differential weight carriage.

Variables	Base	Belly	Sack	Base vs Belly	Base vs Sack	Belly vs Sack
	Mean (SD)	Mean (SD)	Mean (SD)	P value	P value	P value
$HR_{reserve}$ (min^{-1})	115.5 (11.1)	115.4 (16.9)	112.2 (12.4)	0.978	0.087	0.468
$VO_{2\ reserve}$ ($ml.min^{-1}$)	2701 (388)	2553 (375)	2434 (404)	0.016	<0.001	0.007
$SV_{reserve}$ (ml)	80.2 (18.1)	80.5 (19.0)	82.7 (18.9)	0.934	0.553	0.495
$CO_{reserve}$ ($l.min^{-1}$)	19.2 (2.3)	19.5 (2.8)	19.5 (2.6)	0.422	0.560	0.848
$SW_{reserve}$ (g.m)	101.5 (24.8)	112.6 (26.7)	116.2 (26.1)	0.033	0.011	0.416
$CPO_{reserve}$ (watts)	3.80 (0.65)	4.19 (0.68)	4.23 (0.69)	0.002	0.001	0.721

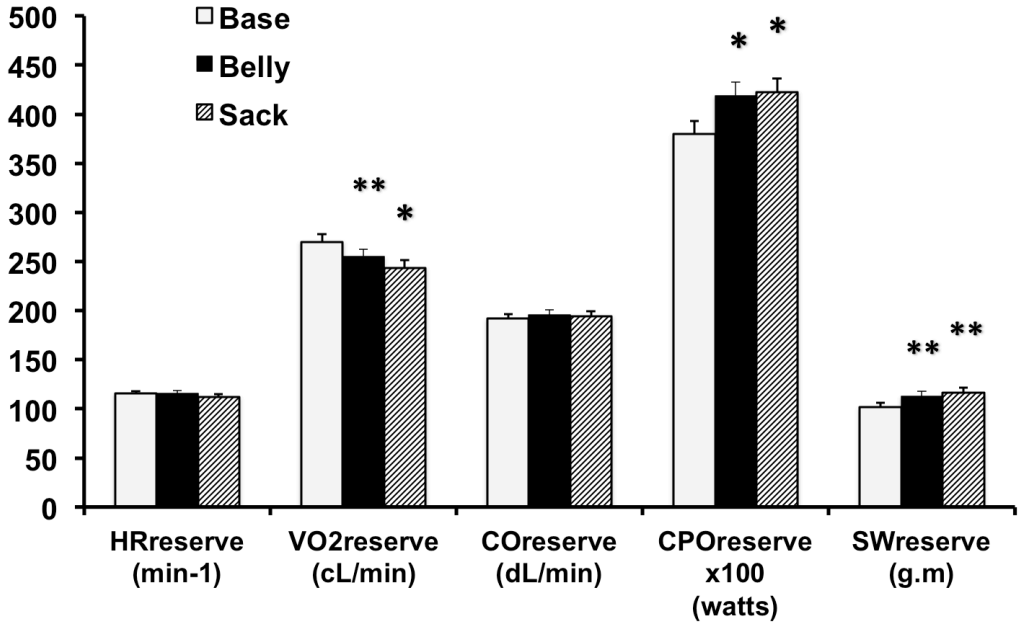
Data presented as mean (SD, standard deviation). CO: cardiac output; CPO: cardiac power output; HR: heart rate; max: values at peak exercise; SV: stroke volume: stroke work; VO_2: oxygen consumption.

Table 5.4 B. Delta changes between reserve variables at baseline and with differential weight carriage.

Variables	Δ Base vs Belly Mean (SD) 95% CI	% Δ Base vs Belly Mean (SD) 95% CI	Δ Base vs Sack Mean (SD) 95% CI	% Δ Base vs Sack Mean (SD) 95% CI	Δ Belly vs Sack Mean (SD) 95% CI	% Δ Belly vs Sack Mean (SD) 95% CI
$HR_{reserve}$	-0.1 (21.4)	1.0 (18.9)	-3.3 (9.3)	-2.7 (7.9)	-3.2 (21.7)	-0.4 (20.0)
(min^{-1})	-8.5, 8.3	-6.4, 8.4	-7.0, 0.33	-5.8, 0.4	-11.7, 5.3	-8.3, 7.4
$VO_{2\ reserve}$	-147 (283)	-4.9 (11.2)	-266 (233)	-9.8 (8.7)	-119 (202)	-4.6 (7.9)
($ml.min^{-1}$)	-258, -36	-9.3, -0.5	-358, -175	-13.2, -6.4	-198, -40	-7.7, -1.5
$SV_{reserve}$	0.3 (17.4)	1.9 (19.0)	2.5 (20.8)	6.2 (25.7)	2.2 (16.0)	5.0 (20.5)
(ml)	-6.5, 7.1	-5.6, 9.4	-5.7, 10.7	-3.8, 16.3	-4.0, 8.5	-3.0, 13.0
$CO_{reserve}$	0.36 (2.22)	2.2 (10.5)	0.27 (2.31)	2.0 (11.7)	-0.09 (2.33)	0.3 (11.9)
($l.min^{-1}$)	-0.51, 1.23	-1.9, 6.3	-0.63, 1.18	-2.6, 6.6	-1.00, 0.82	-4.4, 5.0
$SW_{reserve}$	11.1 (24.5)	13.5 (23.4)	14.7 (26.9)	18.3 (27.5)	3.7 (22.1)	5.5 (21.9)
(g.m)	1.5, 20.7	4.3, 22.6	4.2, 25.3	7.5, 29.1	-5.0, 12.3	-3.1, 14.1
$CPO_{reserve}$	0.39 (0.55)	11.5 (14.7)	0.43 (0.56)	12.6 (15.8)	0.04 (0.52)	1.7 (13.5)
(watts)	0.18, 0.61	5.7, 17.2	0.21, 0.65	6.4, 18.8	-0.17, 0.24	-3.6, 7.0

Data presented as mean (SD, standard deviation). CI: confidence intervals; CO: cardiac output; CPO: cardiac power output; HR: heart rate; max: values at peak exercise; SV: stroke volume: stroke work; VO_2: oxygen consumption.

Figure 5.12 Reserve variables at baseline and with differential inert weight carriage.



HR: heart rate; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SW: stroke work. **Significance in comparison to baseline test. *: p<0.01; **: p<0.05**

5.6 Discussion

This study is the first to determine the effects of incremental weight loading on aerobic capacity and cardiac function at maximal exercise in healthy pre-menopausal female subjects. All subjects exercised to RER_{max} above 1.15, and no significant changes were seen in RER_{max}, $ETpCO_{2max}$ and VE_{max} between loaded tests. We can therefore confidently say that maximum exercise was equivalent in each group.

The results showed that additional inert weight loading, in the form of an "*Empathy Belly*" and rucksack, caused incremental reductions in maximal exercise and aerobic capacity, especially $VO_{2max/kg}$. Additional loading also lead to significantly higher CPO_{max} and SW_{max} over baseline however, did not show significant incremental change with additional loading. There was no significant change in CO_{max}, SV_{max} and $CircP_{max}$ between baseline and different loading conditions. SVR reduced at peak exercise from rest in all tests and was significantly higher at peak exercise in the loaded tests however, was not significantly different between loads.

Cardiac reserve function ($CPO_{reserve}$ and $SW_{reserve}$) increased with loading, although was not incremental, whilst $VO_{2\ reserve}$ incrementally reduced with additional weight loading. These observations supported our first hypothesis that the carriage of additional inert weight, simulating excessive weight gain at full term pregnancy, would result in a further reduction in exercise capacity and VO_{2max}. However, the second hypothesis was not found to be true, and so suggests that there is a ceiling to peak cardiac performance when carrying additional weight. Despite this, opposing responses were again seen between markers of physical performance (Exercise duration and VO_{2max}) and direct markers of cardiac performance and reserve (CPO_{max} and $CPO_{reserve}$) between baseline and loaded tests. Furthermore the study confirmed hypothesis three, that indirect indicators of cardiac function remain unreliable as directly measured overall cardiac function during exercise stress testing with increased weight loading.

One can again infer that, in the context of excessive weight gain, diminution of exercise tolerance or aerobic capacity can no longer be assumed to represent a reduction in cardiac pumping capability. However, it is necessary to conduct further studies tp compare these changes from inert mass loading with perfused mass loading during pregnancy and obesity.

Published studies examining the effects of additional weight loading have estimated that for each kilogram of weight carried, the VO_2 increases by 33.5ml/min [Borghols 1978]. Importantly, no studies have reported the effects of weight carriage on peak oxygen consumption and cardiac function. Additional weight loading with identical submaximal exercise has been shown to cause further increases in heart rate, diastolic blood pressure, mean arterial pressure, oxygen consumption and cardiac output with no significant differences in stroke volume, whilst maintaining low SVR [Bhambhani *et al* 1997, Sagiv *et al* 1994, Sagiv *et al* 2002].

The present study showed similar changes to that seen in Bhambhani and Sagiv's studies however, inversely showed an incremental fall in VO_{2max} with increased loading and so disagree with the suggestion that oxygen uptake increases with incremental weight carriage. It is likely that the primary reason for these differences is that all of the previous studies were performed at sub-maximal exercise.

From the mechanistic viewpoint, carriage of additional weight, one might expect greater isometric muscle response. However, this was not seen and the higher pressure generating capacity was merely sustained between loads with no changes in SBP_{max}, DBP_{max} and MAP_{max}. One could therefore again hypothesize that there is

a limit to the hydraulic pressure that the heart can generate. To confirm this it would be necessary to conduct further studies with even more weight carriage.

5.61 Study Limitations

As well as the technical limitations relating to continuous measurement of flow and pressure mentioned in Chapter 4, the primary limitation of this study related to use of the *"Empathy Belly"* and a rucksack as a simulator of weight gain. However, in order to try and distinguish between effects of weight loading alone, it was necessary to use a weight loading model. One could argue that the distribution of weight loading was not akin to that in obesity however, such weight loading models do not exist. Future studies in pregnant and obese women will allow direct comparison, to see if the effects seen with these simulator models hold true.

5.7 Conclusion

Additional weight loading in healthy females, using a pregnancy simulator and rucksack, resulted in a significant incremental reduction in exercise duration and O_2 consumption during maximal treadmill exercise. Cardiac performance was maintained with additional weight carriage and has a divergent response to physical performance, compared to unloaded exercise. One advises that it is necessary to measure cardiac performance directly, rather than indirectly, during weight loading.

Chapter 6

Longitudinal Cardiovascular Effects of Pregnancy compared to Post-partum

Chapter 6

Study VI: Longitudinal cardiovascular effects of pregnancy compared to post-partum

6.1 Introduction

Heart disease has been the leading indirect (non-obstetric) cause of death in pregnancy for at least the last decade in both the UK and USA [Cantwell *et al* 2011; Creanga *et al* 2015]. However, it has been recognized for nearly a century that cardiac patients need to have enough cardiac reserve to cope with the cardiovascular stress of pregnancy and child birth [Mackenzie 1921]. Physiological changes during pregnancy facilitate the adaptation of the cardiovascular system to increase the metabolic needs of the mother, thus enabling adequate delivery of oxygenated blood to peripheral tissues and the fetus [Silversides & Colman 2007]. Weight gain progressively increases in the majority of women throughout pregnancy and has been suggested that weight contributes to reduced exercise capacity due to the higher baseline metabolic needs and the additional work of weight carriage [Carpenter et al 1990].

There is uncertainty about the best ways of evaluating cardiac function in pregnancy. Routine clinical practice is to assess both cardiac structure and function using echocardiography. Cardiac function is estimated by the fraction of blood that is ejected out the heart with each cycle, i.e. ejection fraction. However, ejection fraction does not change with pregnancy [Geva et al 1997; Vlahović-Stipac et al 2010]. As gestation advances, women become more symptomatic of fatigue and breathlessness [Milne *et al* 1978]. It is often difficult to differentiate whether the worsening symptoms and exercise intolerance are due to progressive cardiac impairment or merely secondary to pregnancy and the additional work of weight gain.

Over the last century, extensive study of healthy women has characterized the haemodynamic responses to pregnancy. The majority of the studies show an increase in heart rate, stroke volume and cardiac output, accompanied by a fall in systemic vascular resistance and blood pressure. As gestation advances blood pressure rises and the improvements in cardiac output level off towards term [Burwell 1938; Hamilton 1949; Robson 1989; Mahendru 2014]. Unfortunately, there

are very few studies examining cardiac reserve and maximal haemodynamics in pregnancy. Most appear to show that VO_{2max} remains unchanged [Lotgering *et al* 1991; Spinnewijn *et al* 1996; Sady *et al* 1989, Heenan *et al* 2001]. However, Artal and South-Paul both showed a significant reduction in VO_{2max} in their cross sectional studies [Artal *et al* 1986; South-Paul *et al* 1988]. Only one study has reported changes in CO at maximal exercise, on a cycle, and found that CO was higher in the third trimester in comparison to post-partum [Sady *et al* 1989]. Importantly, cycle exercise is non-weight bearing and so they are unlikely to have examined the effects weight gain from pregnancy on cardiac output.

Studies IV and V showed divergent responses in physical and cardiac performance to acute inert weight loading and therefore question the role of VO_2 as an indirect marker of cardiac function in pregnancy. One therefore needs to establish if this is the case. A key question is whether cardiac reserve reduces throughout pregnancy because of the higher baseline function and reduced exercise capacity.

6.2 Purpose and hypothesis of the study

The purpose of this study was to determine how pregnancy at each of the trimesters affects resting, peak and reserve metabolic function and cardiovascular haemodynamics in healthy female subjects.

The hypotheses tested in this investigation were

(i) Maximal treadmill exercise testing during pregnancy will result in a reduction in exercise duration and concomitant decrease in VO_{2max}, which will become more marked as gestation increases.

(ii) There will be an improvement in peak cardiac performance, as represented by CPO_{max}, in the latter stages of pregnancy, as weight increases.

(iii) Cardiac reserve will be maintained in pregnancy due to the increased resting and peak cardiac function.

(iv) Conventional indirect indicators of cardiac function are unreliable as measures of overall cardiac function during exercise stress testing in pregnancy.

(v) Post-partum is a reliable surrogate marker for the non-pregnant state

6.3 Ethical approval

Ethical approval was approved by the Leeds (West) Ethics Committee.

6.4 Methods

This was a prospective observational longitudinal study which compared the physiological cardiovascular changes seen in pregnancy with their non-pregnant state (chosen to be 3 months post-partum) in healthy participants.

6.4.1 Study participants

Healthy female volunteers, who were either pregnant or trying to get pregnant, were recruited from a wide range of avenues: Adverts were posted in the regional press, local radio, posters throughout the University of Leeds, Leeds teaching hospitals NHS trust, GP surgery waiting rooms and local gymnasiums. Email invitations were sent to all members of Leeds teaching hospitals NHS trust and the University of Leeds. Both hospital and community midwives were also encouraged to tell pregnant women about the study.

Women contacted the study co-ordinator and were given written and verbal information about the study. Once they were happy to take part, they were initially screened to ensure that they were healthy and taking no medication, apart from vitamin supplements (folic acid), and invited to the Leeds General Infirmary for a first visit. Women were excluded if they were unable to walk on a treadmill or unwilling to perform exercise beyond their anaerobic threshold. Further exclusion criteria included: potential obstetric complications; including placenta praevia after 26 weeks; incompetent cervix; pre-eclampsia; pregnancy induced hypertension; multiple gestation at risk of premature labour; ruptured membranes and uninvestigated vaginal bleeding or abdominal pain.

6.4.2 Visit structure

At the first visit, women who were suitable and willing to give up their time were consented. The testing procedures were explained and then they were shown the laboratory and equipment. Those women who were in their first trimester of pregnancy, who had not undergone their first fetal scan, also had a scan arranged prior to exercise testing.

Following recruitment, women were asked to attend the Leeds General Infirmary cardiology department for up to 5 visits to undergo assessment and physiological testing, depending on which stage of pregnancy they were recruited. The visits included a single visit in pre-conception, if they were trying to become pregnant; three visits in pregnancy: aiming for 10-12 weeks; 24-26 weeks and 36 weeks of gestation; and finally approximately 3 months post-partum.

All subjects underwent full clinical assessment and examination and then had a transthoracic echocardiogram performed to ensure normal cardiac structure and resting function. During each visit, participants were assessed, to ensure their well-being and establish their symptoms. Particular attention was taken to ensure no obstetric complications had occurred and therefore subjects were asked about vaginal bleeding, abdominal pain, headaches, leg pain or swelling in accordance with the Physical Activity Readiness Medical Examination for Pregnancy (Wolfe and Mottola, 2002). NYHA functional class was determined through enquiry about daily activities and exercise, shown below.

Table 6.1 NYHA classification

NYHA class	Functional Capacity
I	No limitations during usual activities (i.e. Flight of stairs)
II	Slight limitation during usual activities
III	Marked limitation during usual activities
IV	Symptoms at rest, unable to carry on usual activities

6.4.3 Cardiopulmonary exercise testing

An initial symptom-limited, maximal treadmill exercise test was performed, using the Bruce protocol, with the Medgraphic Ultima metabolic cart (Medgraphics Corporation, St. Paul, Minnesota, USA) and continuous ECG monitoring to measure and monitor breath-by-breath rates of ventilation, O_2 consumption (VO_2), CO_2 production (VCO_2), beat-by-beat heart rate (HR) and exercise duration. Manual cuff sphygmomanometry was used to measure systolic and diastolic blood pressures (SBP and DBP) in mm Hg. A second peak single-stage exercise test was performed after 45 minutes rest, to target the peak workload attained during the

prior incremental test and enable measurement of cardiac output using the CO_2 re-breathing technique [Vanhees *et al* 2000]. Detailed explanation of the testing procedure and equipment used is outlined in Chapter 2.

6.4.4 Quality of life assessment

Subjects were asked to complete the SF-36 version 2, [Ware and Sherbourne 2000], quality of life questionnaire at each visit. The SF-36v2 has 36 questions which assess functional health and well-being, divided into 8 sections. Scores were then scaled using a norm-based scoring using data from the 1998 National Survey of Functional Health Status, giving a number between 0-100, where 50 is the average score or norm. This is one of the most widely used health questionnaires in the world for measuring patient reported outcomes, having been reported in more than 19000 studies over 20 years.

6.4.5 Statistics

All data were analysed using SPSS. Data are presented as mean and standard deviation. Delta measures and percentage change in measures between trimesters and post-partum are also displayed as a mean and standard deviation with 95% confidence intervals. Statistical comparisons were made with Student's paired, two-tailed t test. A P value of < 0.05 was considered to be statistically significant.

6.5 Results

6.5.1 Study population baseline characteristics

91 healthy females were recruited and underwent testing. A total of 240 tests were performed with 57 participants undergoing tests in post-partum and in at least one gestation and or in pre-conception, shown in Table 6.2. All 57 subjects were healthy and taking no regular medication, and had no impediments to exercise.

The mean age was 32.7 years (SD 4.3). 50 were Caucasian, 5 of Asian and 2 of Afro-Caribbean descent. All were generally active pre-pregnancy. Throughout pregnancy all women remained well and delivered after 37 weeks.

The differences in longitudinal weights are shown in Table 6.2. The maximal weight change was seen in the third trimester, where there was a significant 15% increase in weight.

Table 6.2 Test performed and weight changes

Trimester	PC	T1	T2	T3	PP
Number tested	21	49	59	54	57
Number with PP test	17	36	46	44	
Weight (kg) (SD)	63.5 (9.7)	64.4 (8.9)	69.5 (10.3)	76.2 (14.3)	
Weight at PP (kg) (SD)	65.0 (11.2)	65.7 (9.9)	65.1 (10.4)	66.6 (13.2)	
∆ Weight (%) P value	-2.0 0.057	-1.6 0.052	7.1 <0.001	14.9 <0.001	

PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum; SD: standard deviation.

6.5.3 First Trimester versus Post-partum

Changes in variables at rest and exercise, including reserve variables, between longitudinal tests performed in the first trimester and post-partum are shown in Tables 6.3 to and including Table 6.6 and Figures 6.1 to 6.5. At rest there were no significant differences in HR_{rest}, SBP_{rest}, MAP_{rest} or SVR_{rest}. However, DBP_{rest} was significantly lower in the first trimester by 6%. VO_{2rest} was also lower in the first trimester, but was not accompanied by a significant change in CO_{rest}, CPO_{rest}, SV_{rest} or SW_{rest}.

At maximal exercise, HR_{max} was significantly lower in the first trimester by 4%. There were no differences in SBP_{max}, DBP_{max} or SVR_{max}. Exercise duration was significantly shorter in the first trimester by 45 seconds (6%) however, there were no significant differences in VO_{2max}, $VO_{2max/kg}$, CO_{max}, $CircP_{max}$, SV_{max}, CPO_{max} or SW_{max}. The largest change in cardiac function appeared to be a fall in CPO_{max} in the first trimester by 4%, however this just failed to reach significance ($p = 0.072$).

Table 6.3 shows the differences in markers of exercise effort between tests. No significant difference in RER_{max} or VE_{max} was identified between tests although, $ETpCO_{2max}$ was significantly lower and symptom scores were significantly worse in the first trimester.

$HR_{reserve}$ was significantly lower in the first trimester by 7%. There were no significant changes in $VO_{2reserve}$, $CO_{reserve}$, $SV_{reserve}$, $CPO_{reserve}$ or $SW_{reserve.}$ The nearest significant change in cardiac function was a reduced $CPO_{reserve}$, seen in the first trimester (4%, p = 0.093).

Table 6.3 Markers of exercise effort and symptoms between first trimester and post-partum

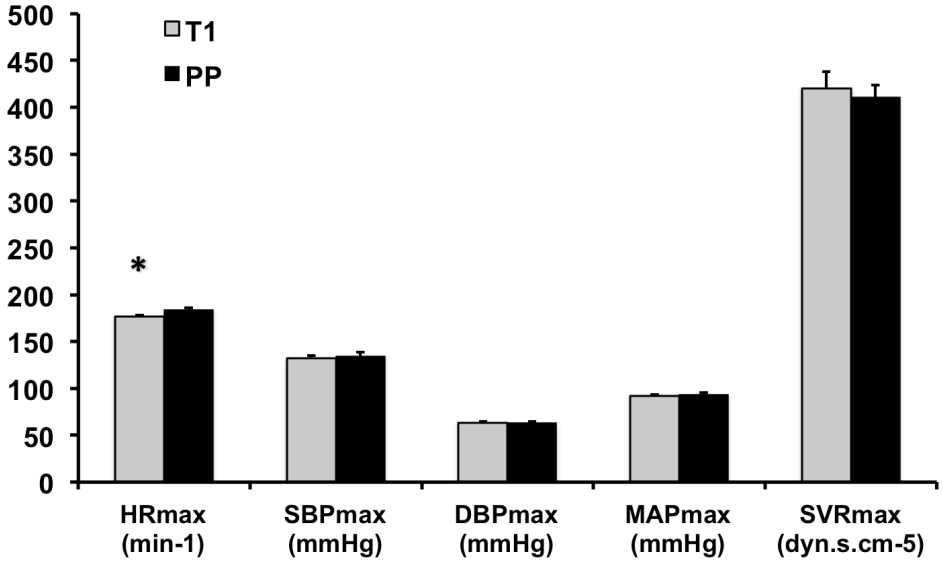
	RER_{max} Mean (SD)	**VE_{max}** Mean (SD)	**$ETpCO_{2max}$** Mean (SD)	**SF-36** Mean (SD)
T1	1.12 (0.09)	81.4 (20.0)	32.0 (3.7)	77.0 (10.4)
PP	1.15 (0.12)	80.5 (17.6)	35.2 (3.6)	81.7 (10.9)
P value	0.275	0.740	<0.0001	0.034

Table 6.4 Maximal exercise variables at first trimester and post-partum

	T1 Mean (SD)	**PP** Mean (SD)	**P value**	**Δ** Mean (SD) 95% CI	**% Δ** Mean (SD) 95% CI
HR_{max} (min^{-1})	176.7 (10.3)	183.9 (10.9)	<0.001	-7.2 (8.9) -10.1, -4.3	- 4.0 (4.9) -5.4, -2.2
SBP_{max} (mmHg)	132.2 (19.6)	134.6 (25.8)	0.501	-2.4 (21.3) -9.4, 4.5	0.1 (15.9) -5.1, 5.3
DBP_{max} (mmHg)	63.6 (8.9)	63.4 (7.7)	0.912	0.2 (9.0) -2.8, 3.1	0.9 (14.1) -3.7, 5.5
MAP_{max} (mmHg)	91.9 (11.1)	93.7 (9.8)	0.256	-1.8 (9.2) -4.8, 1.2	-1.6 (9.7) -4.8, 1.6
SVR_{max} ($dyn.s.cm^{-5}$)	420 (108)	411 (78)	0.570	9 (99) -23, 42	3.4 (23) -4.2, 11.0
Ex Dur (mins)	11.9 (2.7)	12.6 (3.0)	<0.001	-0.75 (1.1) -1.1, -0.4	- 5.5 (9.1) -8.5, -2.5
$VO_{2\ max}$ ($ml.min^{-1}$)	2191 (400)	2220 (433)	0.605	-28 (325) -134, 78	-0.1 (14.1) -4.7, 4.5
$VO_{2\ max/kg}$ ($ml.min^{-1}.kg^{-1}$)	34.4 (6.8)	34.2 (6.9)	0.819	0.2 (5.2) -1.5, 1.9	1.8 (14.8) -3.0, 6.6
CO_{max} ($l.min^{-1}$)	18.1 (3.2)	18.6 (2.5)	0.311	-0.5 (2.7) -1.4, 0.4	-2.0 (14.3) -6.7, 2.7
CPO_{max} (watts)	3.68 (0.70)	3.86 (0.65)	0.072	-0.18 (0.58) -0.37, 0.01	-4.1 (13.7) -8.5, 0.4
$CircP_{max}$ ($mmHg.ml\ O_2.min^{-1}$)	292 (75)	300 (89)	0.473	-9 (70) -32, 14	0.3 (22.8) -7.1, 7.8
SV_{max} (ml)	103.9 (18.9)	103.8 (14.5)	0.973	0.1 (16.7) -5.4, 5.6	0.6 (16.0) -4.6, 5.8
SW_{max} (g.m)	129.6 (26.8)	132.4 (23.8)	0.448	-2.8 (21.5) -9.8, 4.3	-1.5 (15.5) -6.5, 3.6

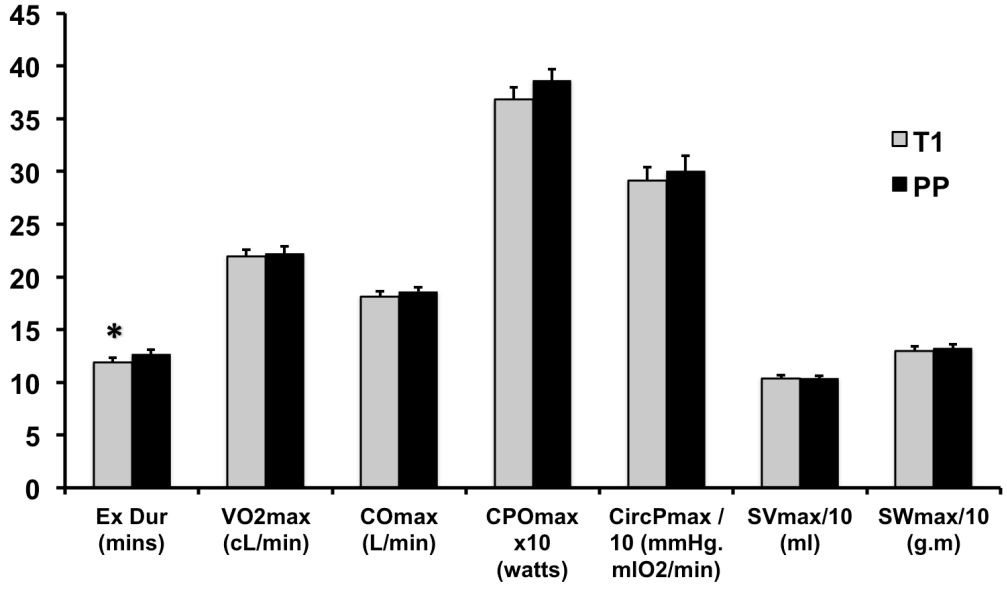
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; Ex Dur: exercise duration; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: circulatory power; SV: stroke volume; SW: stroke work.

Figure 6.1 Maximal exercise haemodynamics at first trimester and post-partum



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. *: p<0.01

Figure 6.2 Maximal exercise variables at first trimester and post-partum



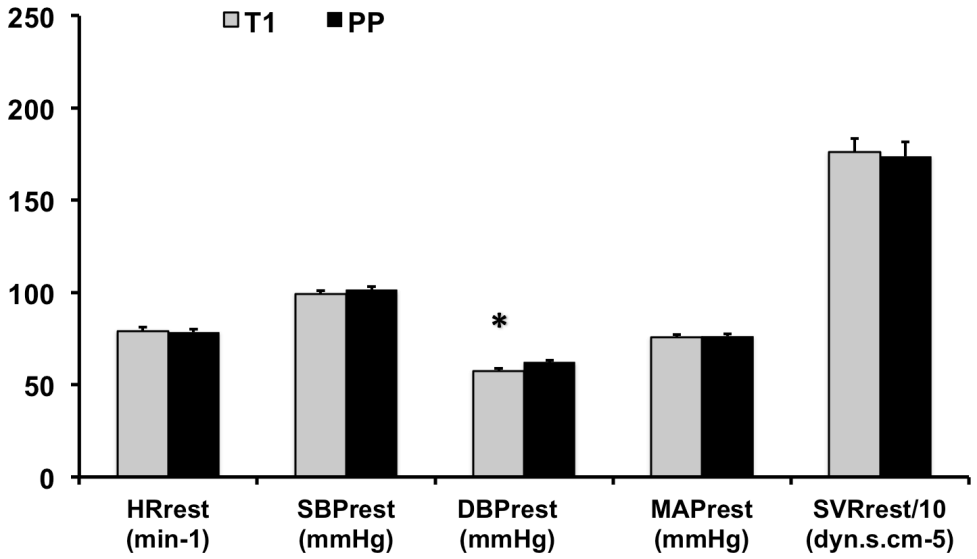
Ex Dur: exercise duration; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: Circulatory power; SV: stroke volume; SW: stroke work. *: p<0.01.

Table 6.5 Resting variables at first trimester and post-partum

	T1 Mean (SD)	**PP** Mean (SD)	**P value**	**Δ** Mean (SD) 95% CI	**% Δ** Mean (SD) 95% CI
HR_{rest} (min^{-1})	79.2 (13.3)	78.4 (10.7)	0.747	0.8 (13.8) -3.8, 5.3	2.0 (17.7) -3.8, 7.8
SBP_{rest} (mmHg)	99.3 (10.5)	101.3 (11.2)	0.308	-1.9 (11.3) -5.6, 1.7	-1.3 (11.0) -4.9, 2.3
DBP_{rest} (mmHg)	57.5 (7.7)	62.1 (8.3)	0.005	-4.6 (9.1) -7.6, -1.6	-6.2 (14.3) -10.9, -1.5
MAP_{rest} (mmHg)	75.6 (8.8)	76.3 (8.3)	0.676	-0.7 (9.9) -3.9, 2.5	-0.2 (12.8) -4.4, 4.0
SVR_{rest} ($dyn.s.cm^{-5}$)	1761 (441)	1737 (471)	0.815	24 (609) -175, 223	6.7 (33.7) -4.3, 17.8
VO_{2rest} ($ml.min^{-1}$)	238 (59)	283 (128)	0.045	-45 (130) -87, -3	-6.8 (34.3) -18.1, 4.4
CO_{rest} ($l.min^{-1}$)	3.63 (0.95)	3.69 (0.79)	0.764	-0.06 (1.20) -0.45, 0.33	3.0 (36.5) -8.9, 14.9
CPO_{rest} (watts)	0.61 (0.18)	0.63 (0.15)	0.717	-0.01 (0.23) -0.09, 0.06	3.3 (39.6) -9.6, 16.2
SV_{rest} (ml)	47.3 (14.7)	50.0 (13.1)	0.361	-2.7 (17.4) -8.3, 3.0	0.07 (38.9) -12.7, 12.8
SW_{rest} (g.m)	48.9 (16.5)	51.8 (15.2)	0.375	-3.1 (20.4) -9.7, 3.6	0.5 (43.0) -13.6, 14.5

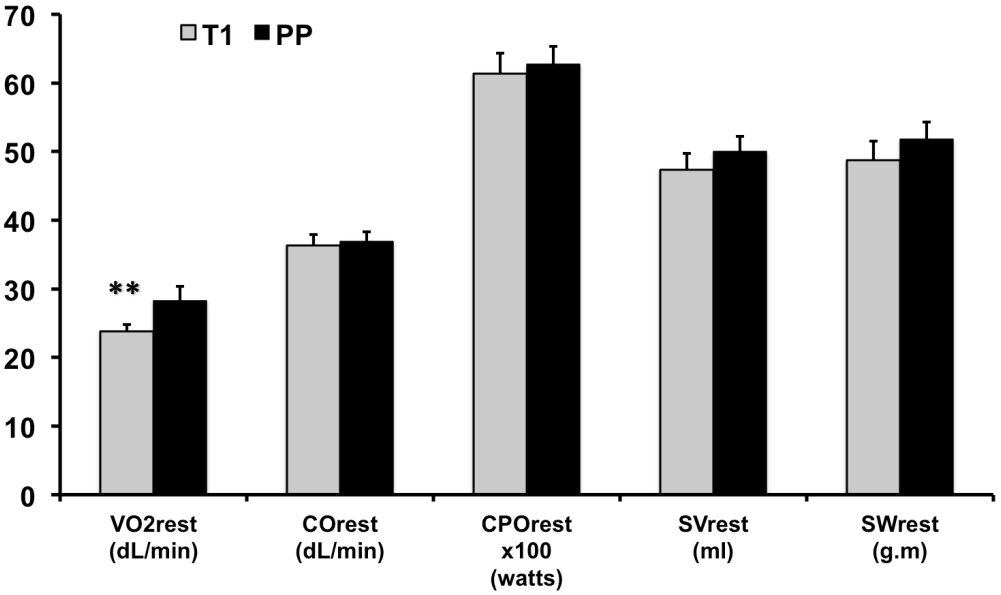
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Figure 6.3 Resting variables at first trimester and post-partum



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. *: p<0.01

Figure 6.4 Resting cardiac variables at first trimester and post-partum



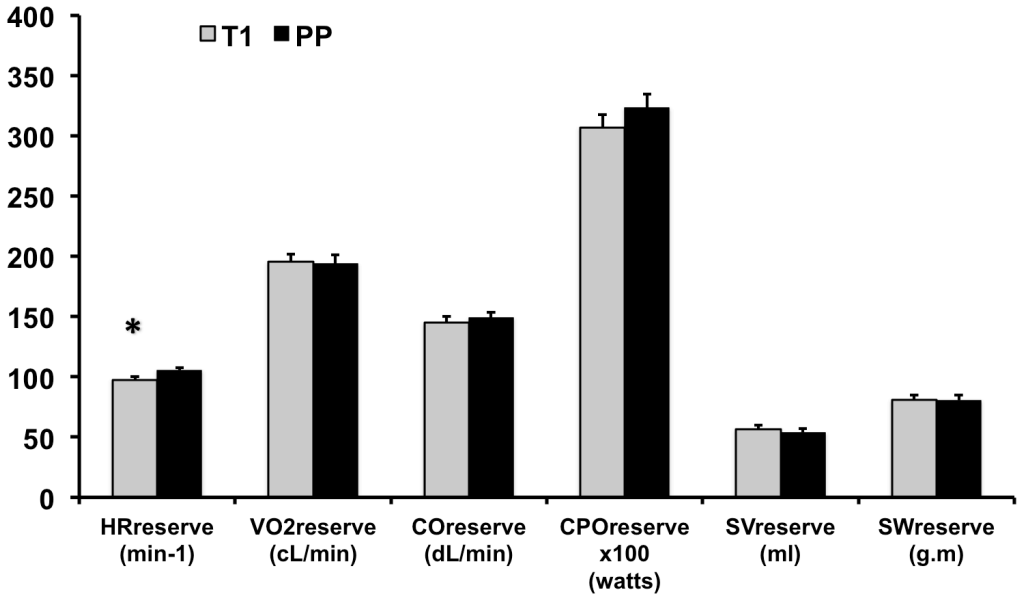
VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work. **: p<0.05

Table 6.6 Reserve variables at first trimester and post-partum

	T1 Mean (SD)	PP Mean (SD)	P value	Δ Mean (SD) 95% CI	% Δ Mean (SD) 95% CI
$HR_{reserve}$ (min^{-1})	97.5 (16.9)	105.5 (11.5)	0.005	-8.0 (15.8) -13.1, -2.8	-7.2 (15.3) -12.1, -2.2
$VO_{2\ reserve}$ ($ml.min^{-1}$)	1954 (399)	1937 (436)	0.792	17 (376) -106, 139	3.1 (19.5) -3.2, 9.5
$CO_{reserve}$ ($l.min^{-1}$)	14.5 (3.3)	14.9 (2.7)	0.407	-0.4 (2.9) -1.4, 0.5	-1.7 (20.0) -8.2, 4.8
$SV_{reserve}$ (ml)	56.6 (21.2)	53.8 (20.4)	0.474	2.8 (23.0) -4.7, 10.3	15.3 (56.2) -3.0, 33.7
$CPO_{reserve}$ (watts)	3.07 (0.65)	3.23 (0.67)	0.093	-0.17 (0.57) -0.35, 0.02	-4.0 (15.8) -9.1, 1.2
$SW_{reserve}$ (g.m)	80.9 (23.9)	80.6 (27.3)	0.946	0.3 (26.4) -8.3, 8.9	7.3 (36.2) -4.5, 19.1

SD: standard deviation; CI: confidence intervals; HR: heart rate; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Figure 6.5 Reserve variables at first trimester and post-partum



HR: heart rate; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work. *: p<0.01.

6.5.4 Second Trimester versus Post-partum

Changes in variables at rest and exercise, including reserve variables, between longitudinal tests performed in second trimester and post-partum are shown in Tables 6.7 to 6.10 and Figures 6.6 to 6.10. At rest HR_{rest} was significantly increased by 10% in the second trimester. This was accompanied by a significant drop in DBP_{rest} by 8%, MAP_{rest} by 4% and SVR_{rest} by 8%. There was no change in SBP_{rest}. There were also no significant changes in VO_{2rest}, CO_{rest}, CPO_{rest}, SV_{rest} or SW_{rest}. However the percentage increase in CO_{rest} in the second trimester compared to post-partum was significant, with a mean increase of 12% (SD: 31.8; CI: 3.3, 21.6).

At maximal exercise, HR_{max} was significantly lower in the second trimester by 4%. There were no significant changes seen in blood pressure or SVR_{max}. Exercise duration was significantly shorter by 90 seconds (11%) in the second trimester, which corresponded with a significantly lower $VO_{2\ max}$ and $VO_{2\ max/kg}$, by 6 and 12% respectively. $CircP_{max}$ was also significantly lower by 5% however, there were no significant changes in CO_{max}, CPO_{max}, SV_{max} or SW_{max}. As shown in Table 6.7, there were no differences in RER_{max} or VE_{max} however, $ETpCO_{2max}$ was significantly lower and symptom scores were significantly worse in the second trimester.

$HR_{reserve}$ was significantly lower the second trimester by 14%. Again there were no significant changes in $VO_{2reserve}$, $CO_{reserve}$, $SV_{reserve}$, $CPO_{reserve}$ or $SW_{reserve}$.

Table 6.7 Markers of exercise effort between second trimester and post-partum

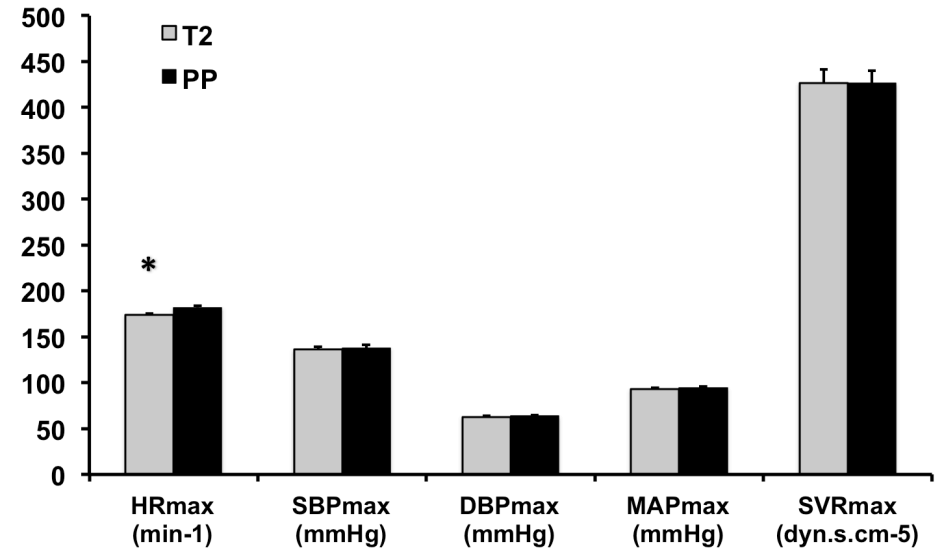
	RER_{max} Mean (SD)	**VE_{max}** Mean (SD)	**$ETpCO_{2max}$** Mean (SD)	**SF-36** Mean (SD)
T2	1.17 (0.10)	76.6 (19.3)	33.6 (4.6)	75.6 (9.5)
PP	1.17 (0.12)	77.9 (19.2)	34.7 (4.0)	81.5 (10.2)
P value	0.754	0.639	0.026	0.001

Table 6.8 Maximal exercise variables at second trimester and post-partum

	T2 Mean (SD)	PP Mean (SD)	P value	Δ Mean (SD) 95% CI	% Δ Mean (SD) 95% CI
HR_{max} (min^{-1})	173.9 (10.4)	182.0 (12.4)	<0.001	-8.1 (8.6) -10.6, -5.6	-4.3 (4.9) -5.7, -2.9
SBP_{max} (mmHg)	136.1 (19.8)	137.8 (25.8)	0.606	-1.7 (21.9) -8.0, 4.6	0.7 (16.5) -4.1, 5.4
DBP_{max} (mmHg)	62.7 (9.5)	63.6 (7.1)	0.505	-0.9 (9.1) -3.5, 1.7	-1.0 (13.9) -5.0, 3.0
MAP_{max} (mmHg)	92.7 (11.1)	94.2 (9.9)	0.197	-1.5 (7.8) -3.7, 0.8	-1.4 (8.3) -3.8, 1.0
SVR_{max} ($dyn.s.cm^{-5}$)	426 (100)	426 (93)	0.994	0.1 (79.7) -23.0, 23.1	1.0 (18.2) -4.2, 6.3
Ex Dur (mins)	10.7 (2.3)	12.2 (3.1)	<0.001	-1.5 (1.5) -1.9, -1.0	-11.0 (10.9) -14.1, -7.8
$VO_{2\ max}$ ($ml.min^{-1}$)	2039 (405)	2186 (446)	0.001	-146 (278) -227, -66	-5.8 (12.7) -9.5, -2.1
$VO_{2\ max/kg}$ ($ml.min^{-1}.kg^{-1}$)	29.6 (6.0)	34.0 (7.2)	<0.001	-4.4 (4.7) -5.7, -3.0	-11.8 (12.9) -15.5, -8.1
CO_{max} ($l.min^{-1}$)	18.0 (2.9)	18.2 (2.7)	0.534	-0.2 (2.4) -0.9, 0.5	-0.5 (13.0) -4.3, 3.2
CPO_{max} (watts)	3.68 (0.66)	3.79 (0.65)	0.210	-0.11 (0.58) -0.28, 0.06	-2.0 (14.7) -6.3, 2.2
$CircP_{max}$ ($mmHg.ml\ O_2.min^{-1}$)	280 (74)	303 (91)	0.018	-23 (64) -41, -5	-5.2 (19.6) -10.9, 0.4
SV_{max} (ml)	104.2 (15.1)	101.2 (15.3)	0.175	3.0 (14.7) -1.3, 7.2	4.0 (14.7) -1.3, 7.2
SW_{max} (g.m)	131.2 (23.6)	129.6 (23.6)	0.606	1.6 (21.3) -4.5, 7.8	2.4 (16.4) -2.3, 7.2

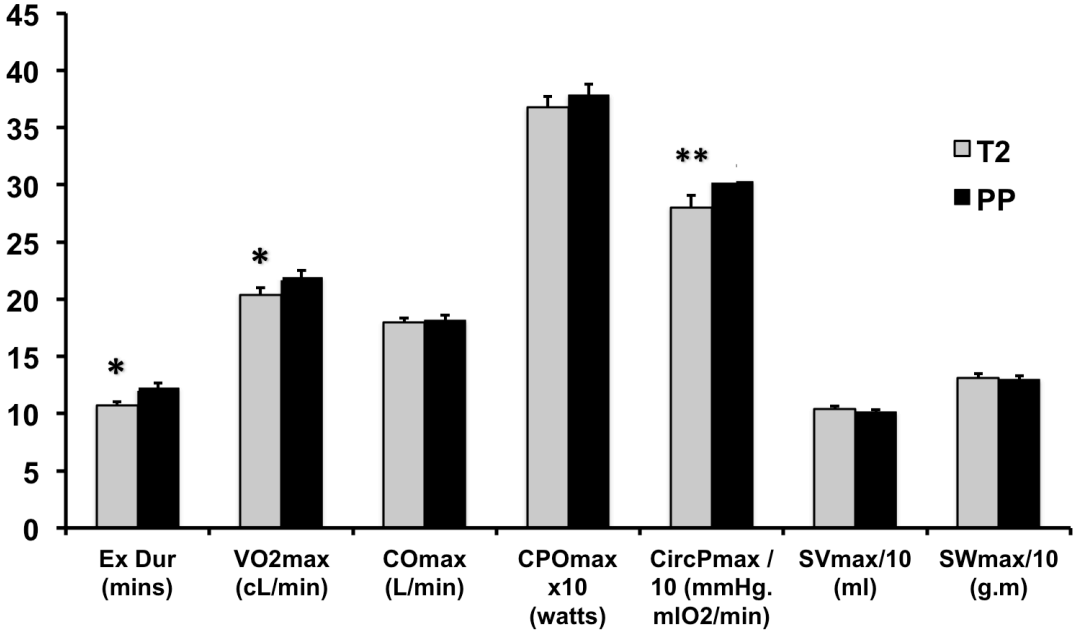
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; Ex Dur: exercise duration; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: circulatory power; SV: stroke volume; SW: stroke work.

Figure 6.6 Maximal exercise haemodynamics at second trimester and post-partum



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. *: p<0.01

Figure 6.7 Maximal exercise variables at second trimester and post-partum



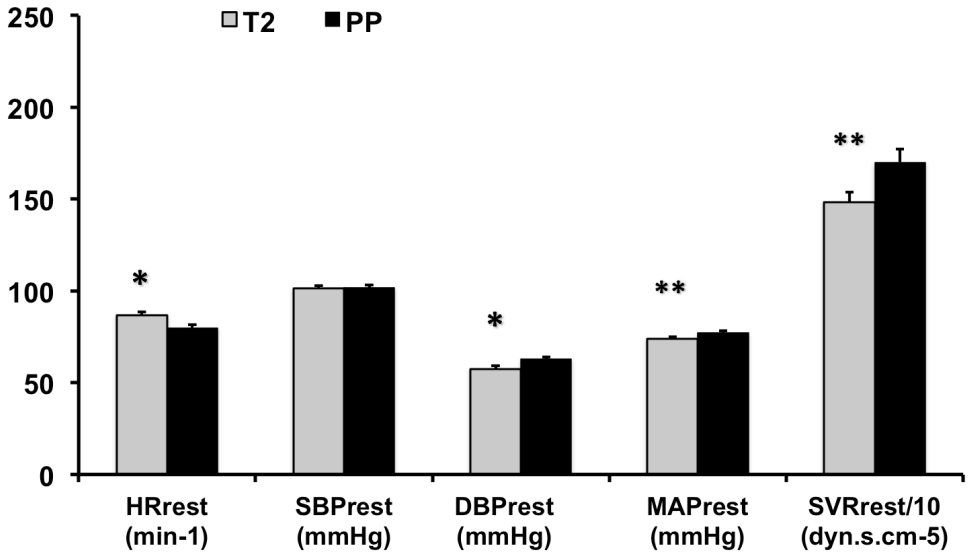
Ex Dur: exercise duration; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: Circulatory power; SV: stroke volume; SW: stroke work. *: p<0.01; **: p<0.05

Table 6.9 Resting variables at second trimester and post-partum

	T2 Mean (SD)	**PP** Mean (SD)	**P value**	**Δ** Mean (SD) 95% CI	**% Δ** Mean (SD) 95% CI
HR_{rest} (min^{-1})	86.7 (13.9)	79.9 (11.2)	0.001	6.8 (13.6) 2.9, 10.8	9.6 (17.7) 4.5, 14.7
SBP_{rest} (mmHg)	101.2 (11.6)	101.7 (10.0)	0.803	-0.5 (13.5) -4.4, 3.4	0.2 (13.3) -3.7, 4.0
DBP_{rest} (mmHg)	57.5 (10.9)	62.9 (7.5)	0.003	-5.4 (11.5) -8.7, -2.0	-7.8 (17.5) -12.9, -2.7
MAP_{rest} (mmHg)	73.8 (8.8)	77.2 (7.4)	0.028	-3.3 (10.0) -6.2, -0.5	-3.7 (12.9) -7.5, -0.02
SVR_{rest} ($dyn.s.cm^{-5}$)	1483 (369)	1700 (499)	0.010	-217 (545) -375, -60	-7.5 (29.3) -16.0, 1.0
$VO_{2\ rest}$ ($ml.min^{-1}$)	269 (83)	279 (121)	0.619	-10 (129) -47, 28	5.2 (34.4) -4.7, 15.2
CO_{rest} ($l.min^{-1}$)	4.22 (1.19)	3.92 (1.20)	0.069	0.30 (1.08) -0.02, 0.61	12.4 (31.8) 3.3, 21.6
CPO_{rest} (watts)	0.70 (0.23)	0.67 (0.22)	0.436	0.02 (0.20) -0.04, 0.08	8.2 (35.2) -2.0, 18.3
SV_{rest} (ml)	49.8 (14.8)	52.4 (17.9)	0.302	-2.6 (16.9) -7.5, 2.3	1.6 (35.9) -8.7, 12.0
SW_{rest} (g.m)	50.5 (18.2)	54.9 (19.7)	0.118	-4.4 (18.7) -9.8, 1.0	-2.1 (40.2) -13.8, 9.5

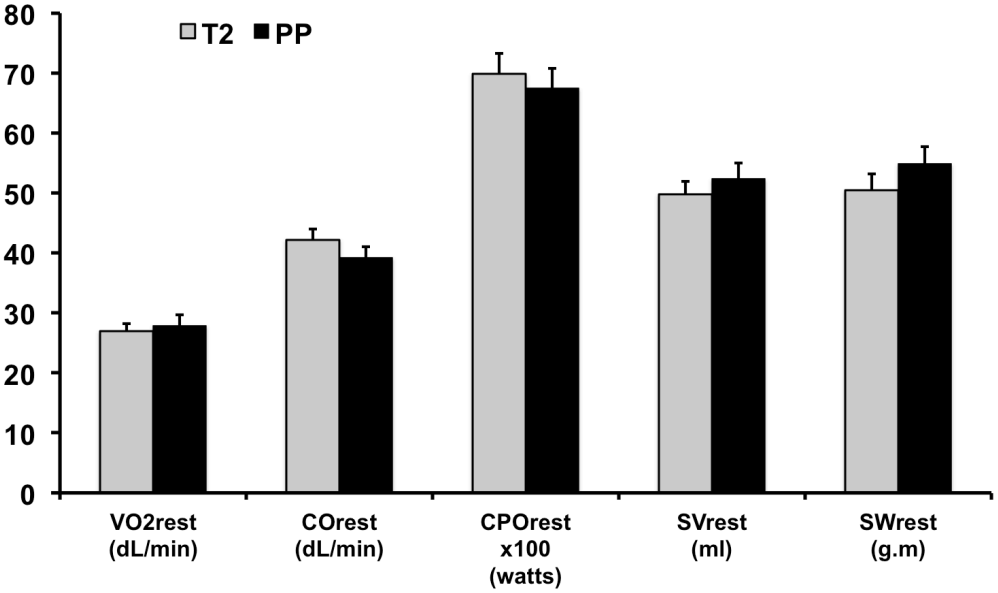
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Figure 6.8 Resting variables at second trimester and post-partum



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. *: p<0.01; **: p<0.05

Figure 6.9 Resting cardiac variables at second trimester and post-partum



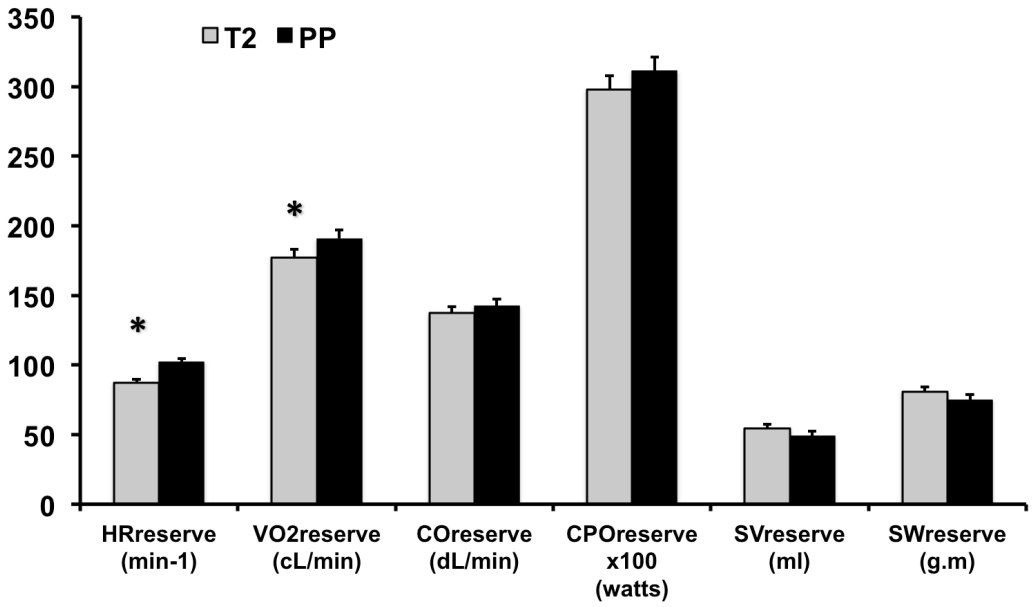
VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Table 6.10 Reserve variables at second trimester and post-partum

	T2 Mean (SD)	**PP** Mean (SD)	**P value**	**Δ** Mean (SD) 95% CI	**% Δ** Mean (SD) 95% CI
$HR_{reserve}$ (min^{-1})	87.2 (17.8)	102.2 (15.7)	<0.001	-14.9 (16.1) -19.6, -10.3	-13.7 (17.9) -18.9, -8.5
$VO_{2\ reserve}$ ($ml.min^{-1}$)	1770 (413)	1907 (441)	0.006	-137 (319) -229, -45	-5.8 (17.3) -10.8, -0.8
$CO_{reserve}$ ($l.min^{-1}$)	13.7 (3.2)	14.3 (3.2)	0.186	-0.5 (2.6) -1.3, 0.2	-1.9 (18.3) -7.2, 3.4
$SV_{reserve}$ (ml)	54.4 (18.9)	48.9 (24.7)	0.081	5.6 (21.2) -0.6, 11.7	33.6 (213) -28.1, 95.2
$CPO_{reserve}$ (watts)	2.98 (0.65)	3.11 (0.69)	0.133	-0.13 (0.58) -0.30, 0.04	-2.6 (18.3) -7.9, 2.7
$SW_{reserve}$ (g.m)	80.8 (23.4)	74.7 (28.9)	0.125	6.0 (26.2) -1.5, 13.6	24.7 (76.3) 2.6, 46.7

SD: standard deviation; CI: confidence intervals; HR: heart rate; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Figure 6.10 Reserve variables at second trimester and post-partum



HR: heart rate; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work. *: p<0.01.

6.5.5 Third Trimester versus Post-partum

Changes in variables at rest and exercise, including reserve variables, between longitudinal tests performed in third trimester and post-partum are shown in Tables 6.11 to 6.14 and Figures 6.11 to 6.15. At rest, HR_{rest} was significantly increased by 21% in the third trimester. There was no significant change in blood pressure or SVR_{rest}. Equally there were no significant changes in $VO_{2\ rest}$, CO_{rest}, CPO_{rest} or SW_{rest}. Interestingly SV_{rest} was significantly lower in the third trimester by 3.6% ($p = 0.046$). The mean percentage difference in CPO_{rest} was also significant higher in the third trimester by 14% (SD: 31.6, CI: 5.1, 23.8).

At maximal exercise, HR_{max} was significantly lower in the third trimester. There were no significant changes in blood pressure, but SVR_{max} was significantly increased by 10%. Exercise duration was significantly shorter by 2 minutes 18 seconds (18%), which corresponded with a lower $VO_{2\ max}$ by 6% and $VO_{2\ max/kg}$ by 18%. CO_{max} was also significantly lower by 4% however, CPO_{max}, $CircP_{max}$, SV_{max} and SW_{max} did not significantly change between tests. As shown in Table 6.11, there were no differences in VE_{max} however, RER_{max} and $ETpCO_{2max}$ were significantly lower and symptom scores were significantly worse in the third trimester.

$HR_{reserve}$ was significantly reduced in the third trimester by 18%. Equally $VO_{2reserve}$ and $CO_{reserve}$ were significantly smaller by 7 and 6% respectively. $CPO_{reserve}$, $SV_{reserve}$ and $SW_{reserve}$ were not significantly different however, the mean percentage difference showed a significant increase in $SW_{reserve}$ in the third trimester by 27% (SD: 75.7, CI: 4.6, 49.4).

Table 6.11 Markers of exercise effort between third trimester and post-partum

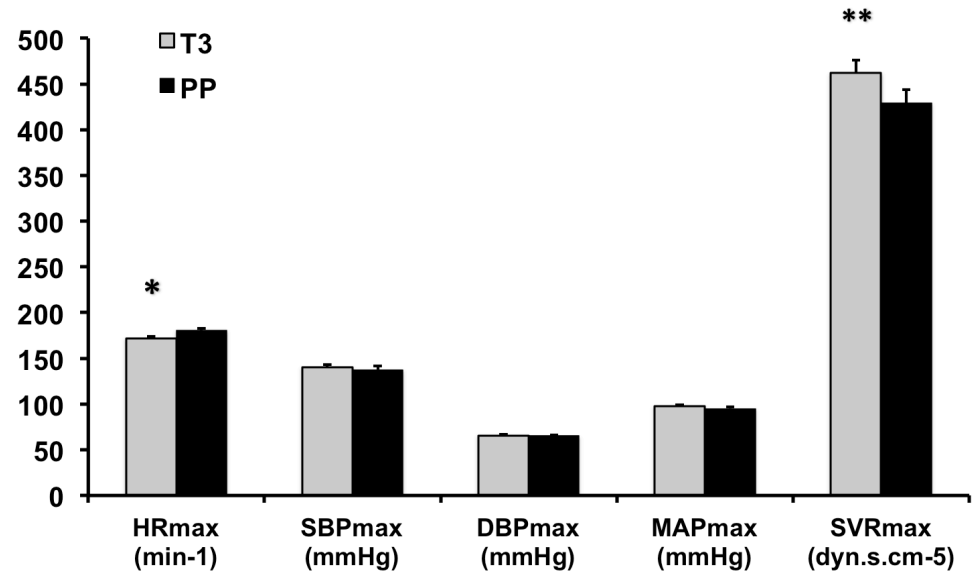
	RER_{max} Mean (SD)	**VE_{max}** Mean (SD)	**$ETpCO_{2\ max}$** Mean (SD)	**SF-36** Mean (SD)
T3	1.11 (0.08)	75.8 (15.3)	32.1 (3.7)	67.9 (11.8)
PP	1.16 (0.13)	78.9 (17.1)	34.9 (3.6)	81.2 (11.0)
P value	0.003	0.176	<0.0001	<0.0001

Table 6.12 Maximal exercise variables at third trimester and post-partum

	T3 Mean (SD)	PP Mean (SD)	P value	Δ Mean (SD) 95% CI	% Δ Mean (SD) 95% CI
HR_{max} (min^{-1})	171.9 (12.0)	180.7 (15.3)	<0.001	-8.8 (12.9) -12.6, -5.0	-4.4 (9.4) -7.1, -1.6
SBP_{max} (mmHg)	140.3 (20.1)	137.4 (26.1)	0.429	2.9 (24.2) -4.2, 10.1	4.5 (18.1) -0.9, 9.8
DBP_{max} (mmHg)	65.7 (8.4)	65.0 (7.8)	0.611	0.7 (8.4) -1.8, 3.1	1.6 (13.0) -2.2, 5.5
MAP_{max} (mmHg)	97.5 (10.7)	95.1 (10.2)	0.095	2.5 (9.6) -0.4, 5.3	3.0 (10.3) 0.01, 6.1
SVR_{max} ($dyn.s.cm^{-5}$)	462 (95)	429 (98)	0.015	33 (85) 7.4, 57.9	9.6 (19.6) 3.8, 15.4
Ex Dur (mins)	10.0 (2.5)	12.3 (3.1)	<0.001	-2.3 (1.6) -2.8, -1.8	-18.1 (12.1) -21.7, -14.5
$VO_{2\ max}$ ($ml.min^{-1}$)	2074 (373)	2222 (421)	0.002	-147 (296) -235, -60	-5.6 (13.0) -9.4, -1.7
$VO_{2\ max/kg}$ ($ml.min^{-1}.kg^{-1}$)	27.7 (5.4)	34.1 (7.3)	<0.001	-6.4 (4.9) -7.8, -5.0	-17.6 (12.5) -21.3, -13.9
CO_{max} ($l.min^{-1}$)	17.3 (2.6)	18.3 (2.9)	0.013	-0.9 (2.4) -1.6, -0.2	-4.1 (12.6) -7.8, -0.4
CPO_{max} (watts)	3.74 (0.68)	3.83 (0.66)	0.345	-0.09 (0.62) -0.27, 0.09	-1.3 (15.1) -5.8, 3.1
$CircP_{max}$ ($mmHg.ml\ O_2.min^{-1}$)	292 (73)	306 (84)	0.248	-13 (76) -36, 9	-0.9 (24.5) -8.1, 6.4
SV_{max} (ml)	103.4 (16.5)	103.7 (20.0)	0.906	-0.4 (19.8) -6.2, 5.5	1.6 (18.0) -3.7, 6.9
SW_{max} (g.m)	136.8 (24.8)	134.1 (30.0)	0.496	2.7 (26.3) -5.0, 10.5	4.2 (18.3) -1.2, 9.6

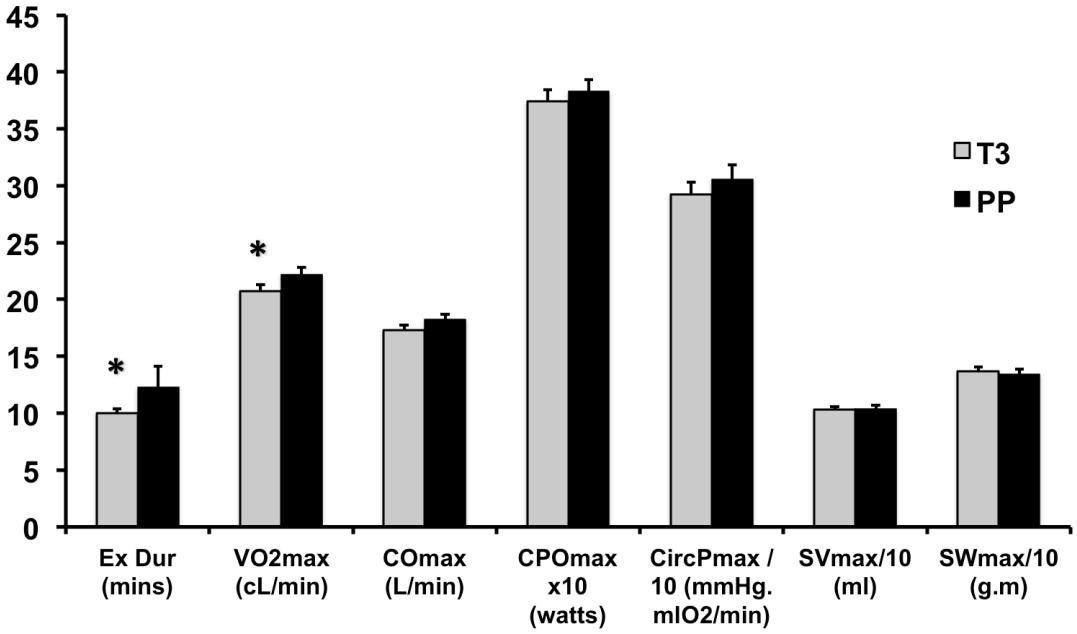
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; Ex Dur: exercise duration; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: circulatory power; SV: stroke volume; SW: stroke work.

Figure 6.11 Maximal exercise haemodynamics at third trimester and post-partum



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. *: p<0.01; **: p<0.05.

Figure 6.12 Maximal exercise variables at third trimester and post-partum



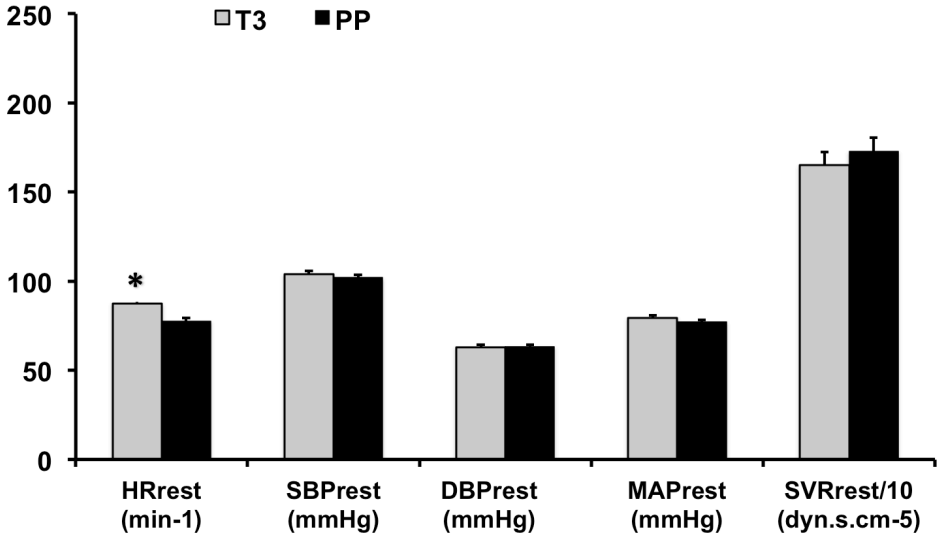
Ex Dur: exercise duration; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: Circulatory power; SV: stroke volume; SW: stroke work. *: p<0.01.

Table 6.13 Resting variables at third trimester and post-partum

	T3 Mean (SD)	PP Mean (SD)	P value	Δ Mean (SD) 95% CI	% Δ Mean (SD) 95% CI
HR_{rest} (min^{-1})	87.4 (14.8)	77.6 (11.8)	<0.001	9.9 (15.3) 5.4, 14.4	21.2 (3.2) 8.1, 20.7
SBP_{rest} (mmHg)	103.9 (12.7)	102.0 (10.5)	0.391	1.9 (14.4) -2.4, 6.2	2.6 (13.9) -1.5, 6.7
DBP_{rest} (mmHg)	63.0 (10.1)	63.3 (8.0)	0.841	-0.3 (10.4) -3.4, 2.8	0.4 (16.2) -4.4, 5.1
MAP_{rest} (mmHg)	79.3 (10.0)	77.1 (7.5)	0.152	2.2 (10.0) -0.8, 5.1	3.3 (12.6) -0.4, 7.0
SVR_{rest} ($dyn.s.cm^{-5}$)	1650 (491)	1727 (524)	0.398	-78 (603) -256, 100	0.95 (32.4) -8.6, 10.5
$VO_{2\ rest}$ ($ml.min^{-1}$)	288 (74)	270 (118)	0.365	18 (132) -21, 57	17.0 (39.3) 5.4, 28.6
CO_{rest} ($l.min^{-1}$)	4.06 (0.86)	3.84 (1.05)	0.193	0.22 (1.10) -0.11, 0.54	11.5 (31.7) 2.1, 20.8
CPO_{rest} (watts)	0.71 (0.17)	0.66 (0.19)	0.080	0.05 (0.20) -0.01, 0.11	14.4 (31.6) 5.1, 23.8
SV_{rest} (ml)	47.7 (11.8)	52.9 (15.9)	0.046	-5.2 (16.8) -10.2, -0.2	-3.6 (31.7) -13.0, 5.8
SW_{rest} (g.m)	51.2 (13.4)	55.4 (17.5)	0.118	-4.3 (17.7) -9.5, 1.0	-1.6 (30.3) -10.5, 7.4

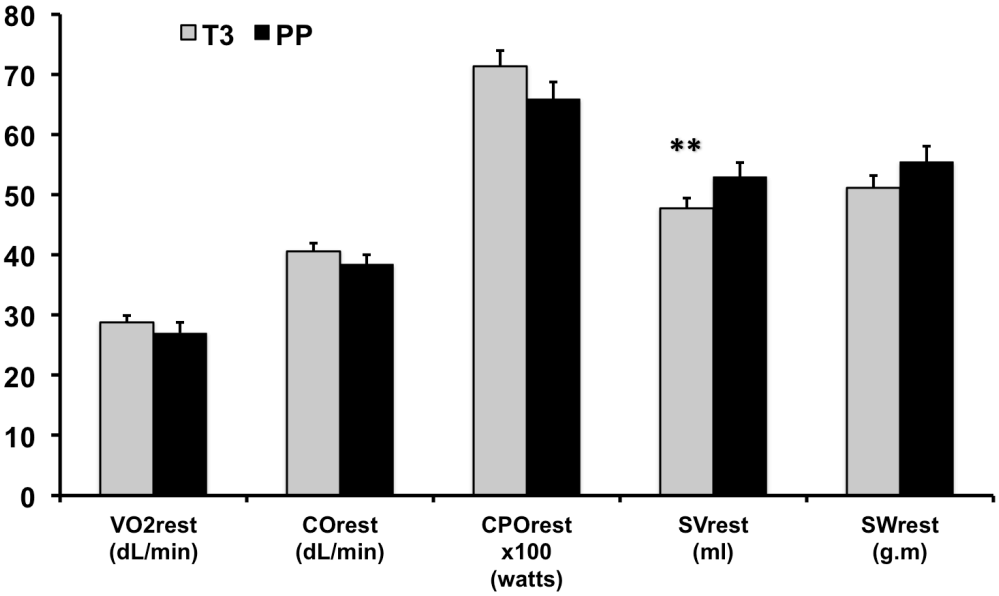
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Figure 6.13 Resting variables at third trimester and post-partum



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. *: p<0.01.

Figure 6.14 Resting cardiac variables at third trimester and post-partum



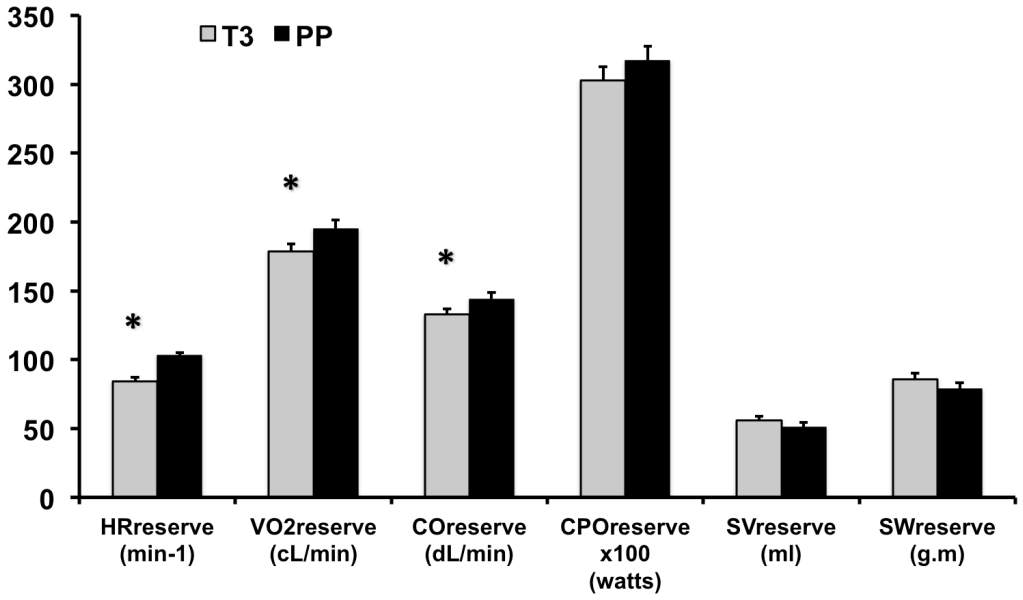
VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work. **: p<0.05.

Table 6.14 Reserve variables at third trimester and post-partum

	T3 Mean (SD)	PP Mean (SD)	P value	Δ Mean (SD) 95% CI	% Δ Mean (SD) 95% CI
$HR_{reserve}$ (min^{-1})	84.5 (18.8)	103.1 (14.0)	<0.001	-18.7 (16.3) -23.5 , -13.9	-17.8 (17.4) -23.0, -12.7
$VO_{2\ reserve}$ ($ml.min^{-1}$)	1786 (365)	1952 (421)	0.001	-166 (317) -259, -72	-7.0 (15.5) -11.5, -2.4
$CO_{reserve}$ ($l.min^{-1}$)	13.3 (2.9)	14.4 (3.2)	0.006	-1.1 (2.6) -1.9, -0.4	-6.0 (17.9) -11.3, -0.8
$SV_{reserve}$ (ml)	55.7 (20.6)	50.83 (23.9)	0.222	4.8 (25.9) -2.8, 12.5	31.6 (179) -21.3, 84.4
$CPO_{reserve}$ (watts)	3.03 (0.64)	3.17 (0.68)	0.145	-0.14 (0.64) -0.33, 0.05	-2.7 (18.9) -8.2, 2.9
$SW_{reserve}$ (g.m)	85.6 (24.2)	78.7 (29.7)	0.156	7.0 (32.0) -2.5, 16.4	27.0 (75.7) 4.6, 49.4

SD: standard deviation; CI: confidence intervals; HR: heart rate; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Figure 6.15 Reserve variables at third trimester and post-partum



HR: heart rate; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work. *: p<0.01.

6.5.2 Post-partum versus Pre-conception

Changes in variables at rest and exercise, including reserve variables, between longitudinal tests performed in pre-conception and post-partum are shown in Tables 6.15 to 6.18 and Figures 6.16 to 6.20. At rest there was significantly lower mean HR_{rest} seen in pre-conception, by 13%. Mean SBP_{rest}, DBP_{rest} and MAP_{rest} were significantly higher in pre-conception by 8%, 14% and 14% respectively. This was accompanied by a significantly higher mean SVR_{rest} by 37%. VO_{2rest} was lower in pre-conception by 14%, although just failed to reach significance ($p = 0.092$). CO_{rest} was also lower by 11% and again just failed to reach significance ($p = 0.058$). However, CPO_{rest}, SV_{rest} and SW_{rest} did not significantly change between tests.

At maximal exercise there were no significant differences in HR_{max} or blood pressure. SVR_{max} was significantly lower in pre-conception by 10%. Exercise duration did not significantly change although, there were significantly higher values for VO_{2max} by 24%, $VO_{2\ max/kg}$ by 27%, CO_{max} by 10%, $CircP_{max}$ by 31% and SV_{max} by 9% seen in pre-conception. Although CPO_{max} appeared to be higher in pre-conception, it just failed to reach significance ($p = 0.062$). As shown in Table 6.15, there were no differences in RER_{max} or symptom scores however, VE_{max} and $ETpCO_{2max}$ were higher in pre-conception.

$HR_{reserve}$ was significantly greater in pre-conception by 12%, as were $VO_{2\ reserve}$ by 32%, $CO_{reserve}$ by 16%, $SV_{reserve}$ by 25% and $CPO_{reserve}$ by 11%.

Table 6.15 Markers of exercise effort and symptoms between pre-conception and post-partum

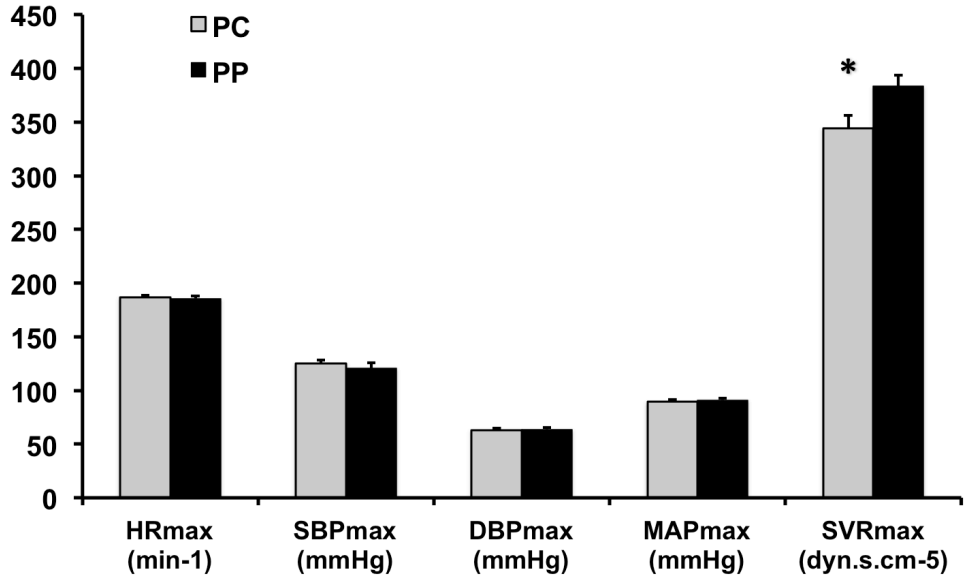
	RER_{max} Mean (SD)	**VE_{max}** Mean (SD)	**$ETpCO_{2max}$** Mean (SD)	**SF-36** Mean (SD)
PC	1.20 (0.10)	95.0 (19.2)	37.1 (3.0)	83.8 (7.8)
PP	1.18 (0.14)	80.1 (18.3)	34.5 (3.8)	80.5 (9.7)
P value	0.286	0.003	0.025	0.103

Table 6.16 Maximal exercise variables at pre-conception and post-partum

	PC Mean (SD)	**PP** Mean (SD)	**P value**	**Δ** Mean (SD) 95% CI	**% Δ** Mean (SD) 95% CI
HR_{max} (min^{-1})	186.9 (7.1)	185.6 (9.8)	0.505	1.2 (7.5) -2.3, 4.8	0.8 (4.1) -1.2, 2.8
SBP_{max} (mmHg)	125.3 (12.3)	120.9 (20.7)	0.297	4.4 (16.9) -3.6, 12.4	5.6 (15.1) -1.6, 12.7
DBP_{max} (mmHg)	63.1 (7.0)	63.8 (6.3)	0.700	-0.7 (7.1) -4.1, 2.7	-0.6 (11.4) -6.0, 4.8
MAP_{max} (mmHg)	89.6 (7.4)	91.2 (7.0)	0.407	-1.6 (7.6) -5.2, 2.1	-1.5 (7.6) -5.2, 2.3
SVR_{max} ($dyn.s.cm^{-5}$)	344 (49)	383 (43)	0.001	-39 (39) -0.58, -21	-10.0 (9.9) -14.7, -5.3
Ex Dur (mins)	12.8 (3.5)	12.9 (3.7)	0.848	-0.07 (1.4) -0.8, 0.6	-0.01 (12.2) -5.8, 5.8
$VO_{2\ max}$ ($ml.min^{-1}$)	2584 (476)	2115 (437)	<0.001	469 (352) 301, 636	24.1 (20.4) 14.5, 33.8
$VO_{2\ max/kg}$ ($ml.min^{-1}.kg^{-1}$)	41.0 (7.0)	33.1 (7.9)	<0.001	7.9 (5.6) 5.2, 10.6	26.9 (21.0) 5.2, 10.6
CO_{max} ($l.min^{-1}$)	21.1 (2.9)	19.2 (2.2)	0.002	1.9 (2.2) 0.9, 3.0	10.4 (11.8) 4.8, 16.0
CPO_{max} (watts)	4.21 (0.76)	3.89 (0.64)	0.062	0.32 (0.66) 0.01, 0.64	9.0 (16.6) 1.2, 16.9
$CircP_{max}$ ($mmHg.ml\ O_2.min^{-1}$)	325 (75)	256 (68)	0.001	69 (60) 41, 97	31.0 (28.3) 17.6, 44.5
SV_{max} (ml)	115.3 (17.3)	105.7 (12.6)	0.010	9.5 (13.5) 3.1, 16.0	9.3 (13.6) 2.9, 15.8
SW_{max} (g.m)	141.1 (28.3)	131.6 (22.6)	0.128	9.5 (24.4) -2.1, 21.1	8.1 (18.5) -0.7, 16.9

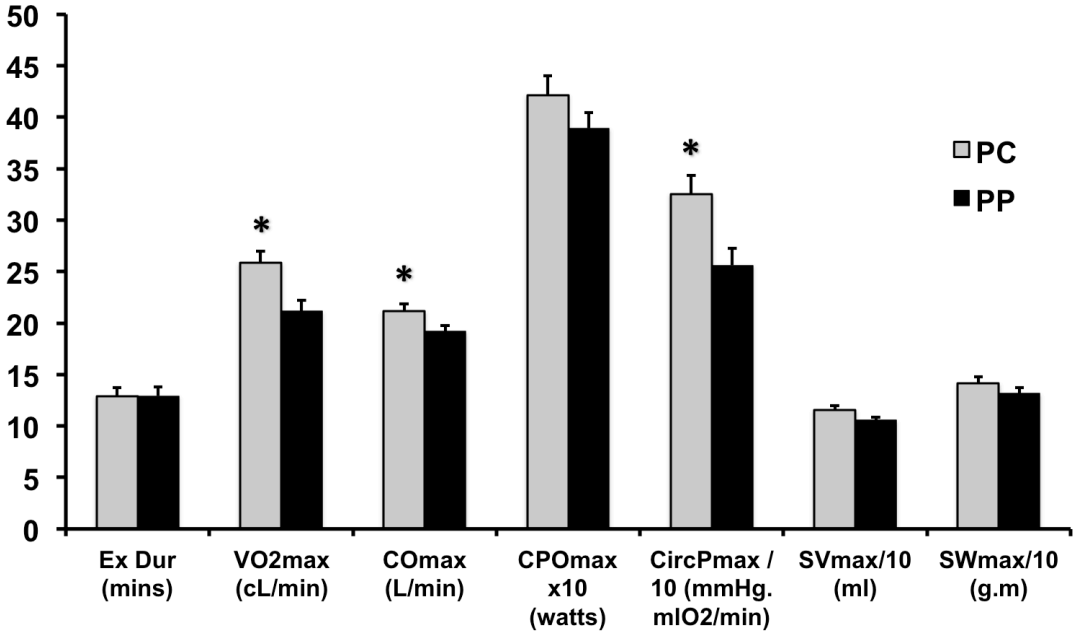
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; Ex Dur: exercise duration; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: circulatory power; SV: stroke volume; SW: stroke work.

Figure 6.16 Maximal exercise haemodynamics at pre-conception and post-partum



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. *: p<0.01

Figure 6.17 Maximal exercise variables at pre-conception and post-partum



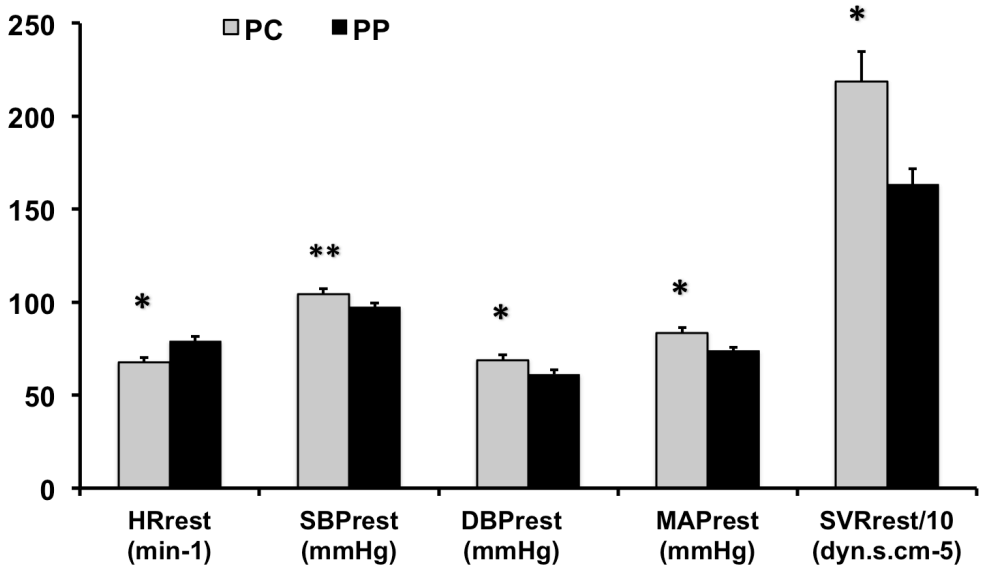
Ex Dur: exercise duration; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: Circulatory power; SV: stroke volume; SW: stroke work. *: p<0.01

Table 6.17 Resting variables at pre-conception and post-partum

	PC Mean (SD)	**PP** Mean (SD)	**P value**	**Δ** Mean (SD) 95% CI	**% Δ** Mean (SD) 95% CI
HR_{rest} (min^{-1})	67.8 (10.2)	79.1 (11.2)	0.002	-11.2 (12.2) -17.0, -5.4	-13.3 (13.6) -19.7, -6.8
SBP_{rest} (mmHg)	104.4 (12.1)	97.2 (10.3)	0.045	7.2 (13.6) 0.7, 13.7	8.1 (14.1) 1.4, 14.8
DBP_{rest} (mmHg)	68.9 (11.8)	61.2 (9.4)	0.005	7.8 (10.0) 3.0, 12.5	13.7 (19.3) 4.6, 22.9
MAP_{rest} (mmHg)	88.5 (11.3)	73.8 (8.5)	0.001	9.8 (10.0) 5.0, 14.5	13.9 (14.8) 6.8, 20.9
SVR_{rest} ($dyn.s.cm^{-5}$)	2187 (670)	1633 (345)	0.002	553 (602) 267, 839	36.6 (38.8) 18.1, 55.0
VO_{2rest} ($ml.min^{-1}$)	200 (44)	263 (158)	0.092	-63 (144) -131, 6	-13.7 (29.1) -27.6, 0.2
CO_{rest} ($l.min^{-1}$)	3.25 (0.77)	3.73 (0.72)	0.058	-0.49 (0.98) -0.95, -0.02	-10.9 (26.0) -23.2, 1.5
CPO_{rest} (watts)	0.61 (0.17)	0.61 (0.14)	0.876	-0.01 (0.20) -0.10, 0.09	2.3 (36.8) -15.2, 19.8
SV_{rest} (ml)	46.7 (14.7)	49.4 (11.0)	0.419	-2.7 (13.5) -9.1, 3.7	-3.7 (27.3) -16.7, 9.2
SW_{rest} (g.m)	53.2 (17.9)	49.3 (11.5)	0.359	4.0 (17.2) -4.2, 12.1	10.5 (39.2) -8.1, 29.2

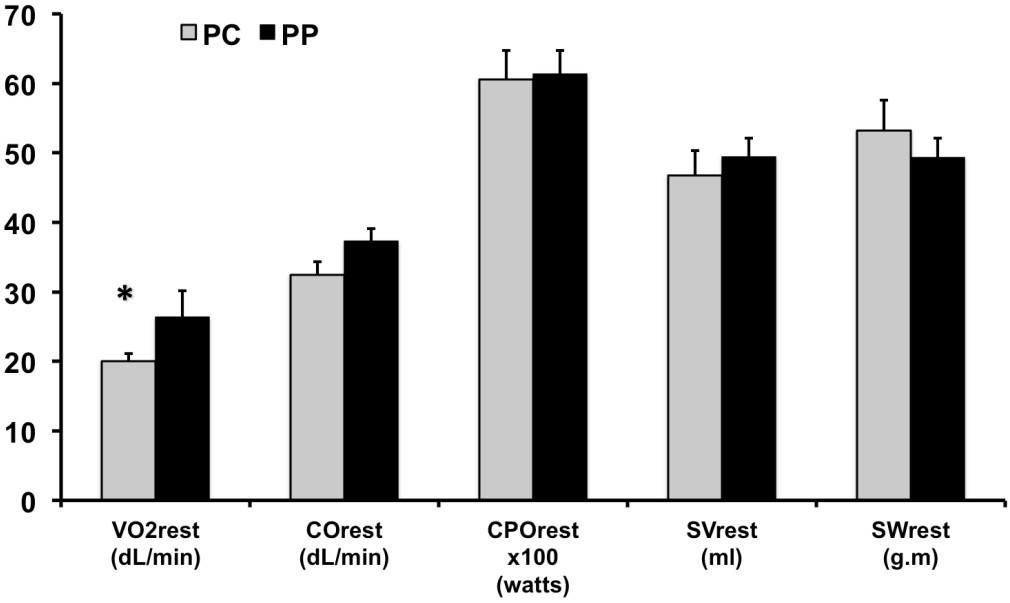
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Figure 6.18 Resting variables at pre-conception and post-partum



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. *: p<0.01; **: p<0.05

Figure 6.19 Resting cardiac variables at pre-conception and post-partum



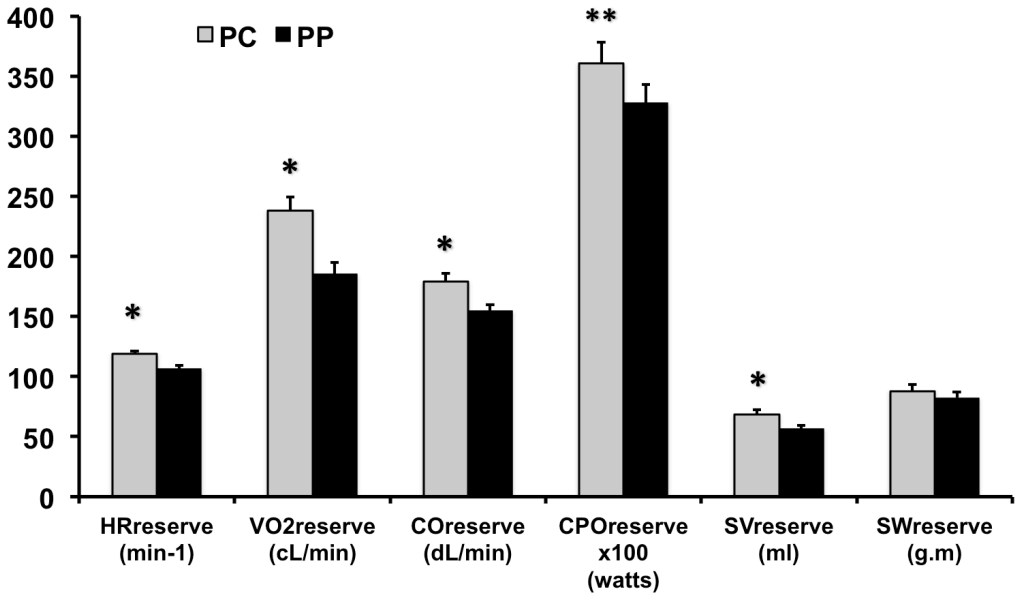
VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work. *: p<0.01

Table 6.18 Reserve variables at pre-conception and post-partum

	PC Mean (SD)	PP Mean (SD)	P value	Δ Mean (SD) 95% CI	% Δ Mean (SD) 95% CI
$HR_{reserve}$ (min^{-1})	119.1 (10.0)	106.6 (11.5)	<0.001	12.5 (8.9) 8.3, 16.7	12.3 (9.2) 7.9, 16.7
$VO_{2reserve}$ ($ml.min^{-1}$)	2383 (457)	1852 (413)	<0.001	532 (361) 360, 703	31.8 (26.4) 19.2, 44.3
$CO_{reserve}$ ($l.min^{-1}$)	17.9 (2.9)	15.5 (2.2)	<0.001	2.4 (2.2) 1.4, 3.5	16.3 (16.1) 8.6, 23.9
$SV_{reserve}$ (ml)	68.6 (16.0)	56.3 (11.9)	0.004	12.2 (14.9) 5.2, 19.3	24.9 (31) 10.2, 39.6
$CPO_{reserve}$ (watts)	3.61 (0.72)	3.28 (0.64)	0.043	0.33 (0.62) 0.04, 0.62	11.2 (19.5) 1.9, 20.5
$SW_{reserve}$ (g.m)	87.9 (22.3)	82.3 (20.7)	0.301	5.6 (21.4) -4.6, 15.7	9.4 (26.7) -3.3, 22.1

SD: standard deviation; CI: confidence intervals; HR: heart rate; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Figure 6.20 Reserve variables at pre-conception and post-partum



HR: heart rate; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work. *: p<0.01; **: p<0.05.

6.6 Discussion

The purpose of this study was to determine how pregnancy at each trimester affects resting, peak and reserve metabolic function and cardiovascular haemodynamics. As the study used post-partum as a baseline, it was also important to establish whether, three months after completed pregnancy, reserve metabolic function and cardiovascular haemodynamics were different from pre-conception.

Longitudinal measures were taken in each trimester and then 3 months post-partum to allow direct comparison. However, comparisons between trimesters were not performed because of the differences in the numbers and individuals recruited. The changes seen in each trimester were as follows:

1st trimester: HR_{max}, $HR_{reserve}$ and exercise duration were significantly reduced in the 1st trimester compared to post-partum by 4%, 7% and 6% respectively. DBP_{rest} and VO_{2rest} were significantly reduced in the 1st trimester compared to post-partum by 6% and 7% respectively.

2nd trimester: HR_{max}, $HR_{reserve,}$ exercise duration, VO_{2max}, $VO_{2reserve}$ and $CircP_{max}$ were all significantly reduced in the 2nd trimester compared to post-partum by 4%, 14%, 11%, 6%, 6%, 5% respectively. DBP_{rest}, MAP_{rest} and SVR_{rest} were significantly reduced in the 2nd trimester compared to post-partum by 8%, 4% and 8% respectively.

3rd trimester: HR_{max}, $HR_{reserve,}$ exercise duration, VO_{2max}, $VO_{2reserve}$ and $CO_{reserve}$ were all significantly reduced in the 3rd trimester compared to post-partum by 4%, 18%, 18%, 6%, 7%, 6% respectively.

Based on these findings and using post-partum as a surrogate for the non-pregnant state, the present study has shown that markers of physical performance, including HR_{max}, $HR_{reserve,}$ exercise duration, VO_{2max}, $VO_{2reserve}$ all reduce in pregnancy. Although no comparison was made between trimesters, the physical function appeared to progressively worsen as gestation advanced and so is in agreement with the first hypothesis. The progressive reduction in reserve HR and VO_2 appeared to be because of the increase in basal metabolic demands and limited aerobic capacity with exercise. Inevitably a large proportion of those demands were likely to be driven by the added weight gain.

Despite the reduction in physical performance and physiological lowering of blood pressure and SVR in the early stages of pregnancy, CPO_{max} or $CPO_{reserve}$ remained

unchanged throughout pregnancy compared to post-partum. This suggests a protective or adaptive mechanism arises, where there is maintenance of both CPO_{rest} and CPO_{max}. At rest, this response is driven by a maintenance and eventual increase in flow generating capacity in pregnancy, whilst the pressure generating capacity only improves in the latter stage of pregnancy, as more weight is carried. , blood pressure returns to normal, and CO is maintained, and so maintaining overall cardiac reserve. It is likely that the blood pressure recovery in the latter stages of pregnancy, is in part due to the chronic isometric exercise of carrying the foetus. At maximal exercise both the flow and pressure generating capacity were maintained in each trimester. There was no increase in CPO_{max} in the third trimester when there was the most weight gain and so is in disagreement with hypothesis ii.

Again a differing response was seen between indirect markers of cardiac performance, namely VO_{2max} and $CircP_{max}$, and the direct measure CPO_{max}. This follows on from what was shown in study IV and V and therefore one can advise that it is necessary to measure cardiac performance directly, rather than indirectly, during pregnancy to establish cardiac reserve.

Importantly, there were a number of differences in post-partum, compared to pre-conception. Exercise duration did not change however, VO_{2max}, CO_{max}, $CircP_{max}$, SV_{max}, $HR_{reserve}$, $VO_{2reserve}$, $CO_{reserve}$, $SV_{reserve}$ and $CPO_{reserve}$ were all significantly lower, whilst SVR_{max} was significantly higher in post-partum. At rest, HR_{rest}, SBP_{rest}, DBP_{rest}, MAP_{rest} and SVR_{rest} were significantly lower, whilst VO_{2rest} and CO_{rest} were significantly higher in post-partum. This clearly highlights significant physiological differences between both states. There was a non-significant 2kg increase in weight in post-partum and a minor non-significant reduction in quality of life score. In addition to this many women stated that they significantly reduced the amount of routine exercise both in pregnancy and in the post-partum period. However despite this it appears implausible that the differences can be explained by a minor change in weight gain and drop in cardiovascular fitness, especially as there was no difference in overall exercise time performed. It therefore suggests that the physiological changes that occurred in pregnancy have not reversed by 3 months. Although there are many studies investigating cardiovascular changes in pregnancy, there are very few studies that made assessments in both pre-conception and post-partum. This appears to be the first study that studied the changes in peak cardiac function from pre-conception to post-partum. Capeless and Clapp [Capeless and Clapp 1991] used echocardiography to measure resting stroke volume and found that stroke volume remained elevated over pre-conception levels up to 12 weeks. However, Atkin *et al* [Atkin *et al* 1981] found that cardiac output fell in the post-partum period to levels lower than that in pre-conception,

before eventually rising to pre-conception levels by 10 months. Their data however showed a fall in cardiac output at the end of pregnancy, which is out of keeping with all the other data and raised questions about the validity of their technique. Robson et al [Robson *et al* 1987] studied the change in resting cardiac output using echocardiography from 38 weeks pregnant up to 24 weeks post-partum with serial measurements and found that the resting cardiac output fell significantly in the first 2 weeks and then more gradually fell up until 24 weeks. Mahendru *et al* [Mahendru *et al* 2014] studied blood pressure and cardiac output changes using an inert gas technique and found that resting cardiac output and changes in SVR and blood pressure had returned to baseline by 14-17 weeks post-partum and SVR. Sady *et al* [Sady *et al* 1990] examined changes in cardiac output, using an acetylene rebreathing technique, at rest, sub-maximal and maximal upright cycle exercise in pregnancy and then 2 months and 7 months post-partum. She found that submaximal antepartum VO_2, HR and SV were higher than at 7, but not 2 months post-partum. There was no difference in maximal HR or VO_2 between groups, although cardiac output and stroke volume was higher in antepartum compared to both post-partum groups. The present study seems to agree with the finding that resting cardiac function remains elevated at 3 months post-partum, however in contrast to this suggests that CO_{max}, VO_{2max} and cardiac reserve are diminished in the post-partum at 3 months. This study however does not tell us if and when these changes return to baseline.

6.61 Study Limitations

The study was limited by the inability to measure cardiac output and blood pressure continuously, using non-invasive methods, during exercise. This is not technically possible with the methods used, and can only be more accurately done with invasive measurements, which were felt not to be ethically appropriate. The non-pregnant state chosen in this study was at 3 months post-partum. As shown in the final comparison of data between pre-conception and post-partum, this is likely to be a non valid technique due to the ongoing differences in haemodynamics. Recruiting and studying women from pre-conception is much more difficult, predominantly due to the uncertain timeframe within which women become pregnant. The study was also performed with a predominantly Caucasian population, and therefore one has to apply caution applying these results to a non-caucasian population.

6.7 Conclusions

This study examined the differences in resting, peak and reserve metabolic function and cardiovascular haemodynamics during pregnancy and post-partum. Overall the consistent theme through pregnancy is worsening exercise tolerance with a reduction in HR_{max}, $HR_{reserve}$, VO_{2max} and $VO_{2reserve}$, whilst maintaining the flow and pressure generating cardiac performance, i.e. CPO_{max}, $CPO_{reserve}$, SW_{max} and $SW_{reserve}$. This shows that the deterioration in exercise and aerobic capacity throughout pregnancy are more likely to be secondary to the increased metabolic demands of pregnancy and are not caused by worsening cardiac function. The adaptation in cardiac performance and cardiac reserve is therefore likely to be related to the increased circulating blood volume and weight carriage.

Chapter 7

Longitudinal cardiovascular physiological effects of pregnancy from pre-conception to post-partum

Chapter 7

Study VII: Longitudinal cardiovascular effects of pregnancy from pre-conception to post-partum

7.1 Introduction

Optimal management of women with heart disease in pregnancy requires the correct appraisal of the abnormal heart to make the necessary adaptations to the major haemodynamic and respiratory changes that take place in pregnancy, labour and delivery [Oakley 2007]. Therefore, it is absolutely essential that there is a comprehensive understanding of how the healthy heart adapts in pregnancy. Cardiovascular physiological changes have been studied extensively at rest with only a handful of studies examining dynamic changes with exercise and even less at maximal exercise. The advantage of testing cardiovascular haemodynamics at maximal exercise is to enable measurement of cardiac reserve [Tan 1991]. In addition, many of the earliest studies during exercise were cross sectional design, rather than longitudinal and so making causal inference less certain [Artal *et al* 1986; Heenan *et al* 1986]. Longitudinal studies generally demand additional money and time and are often difficult to implement. Hence the sample sizes are often much lower due to the attrition of volunteers over the study period [Rindfleisch *et al* 2008]. Furthermore the majority of studies use post-partum as a surrogate of the non pregnant state, rather than pre-conception. The differences in resting cardiac output and cardiac dimensions at pre-conception and post-partum has been examined and reported [Robson *et al* 1987; Capeless and Clapp 1991; Clapp and Capeless 1997]. Robson *et al* showed a significant fall in cardiac output of 27-29% by 2 weeks, with a much more gradual decline up to 24 weeks. Capeless and Clapp showed that cardiac output remained elevated above pre-conception levels at 52 weeks post-partum. Study VI also found that CO_{rest} was significantly higher at 3 months post-partum and that CO_{max}, $CO_{reserve}$ and $CPO_{reserve}$ were all significantly lower in post-partum. This highlights the importance of good study design, to allow us to try and establish a causal relationship to the cardiovascular physiological changes in pregnancy.

Longitudinal studies, that have used pre-conception as the non-pregnant baseline, have shown that that resting HR and CO increases, whilst blood pressure and SVR decreases, from as early as 5 weeks [Atkins *et al* 1981; Robson *et al* 1989;

Capeless and Clapp 1989; Desai *et al* 2004; Mahendru *et al* 2014]. Longitudinal changes in CO_{max} or CPO_{max} between pre-conception and pregnancy have not been previously reported.

7.2 Purpose and hypothesis of the study

The purpose of this study was to establish what physiological cardiovascular changes occur at rest and maximal exercise between pre-conception and pregnancy in healthy female subjects.

The hypotheses tested in this investigation were

(i) Pregnancy is associated with an increase in resting cardiac function compared to pre-conception.

(ii) Cardiac performance and cardiac reserve remains preserved in pregnancy compared to pre-conception.

(iii) Cardiac performance is maintained in pregnancy, despite a reduction in exercise duration and VO_{2max}, with advancing gestation and weight gain.

(iv) Blood pressure will increase at rest and maximal exercise, as weight increases with advancing gestation.

7.3 Ethical Approval

Ethical approval was approved by the Leeds (West) Ethics Committee.

7.4 Methods

This was a prospective observational longitudinal study which compared the physiological cardiovascular changes seen in pregnancy and post-partum with pre-conception in healthy participants.

7.4.1 Study participants and visit structure

Healthy female volunteers were recruited using the same methods as per study VI however, all these women were not pregnant and were actively trying to get

pregnant. Once recruited, women underwent screening and testing as per study VI. All women had their first fetal scan organised by the study co-ordinator and performed in the Obstetric ante-natal clinic shortly after they became aware they were pregnant. This was done to confirm gestational age and prevent delays in women waiting for their scans through the routine pathways via community midwives. This also gave women confidence, prior to commencing exercise testing, and limited attribution of blame of any miscarriage to participating in the study.

7.4.2 Cardiopulmonary exercise testing

Physiological exercise testing was identical to study VI.

7.4.3 Quality of life assessment

The SF-36v2 questionnaire was used to assess quality of life at each visit [Ware 2000]. Explanation of the questionnaire is in chapter 6.

7.4.4 Statistical analysis

All data were analysed using SPSS. Data are presented as mean and standard deviation. Delta measures and percentage change in measures from pre-conception are also displayed as a mean and standard deviation with 95% confidence intervals. Statistical comparisons were made with Student's paired, two-tailed t test. One-way repeated measures ANOVA with a Bonferroni correction was used for multiple comparisons between measures during pregnancy. A P value of < 0.05 was considered to be statistically significant.

7.5 Results

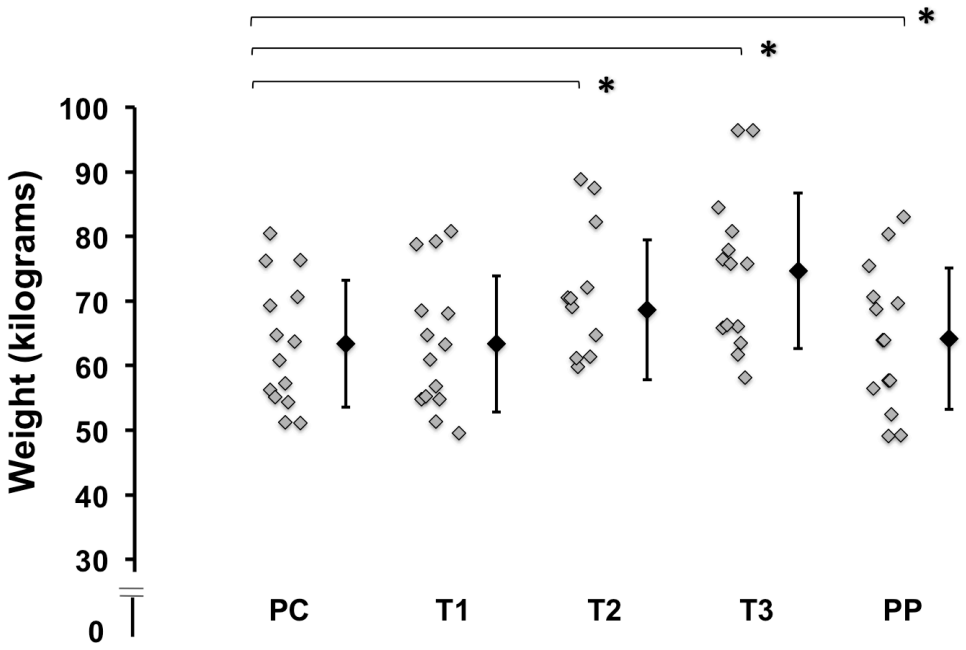
7.5.1 Study population baseline characteristics

36 healthy females were recruited and underwent baseline visits and testing as outlined in the methods. 16 were unable to become pregnant within the recruitment time frame of 12 months, 6 either pulled out mid-way through the study or did not complete all 5 tests, leaving 14 subjects who underwent complete testing.

13 participants were Caucasian and 1 of Asian descent. All subjects were healthy and taking no regular medication, and had no impediments to exercise. They were all non-smokers and generally active and participated in some form of regular exercise pre-pregnancy, with one subject classified as an athlete. Throughout pregnancy all women remained well and delivered after 38 weeks.

The mean age was 32.3 ± 4.5 years with baseline weight of 63.4 ± 9.8 kg and BMI 25.9 ± 3.4 $kg.m^{-2}$. The changes in weight are shown in Figure 7.1 and Table 7.1. The greatest magnitude of change was seen in the third trimester, where there was a significant 18% increase from baseline. The mean time for subjects to get pregnant was 71 ± 87 days. The mean time of assessment post pregnancy was at 127 ± 41 days.

Figure 7.1 Weight at pre-conception, through pregnancy and at post-partum



PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01

Table 7.1 Change in weight from pre-conception, through pregnancy and in post-partum

	PC	T1	T2	T3	PP
Weight (kg) Mean (SD)	63.4 (9.8)	63.3 (10.5)	68.7 (10.9)	74.7 (12.0)	64.2 (11.0)
∆ Weight (%) **P value**		-0.2 (2.5) 0.918	8.4 (4.7) <0.001	17.9 (6.6) <0.001	1.0 (3.9) 0.276

7.5.2 Resting measures

Changes in longitudinal resting variables from pre-conception, through pregnancy and in post-partum are shown in Figures 7.2 to 7.4 and Tables 7.2 to 7.5. There were significant and successive increases in resting heart rate through pregnancy (F ratio 5.57, p = 0.01). The initial increase was by 9 beats per minute in the first trimester, increasing to 20 beats per minute higher than pre-conception in the third trimester. This then significantly dropped in post-partum, but was still significantly higher than pre-conception HR_{rest} by 14 beats per minute (p = 0.015).

Initial drops in systolic, diastolic and mean arterial pressures were seen in the first trimester by 6%, 18% and 12% respectively, although the drop in SBP failed to reach significance (p = 0.10). All blood pressures steadily rose through pregnancy, without reaching significance (SBP: p = 0.374, DBP: p = 0.126, MAP: p = 0.078), although this remained below pre-conception levels (significance only seen in DBP: p = 0.025). All blood pressures in post-partum then dropped however, only SBP had a significance decrease from third trimester (p = 0.047). All blood pressures were significantly lower than pre-conception levels by: SBP- 7% (p = 0.015), DBP- 12% (p = 0.001), MAP- 10% (p = 0.002).

Significant drops in systemic vascular resistance were seen in first trimester by 21% (p = 0.002), but then did not significantly change through pregnancy (F ratio 0.78, p = 0.469). In post-partum SVR_{rest} did not significantly change (p = 0.61), but remained significantly lower than pre-conception SVR_{rest} by 26% (p= 0.001).

Table 7.2 Resting variables at pre-conception, through pregnancy and at post-partum

	PC Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	PP Mean (SD)
HR_{rest} (min^{-1})	66.8 (9.3)	75.9 (13.9)	82.6 (10.0)	86.5 (11.0)	76.6 (14.6)
SBP_{rest} (mmHg)	103.0 (14.5)	95.2 (11.2)	99.7 (11.3)	99.9 (13.4)	94.3 (8.6)
DBP_{rest} (mmHg)	69.7 (12.9)	55.4 (8.1)	58.6 (9.8)	61.4 (8.0)	60.9 (9.9)
MAP_{rest} (mmHg)	83.4 (13.1)	71.8 (8.4)	73.4 (8.2)	77.3 (8.9)	74.2 (8.2)
SVR_{rest} ($dyn.s.cm^{-5}$)	2293 (671)	1765 (407)	1632 (354)	1696 (408)	1635 (347)
$VO_{2\ rest}$ ($ml.min^{-1}$)	193 (43)	218 (65)	232 (39)	273 (57)	231 (51)
CO_{rest} ($l.min^{-1}$)	3.06 (0.69)	3.40 (0.81)	3.73 (0.79)	3.78 (0.72)	3.76 (0.78)
CPO_{rest} (watts)	0.57 (0.18)	0.55 (0.16)	0.61 (0.17)	0.65 (0.15)	0.62 (0.15)
SV_{rest} (ml)	44.5 (11.5)	43.9 (15.5)	44.0 (10.3)	43.7 (10.1)	49.8 (11.8)
SW_{rest} (g.m)	50.8 (16.1)	43.1 (16.9)	44.4 (13.9)	45.6 (9.9)	50.0 (12.6)

SD: standard deviation; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Table 7.3 P values for difference between resting variables at pre-conception, through pregnancy and at post-partum

	PC v T1 P value	PC v T2 P value	PC v T3 P value	T3 v PP P value	PC v PP P value	T1 to T3 F ratio P value
HR_{rest} (min^{-1})	0.007	<0.001	<0.001	0.017	0.003	5.57 0.010
SBP_{rest} (mmHg)	0.100	0.212	0.468	0.047	0.015	1.02 0.374
DBP_{rest} (mmHg)	0.002	0.004	0.025	0.822	0.001	2.25 0.126
MAP_{rest} (mmHg)	0.009	0.006	0.087	0.181	0.002	2.81 0.078
SVR_{rest} ($dyn.s.cm^{-5}$)	0.002	0.001	0.004	0.610	0.001	0.78 0.469
$VO_{2\ rest}$ ($ml.min^{-1}$)	0.107	0.029	<0.001	0.024	0.064	4.84 0.016
CO_{rest} ($l.min^{-1}$)	0.114	0.006	0.013	0.929	0.008	1.57 0.228
CPO_{rest} (watts)	0.638	0.415	0.224	0.513	0.336	2.46 0.105
SV_{rest} (ml)	0.863	0.873	0.788	0.088	0.110	0.003 0.997
SW_{rest} (g.m)	0.175	0.137	0.264	0.220	0.847	0.17 0.847

HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum.

Table 7.4 Changes between resting variables at pre-conception and through pregnancy and at post-partum

	Δ PC v T1 Mean (SD) 95% CI	Δ PC v T2 Mean (SD) 95% CI	Δ PC v T3 Mean (SD) 95% CI	Δ PC v PP Mean (SD) 95% CI
HR_{rest} (min^{-1})	9.1 (10.7) 3.5, 14.7	15.9 (11.0) 10.1, 21.6	19.7 (11.5) 13.7, 25.7	9.9 (10.0) 4.6, 15.1
SBP_{rest} (mmHg)	-7.8 (16.4) -16.4, 0.8	-3.3 (9.4) -8.2, 1.6	-3.1 (15.4) -11.1, 5.0	-8.7 (11.7) -14.8, -2.6
DBP_{rest} (mmHg)	-14.3 (13.5) -21.4, -7.2	-11.1 (12.1) -17.5, -4.8	-8.3 (12.2) -14.7, -1.9	-8.9 (7.7) -12.9, -4.8
MAP_{rest} (mmHg)	-11.6 (14.1) -19.0, -4.2	-10.0 (11.5) -16.0, -4.0	-6.1 (12.4) -12.6, 0.4	-9.3 (9.1) -14.1, -4.5
SVR_{rest} ($dyn.s.cm^{-5}$)	-529 (526) -804, -253	-662 (570) -960, -363	-597 (631) -928, -267	-658 (552) -948, -369
$VO_{2\ rest}$ ($ml.min^{-1}$)	24.6 (53.1) -3.3, 52.4	39.2 (59.9) 7.9, 70.6	79.4 (63.5) 46.2, 112.7	37.6 (69.5) 1.2, 74.0
CO_{rest} ($l.min^{-1}$)	0.34 (0.76) -0.05, 0.74	0.67 (0.76) 0.27, 1.07	0.72 (0.94) 0.23, 1.22	0.70 (0.84) 0.26, 1.14
CPO_{rest} (watts)	-0.03 (0.20) -0.13, 0.08	0.04 (0.17) -0.05, 0.13	0.08 (0.23) -0.04, 0.20	0.05, (0.18) -0.05, 0.15
SV_{rest} (ml)	-0.6 (12.3) -7.0, 5.9	-0.5 (11.2) -6.4, 5.4	-0.8 (10.4) -6.2, 4.7	5.3 (11.5) -0.7, 11.3
SW_{rest} (g.m)	-7.7 (20.0) -18.2, 2.8	-6.4 (15.1) -14.3, 1.5	-5.1 (16.4) -13.7, 3.5	-0.8 (14.4) -8.3, 6.8

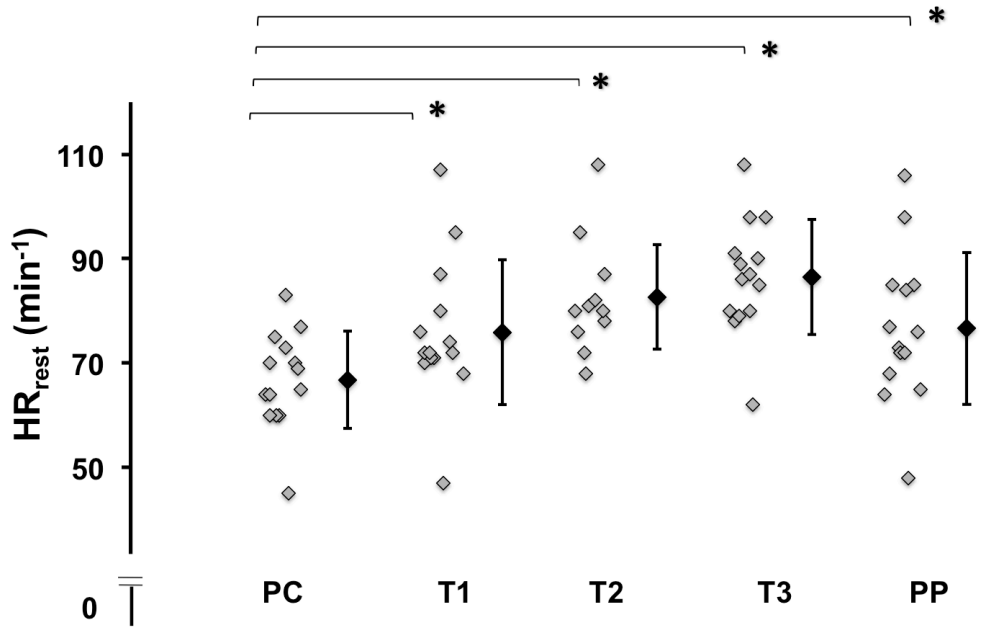
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum.

Table 7.5 Percentage changes between resting variables at pre-conception and through pregnancy and at post-partum

	%Δ PC v T1 Mean (SD) 95% CI	**%Δ PC v T2** Mean (SD) 95% CI	**%Δ PC v T3** Mean (SD) 95% CI	**%Δ PC v PP** Mean (SD) 95% CI
HR_{rest} (min^{-1})	13.9 (15.6) 5.7, 22.0	25.4 (18.4) 15.8, 35.0	31.0 (19.5) 20.8, 41.3	14.7 (14.7) 7.0, 22.4
SBP_{rest} (mmHg)	-6.0 (15.8) -14.3, 2.2	-2.5 (9.1) -7.3, 2.3	-1.9 (13.6) -9.1, 5.2	-7.4 (10.4) -12.9, -2.0
DBP_{rest} (mmHg)	-17.7 (19.5) -27.9, -7.6	-14.1 (15.6) -22.3, -5.9	-9.4 (16.8) -18.2, -0.6	-11.7 (10.5) -17.1, -6.2
MAP_{rest} (mmHg)	-12.0 (16.2) -20.5, -3.5	-10.6 (12.8) -17.3, -3.9	-5.8 (13.4) -12.9, 1.2	-10.0 (10.1) -15.3, -4.8
SVR_{rest} ($dyn.s.cm^{-5}$)	-20.5 (18.0) -29.9, -11.1	-25.9 (17.1) -34.8, -16.9	-22.8 (20.9) -33.7, -11.9	-26.1 (16.0) -17.7, -34.5
$VO_{2\ rest}$ ($ml.min^{-1}$)	14.3 (26.8) 0.2, 28.3	26.3 (37.8) 6.5, 46.1	46.2 (41.4) 24.5, 67.9	25.1 (40.1) 4.1, 46.1
CO_{rest} ($l.min^{-1}$)	14.3 (26.9) 0.2, 28.4	26.0 (30.8) 9.9, 42.1	29.8 (37.4) 10.1, 49.4	27.2 (29.4) 11.8, 42.5
CPO_{rest} (watts)	2.8 (38.5) -17.4, 23.0	13.1 (31.7) -3.5, 29.7	24.5 (44.6) 1.2, 47.9	15.4, (30.9) -0.8, 31.6
SV_{rest} (ml)	1.4 (29.6) -14.1, 16.9	3.8 (30.0) -11.9, 19.6	2.1 (24.8) -11.0, 15.1	17.5 (37.1) -1.9, 36.9
SW_{rest} (g.m)	-8.5 (39.4) -29.1, 12.2	-6.9 (31.9) -23.6, 9.9	-3.0 (29.5) -18.4, 12.5	5.9 (34.9) -12.4, 24.2

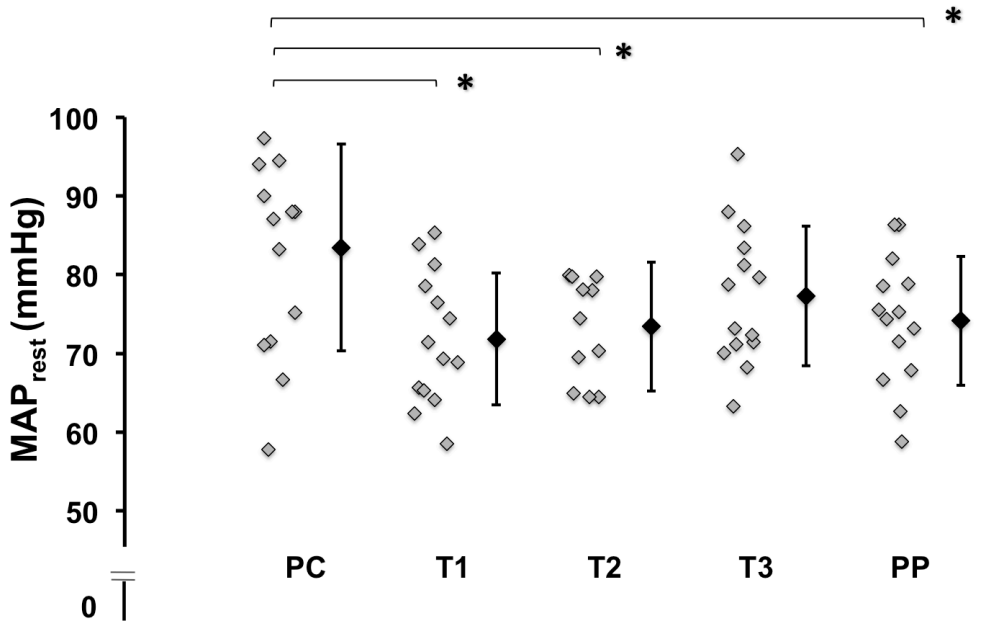
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum.

Figure 7.2 Resting heart rate at pre-conception, through pregnancy and at post-partum



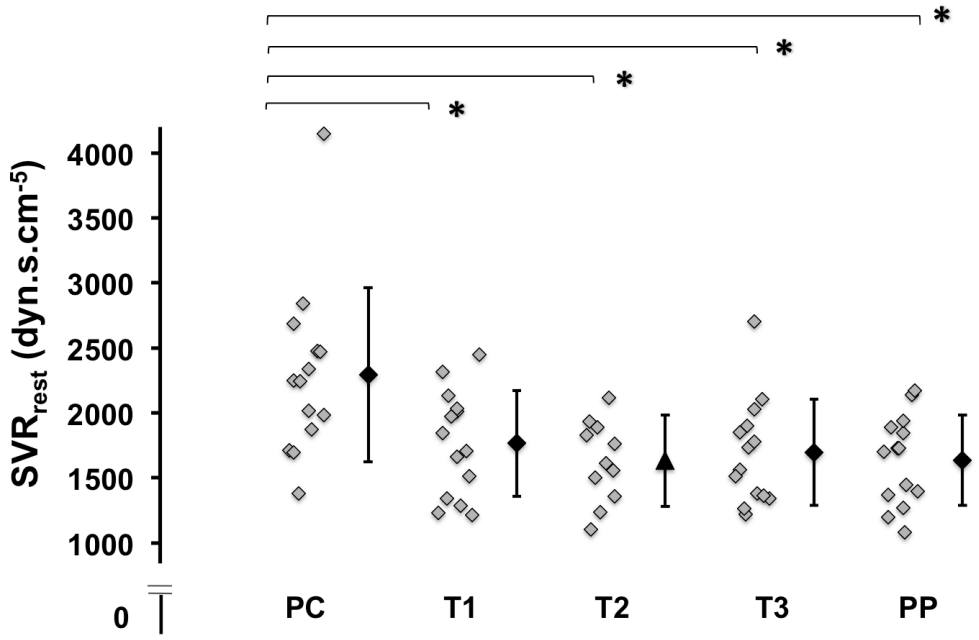
PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01

Figure 7.3 MAP$_{rest}$ at pre-conception, through pregnancy and at post-partum



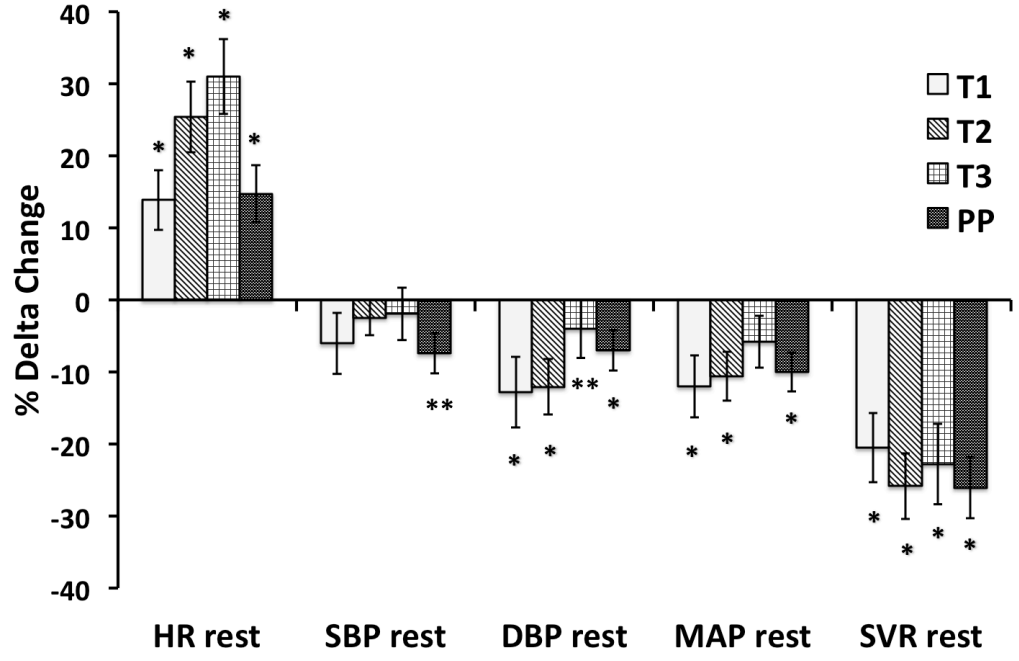
MAP: mean arterial blood pressure; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01

Figure 7.4 SVR_{rest} at pre-conception, through pregnancy and at post-partum



SVR: systemic vascular resistance; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01

Figure 7.5 Percentage changes of resting variables at pre-conception, through pregnancy and at post-partum



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: P<0.01; **:p<0.05

7.5.3 Resting cardiac function

Changes in longitudinal resting cardiac variables from pre-conception, through pregnancy and in post-partum are shown in Figures 7.6 to 7.11 and Tables 7.2 to 7.5.

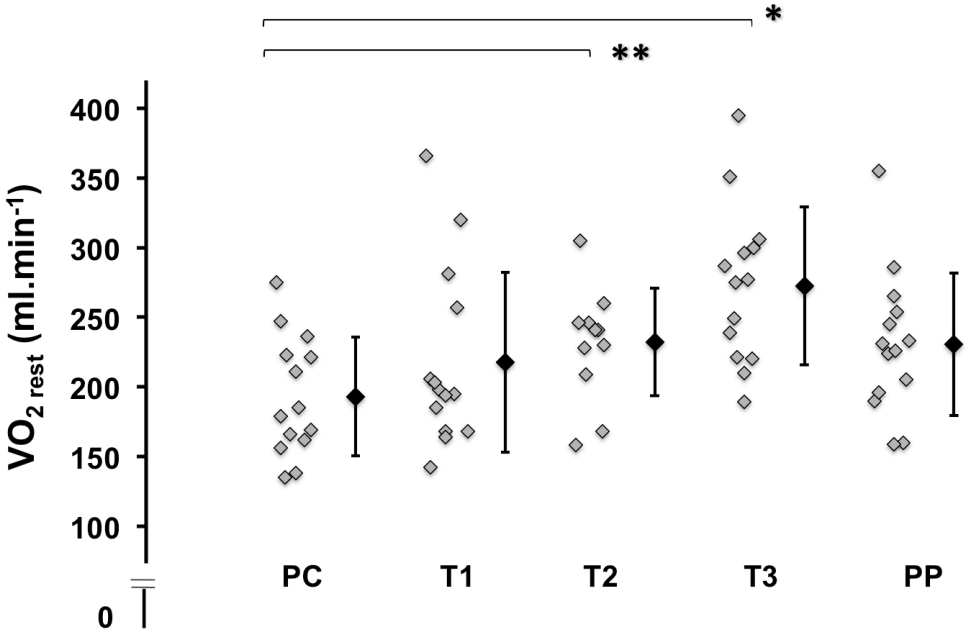
There was a significant increase in $VO_{2\ rest}$ in the first trimester by 14%, then a significant rise in oxygen consumption through pregnancy (F ratio 4.84, $p = 0.016$). In the third trimester $VO_{2\ rest}$ was significantly higher by 46% from pre-conception ($p < 0.001$). $VO_{2\ rest}$ then significantly fell in post-partum ($p = 0.024$).

There were significant increases in resting cardiac output in the first trimester by 14%. This then non- significantly rose through pregnancy (F value 1.57, $p = 0.228$), with the highest CO_{rest} seen in third trimester (30% higher than pre-conception, $p = 0.013$). CO_{rest} did not drop in post-partum and remained significantly higher than pre-conception by 27% ($p = 0.008$).

Resting cardiac power output did not significantly change from pre-conception, throughout pregnancy or in post-partum. However there was a steady rise seen from the second trimester, peaking in third trimester at 25% above pre-conception CPO_{rest}. Post-partum CPO_{rest} did not significantly decrease and was non-significantly higher than pre-conception by 15%.

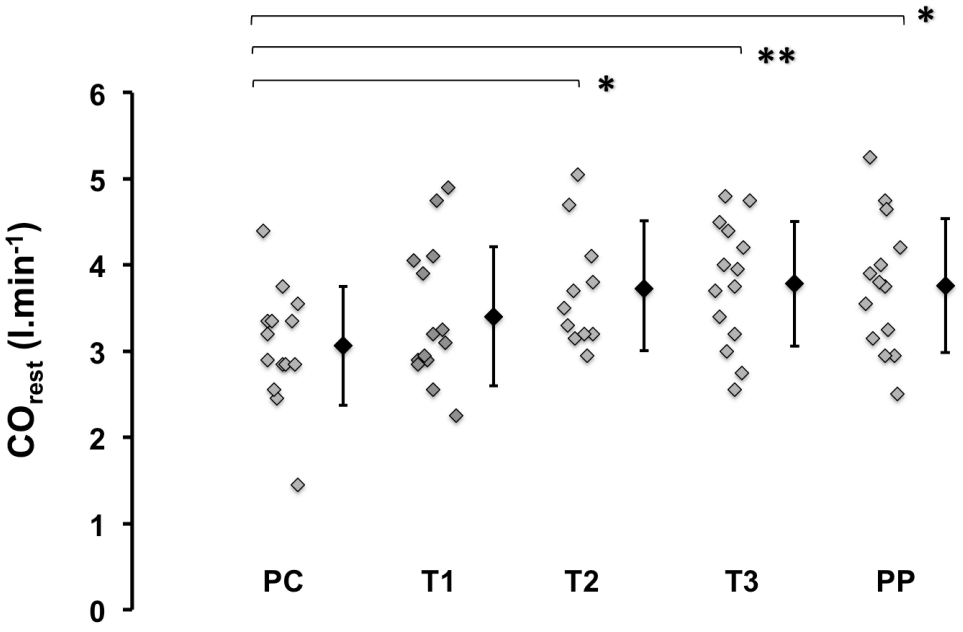
There were no significant changes seen in either resting stroke volume or stroke work from pre-conception or through pregnancy. There was a non-significant rise in SV_{rest} in post-partum, which was just non-significantly higher than pre-conception by 18%.

Figure 7.6 $VO_{2\ rest}$ at pre-conception, through pregnancy and at post-partum



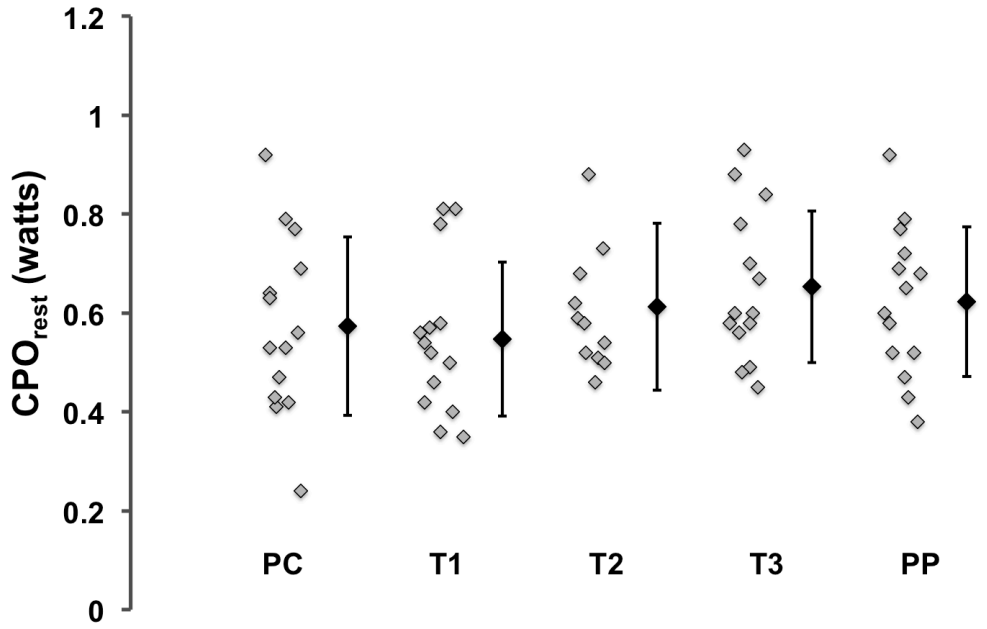
VO_2: oxygen consumption; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01; **: p<0.05

Figure 7.7 Resting cardiac output at pre-conception, through pregnancy and at post-partum



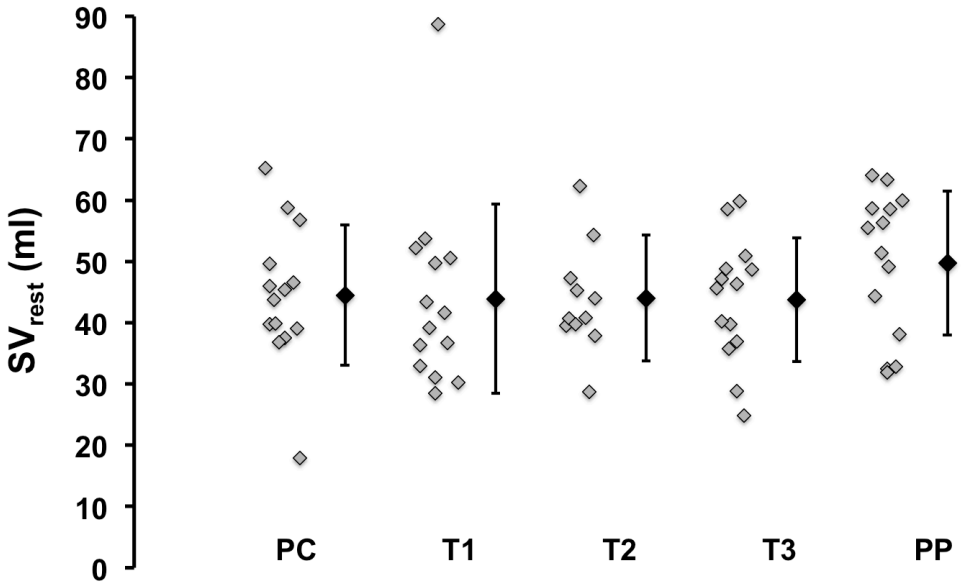
PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01; **: p<0.05

Figure 7.8 CPO_{rest} at pre-conception, through pregnancy and at post-partum



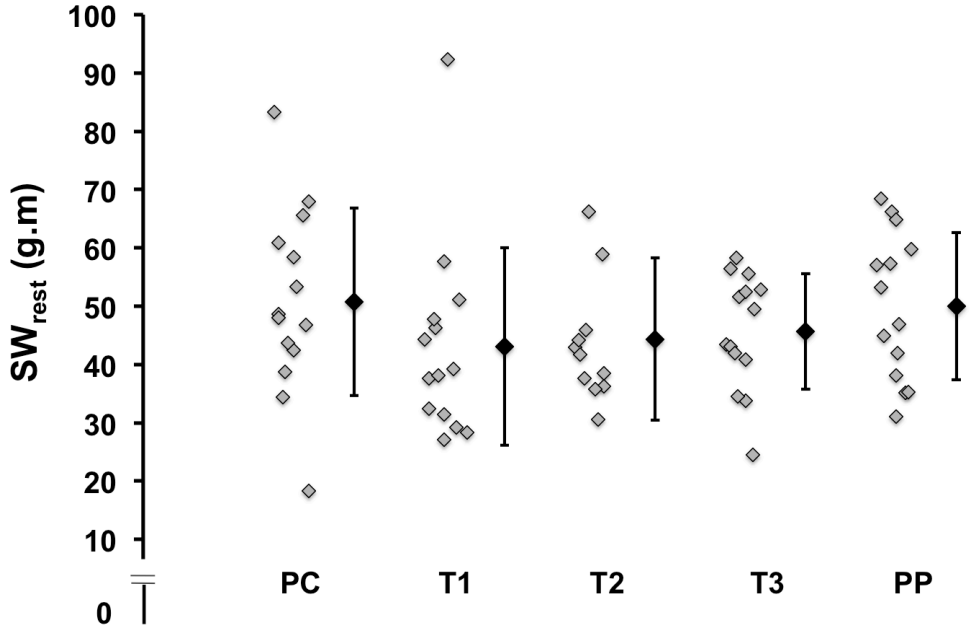
CPO: cardiac power output; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum.

Figure 7.9 Resting stroke volume at pre-conception, through pregnancy and at post-partum



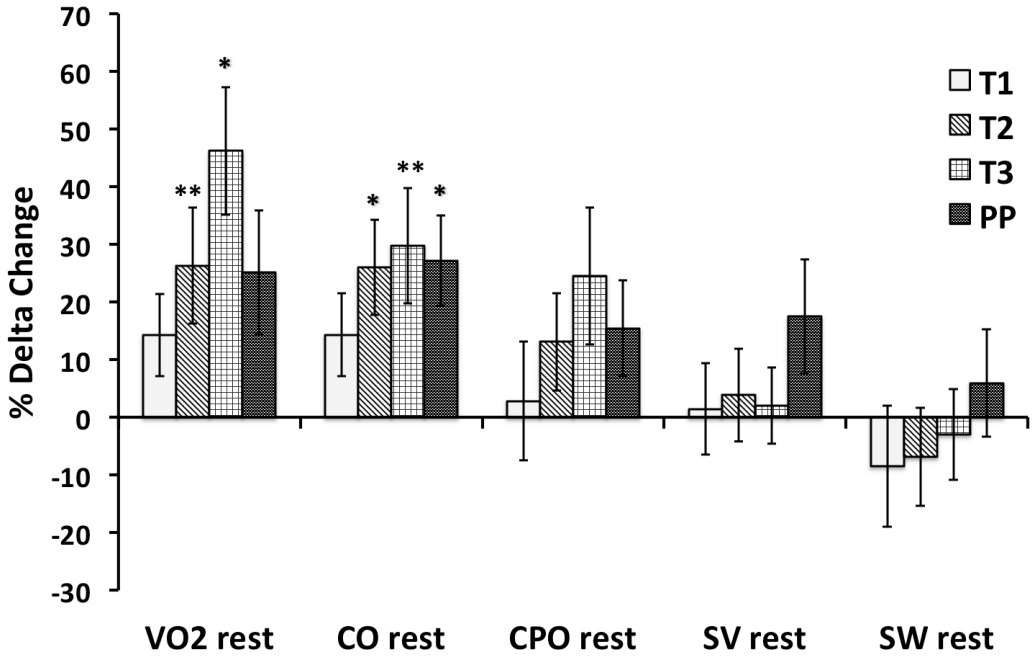
PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum.

Figure 7.10 Resting stroke work at pre-conception, through pregnancy and at post-partum



PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum.

Figure 7.11 Percentage changes of resting cardiac variables at pre-conception, through pregnancy and at post-partum



VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01; **:p<0.05

7.5.2 Exercise and Aerobic Capacity

Changes in longitudinal exercise and aerobic capacity from pre-conception, through pregnancy and in post-partum are shown in Figures 7.12 and 7.13 and Tables 7.7 to 7.10.

There was a minor non-significant reduction in peak exercise capacity in the first trimester (5%, p = 0.10). However exercise capacity significantly continuously fell during pregnancy (F ratio 13.25, p < 0.001). In the third trimester there was a significant 19% fall from pre-conception (p < 0.001), which then recovered in post-partum (18 weeks) to similar times seen in pre-conception. This pattern also mirrored the subjects' perceived function (NYHA class), which falls progressively through pregnancy and returned to normal in post-partum, shown in Table 8.6.

Maximal oxygen consumption also significantly fell initially in the first trimester by 5% (p <0.001). During pregnancy there was a significant progressive fall in $VO_{2\,max}$ (F ratio 5.78, p = 0.008). The greatest change from pre-conception was seen in the third trimester, where $VO_{2\,max}$ was 23% lower (p <0.001). There was a no significant rise in $VO_{2\,max}$ in post-partum, with significantly lower values than pre-conception by 19% (p <0.001).

Subjects' volition to complete a maximal exercise test worsened though pregnancy, shown in Table 8.6 by a drop in respiratory exchange ratio and VE_{max}, neither of which returned to the pre-pregnancy levels in the post-partum period. However all exercise tests did reach acceptable limits of RER > 1.10, between study periods.

Table 7.6 Markers of exercise effort and symptoms between pre-conception, pregnancy and post-partum

	RER_{max} Mean (SD)	**VE_{max}** Mean (SD)	**$ETpCO_{2\,max}$** Mean (SD)	**NYHA** Mean (SD)
PC	1.21 (0.10)	98.5 (19.8)	37.1 (5.3)	1.0 (0)
T1	1.15 (0.08)	91.8 (18.6)	31.9 (4.1)	1.31 (0.48)
T2	1.19 (0.10)	86.5 (22.2)	34.1 (6.3)	1.64 (0.74)
T3	1.11 (0.07)	82.7 (17.3)	31.4 (4.2)	2.2 (0.89)
PP	1.15 (0.15)	81.3 (19.3)	34.6 (3.7)	1.0 (0)

SD: standard deviation; RER: respiratory exchange ration; VE: minute ventilation; $ETpCO_2$: partial pressure of end tidal Carbon dioxide; NYHA: New York Heart Association symptomatic class; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum.

Table 7.7 Maximal exercise variables at pre-conception, through pregnancy and at post-partum

	PC Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	PP Mean (SD)
Ex Dur (mins)	13.6 (2.9)	12.8 (3.0)	11.7 (2.8)	11.0 (2.7)	13.6 (3.7)
$VO_{2\ max}$ ($ml.min^{-1}$)	2720 (442)	2320 (389)	2150 (356)	2091 (428)	2184 (383)
$VO_{2\ max/kg}$ ($ml.min^{-1}.kg^{-1}$)	43.5 (8.4)	37.2 (7.1)	31.8 (6.2)	31.6 (7.2)	34.7 (7.6)
HR_{max} (min^{-1})	188.0 (6.9)	181.4 (8.2)	179.5 (6.6)	176.3 (19.2)	187.4 (8.0)
SBP_{max} (mmHg)	126.9 (14.6)	122.1 (15.7)	127.5 (18.6)	138.6 (20.3)	120.7 (22.8)
DBP_{max} (mmHg)	63.8 (6.5)	60.9 (6.1)	59.1 (5.9)	62.5 (8.3)	63.9 (6.9)
MAP_{max} (mmHg)	90.3 (7.4)	86.3 (7.6)	87.5 (8.2)	92.8 (9.7)	90.8 (7.4)
SVR_{max} ($dyn.s.cm^{-5}$)	342 (44)	356 (32)	361 (38)	399 (41)	381 (44)
$CircP_{max}$ (mmHg.ml $O_2.min^{-1}$)	349 (86)	287 (73)	275 (62)	292 (81)	264 (64)
CO_{max} ($l.min^{-1}$)	21.4 (2.6)	19.6 (2.6)	19.5 (2.1)	18.7 (2.1)	19.2 (2.1)
CPO_{max} (watts)	4.29 (0.73)	3.77 (0.77)	3.80 (0.63)	3.87 (0.74)	3.88 (0.63)
SV_{max} (ml)	115.9 (17.2)	110.5 (18.9)	109.7 (13.1)	108.2 (13.1)	104.2 (12.8)
SW_{max} (g.m)	143.0 (28.2)	130.8 (31.1)	131.0 (23.1)	137.2 (25.4)	129.2 (22.9)

SD: standard deviation; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; Ex Dur: exercise duration; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: circulatory power; SV: stroke volume; SW: stroke work.

Table 7.8 P values for difference between maximal exercise variables at pre-conception, through pregnancy and at post-partum

	PC v T1 P value	PC v T2 P value	PC v T3 P value	T3 v PP P value	PC v PP P value	T1 toT3 F ratio P value
Ex Dur (mins)	0.100	<0.001	<0.001	<0.001	0.980	13.45 <0.001
$VO_{2\ max}$ ($ml.min^{-1}$)	<0.001	<0.001	<0.001	0.239	<0.001	5.78 0.008
$VO_{2\ max/kg}$ ($ml.min^{-1}.kg^{-1}$)	<0.001	<0.001	<0.001	0.041	<0.001	13.45 <0.001
HR_{max} (min^{-1})	0.002	0.001	<0.001	0.001	0.765	2.74 0.099
SBP_{max} (mmHg)	0.301	0.904	0.038	0.009	0.169	8.11 0.002
DBP_{max} (mmHg)	0.074	0.002	0.592	0.554	0.954	1.47 0.249
MAP_{max} (mmHg)	0.031	0.084	0.292	0.295	0.788	8.92 0.001
SVR_{max} ($dyn.s.cm^{-5}$)	0.231	0.112	<0.001	0.069	0.003	14.01 <0.001
$CircP_{max}$ ($mmHg.ml\ O_2.min^{-1}$)	0.008	0.001	0.021	0.116	<0.001	0.72 0.492
CO_{max} ($l.min^{-1}$)	0.007	0.004	0.001	0.086	0.006	1.62 0.217
CPO_{max} (watts)	0.004	0.002	0.037	0.915	0.049	0.22 0.801
SV_{max} (ml)	0.186	0.072	0.051	0.098	0.06	0.21 0.814
SW_{max} (g.m)	0.059	0.022	0.337	0.076	0.052	0.97 0.392

HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; Ex Dur: exercise duration; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: circulatory power; SV: stroke volume; SW: stroke work.

Table 7.9 Changes between maximal exercise variables at pre-conception and through pregnancy and at post-partum

	Δ PC v T1 Mean (SD) 95% CI	**Δ PC v T2** Mean (SD) 95% CI	**Δ PC v T3** Mean (SD) 95% CI	**Δ PC v PP** Mean (SD) 95% CI
Ex Dur (mins)	-0.8 (1.7) -1.7, 0.1	-1.9 (1.5) -2.6, -1.1	-2.6 (1.4) -3.3, -1.9	-0.01 (1.6) -0.9, 0.8
$VO_{2\ max}$ ($ml.min^{-1}$)	-400 (300) -557, -242	-570 (318) -736, -403	-629 (377) -827, -431	-536 (386) -738, -334
$VO_{2\ max/kg}$ ($ml.min^{-1}.kg^{-1}$)	-6.3 (4.7) -8.8, -3.9	-11.7 (5.3) -14.5, -9.0	-12.0 (5.8) -15.0, -8.9	-8.8 (6.1) -12.0, -5.6
HR_{max} (min^{-1})	-6.6 (6.7) -10.1, -3.2	-8.5 (6.9) -12.1, -4.9	-11.7 (9.2) -16.5, -6.9	-0.6 (7.0) -4.2, 3.1
SBP_{max} (mmHg)	-4.8 (16.6) -13.5, 3.9	0.6 (17.5) -8.6, 9.7	11.6 (18.9) 1.8, 21.5	-6.2 (16.0) -14.6, 2.2
MAP_{max} (mmHg)	-4.0 (6.2) -7.2, -0.8	-2.7 (5.5) -5.6, 0.1	2.6 (8.7) -2.0, 7.1	0.5 (7.3) -3.3, 4.4
SVR_{max} ($dyn.s.cm^{-5}$)	14 (42) -8, 36	20 (43) -3, 42	58 (46) 34, 82	39 (40) 18, 60
$CircP_{max}$ ($mmHg.ml\ O_2.min^{-1}$)	-62 (74) -101, -23	-73 (66) -108, -39	-56 (80) -98, -14	-85 (59) -116, -54
CO_{max} ($l.min^{-1}$)	-1.8 (2.1) -2.9, -0.7	-1.9 (2.0) -2.9, -0.8	-2.7 (2.3) -3.9, -1.5	-2.1 (2.4) -3.4, -0.9
CPO_{max} (watts)	-0.52 (0.55) -0.81, -0.23	-0.49 (0.47) -0.74, -0.25	-0.42 (0.68) -0.78, -0.07	-0.41 (0.70) -0.78, -0.04
SV_{max} (ml)	-5.5 (14.7) -13.1, 2.2	-6.3 (12.0) -12.5, 0.01	-7.7 (13.5) -14.8, -0.7	-11.7, (13.4) -18.7, -4.7
SW_{max} (g.m)	-12.1 (22.0) -23.6, -0.6	-11.9 (17.2) -20.9, -3.0	-5.8 (21.6) -17.1, 5.6	-13.8 (24.1) -26.4, -1.1

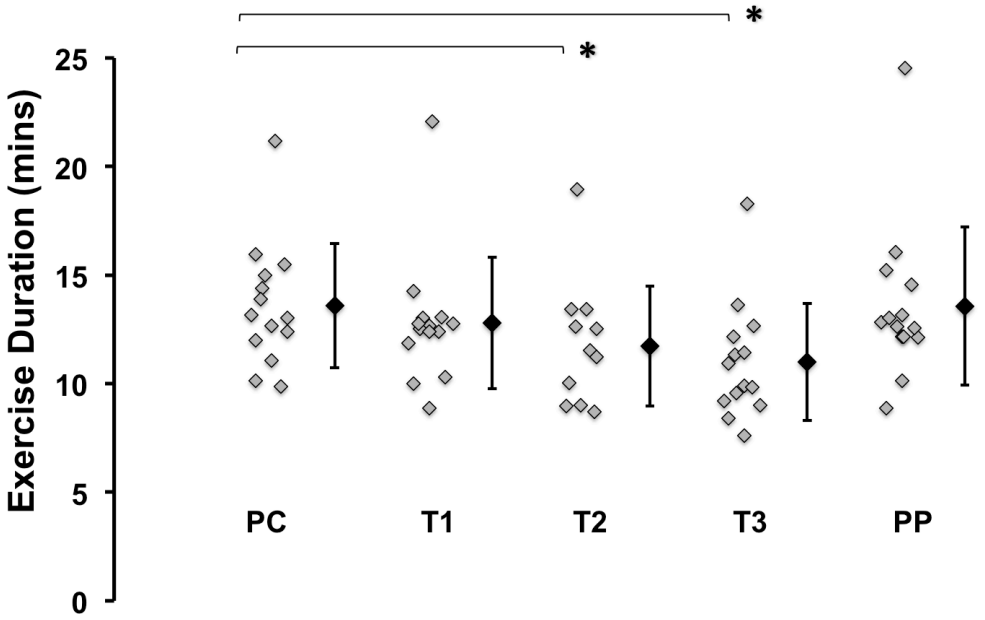
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; Ex Dur: exercise duration; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: circulatory power; SV: stroke volume; SW: stroke work.

Table 7.10 Percentage changes between maximal exercise variables at pre-conception and through pregnancy and at post-partum

	%Δ PC v T1 Mean (SD) 95% CI	**%Δ PC v T2** Mean (SD) 95% CI	**%Δ PC v T3** Mean (SD) 95% CI	**%Δ PC v PP** Mean (SD) 95% CI
Ex Dur (mins)	-5.2 (13.8) -12.5, 2.0	-13.3 (11.5) -19.3, -7.3	-18.9 (10.1) -24.2, -13.6	-0.3 (12.2) -6.7, 6.1
$VO_{2\ max}$ ($ml.min^{-1}$)	-14.2 (10.1) -19.5, -8.9	-20.4 (10.0) -25.7, -15.1	-22.8 (12.6) -29.4, -16.2	-18.9 (13.4) -25.9, -11.9
$VO_{2\ max/kg}$ ($ml.min^{-1}.kg^{-1}$)	-14.1 (9.5) -19.0, -9.1	-26.5 (9.4) -31.4, -21.6	-27.2 (10.6) -32.8, -21.7	-19.6 (13.5) -26.7, -12.5
HR_{max} (min^{-1})	-3.5 (3.6) -5.4, -1.6	-4.5 (3.7) -6.4, -2.5	-6.2 (5.0) -8.8, -3.6	-0.3 (3.6) -2.2, 1.6
SBP_{max} (mmHg)	-3.0 (13.5) -10.1, 4.0	1.0 (14.7) -6.7, 8.6	9.8 (15.0) 1.9, 17.6	-6.2 (16.0) -14.6, 2.2
MAP_{max} (mmHg)	-4.2 (6.7) -7.8, -0.7	-3.0 (6.1) -6.2, 0.2	3.1 (9.7) -2.0, 8.1	0.9 (8.1) -3.3, 5.1
SVR_{max} ($dyn.s.cm^{-5}$)	5.1 (11.1) -0.8, 10.9	6.7 (12.7) 0.02, 13.3	18.0 (14.2) 10.6, 25.5	12.3 (12.6) 5.7, 18.9
$CircP_{max}$ ($mmHg.ml\ O_2.min^{-1}$)	-16.1 (19.1) -26.1, -6.1	-19.4 (16.9) -28.2, -10.5	-14.5 (22.2) -26.1, -2.9	-85.0 (59.1) -115.9, -54.1
CO_{max} ($l.min^{-1}$)	-8.0 (10.3) -13.4, -2.6	-8.2 (9.3) -13.0, -3.3	-11.9 (10.1) -17.2, -6.6	-9.3 (10.6) -14.9, -3.8
CPO_{max} (watts)	-11.7 (12.8) -18.4, -5.0	-10.9 (9.8) -16.1, -5.8	-9.0 (15.3) -17.0, -1.0	-8.2 (15.5) -16.3, -0.05
SV_{max} (ml)	-4.2 (13.1) -11.0, 2.7	-4.5 (10.8) -10.1, 1.2	-5.7 (11.9) -11.9, 0.5	-9.2 (10.9) -3.5, -14.9
SW_{max} (g.m)	-8.0 (15.3) -16.0, -0.02	-7.4 (10.9) -13.1, -1.7	-2.8 (15.5) -10.8, 5.3	-8.0 (16.0) -16.4, 0.4

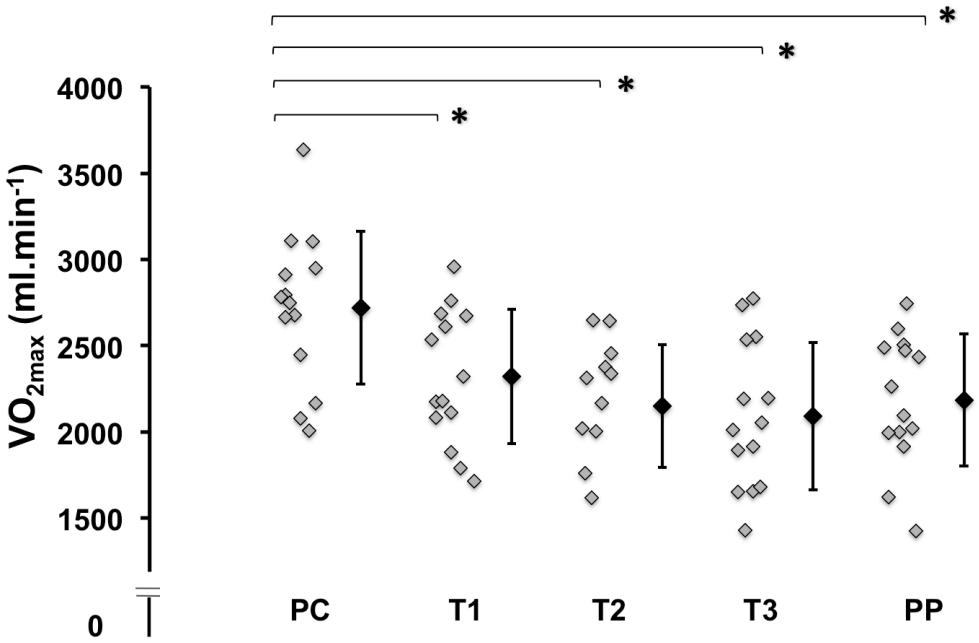
SD: standard deviation; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; Ex Dur: exercise duration; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: circulatory power; SV: stroke volume; SW: stroke work.

Figure 7.12 Exercise duration at pre-conception, through pregnancy and at post-partum



PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01

Figure 7.13 VO_{2max} at pre-conception, through pregnancy and at post-partum



VO_2: oxygen consumption ; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01

7.5.3 Maximal exercise haemodynamics

Changes in longitudinal exercise haemodynamics from pre-conception, through pregnancy and in post-partum are shown in Figures 7.14 to 7.17 and Tables 7.7 to 7.10.

At maximal exercise, heart rate significantly fell in the first trimester by 3.5% ($p = 0.002$). Through pregnancy heart rate did not significantly fall (F ratio 2.74, $p = 0.099$), however the greatest change from pre-conception was seen in the third trimester, where there was a significant 6% fall ($p = 0.001$). Heart rate then returned to baseline levels in post-partum.

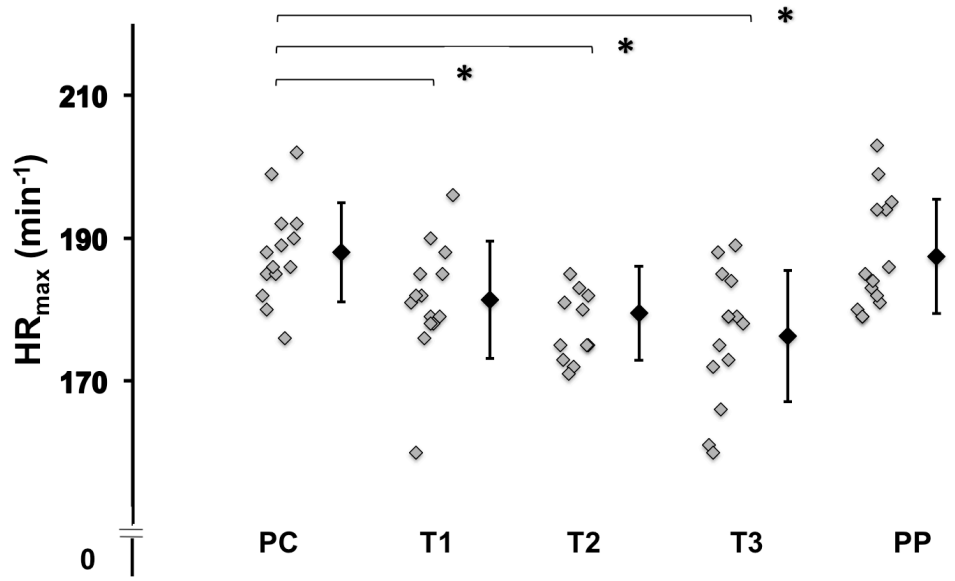
At maximal exercise, systolic blood pressure appeared to non-significantly fall initially. It then significantly increased through pregnancy (F ratio 8.11, $p = 0.002$). The largest change was seen in the third trimester, where there was a 10% increase from pre-conception ($p = 0.034$). SBP_{max} then significantly fell in the post-partum period.

At maximal exercise, diastolic blood pressure significantly fell in the first trimester ($p = 0.074$) and remained low in the second trimester, however did not significantly change through pregnancy (F ratio 1.47, $p = 0.249$). Despite this there appeared to be a rise in the third trimester and further non-significant rise in post-partum, when levels returned to baseline.

At maximal exercise, mean arterial pressure significantly fell in the first trimester by 4% ($p= 0.031$). There was then a significant rise in MAP_{max} seen through pregnancy (F ratio 8.92, $p = 0.002$). MAP_{max} in the third trimester appeared non-significantly increased from levels seen in pre-conception, ($p = 0.292$). MAP_{max} then remained similar in post-partum.

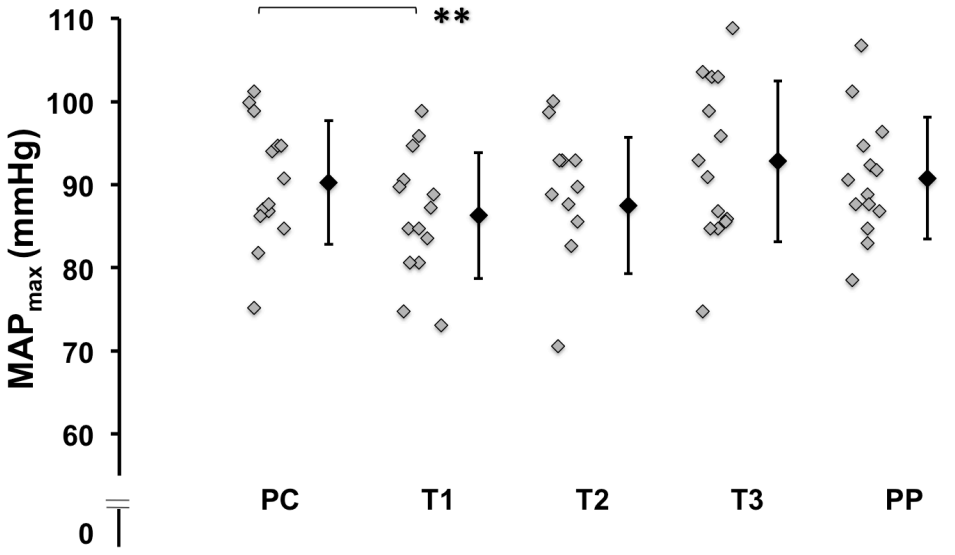
At maximal exercise, systemic vascular resistance non-significantly increased in the first trimester by 5% ($p = 0.231$). There was then a significant increase in SVR_{max} throughout pregnancy (F ratio 14.01, $p <0.001$). The greatest change from pre-conception was seen in the third trimester, where there was a significant increase of 18% ($p <0.001$). SVR_{max} then non-significantly fell in post-partum ($p = 0.069$) and remained significantly 12% higher than in pre-conception ($p = 0.003$).

Figure 7.14 Maximal heart rate at pre-conception, through pregnancy and at post-partum



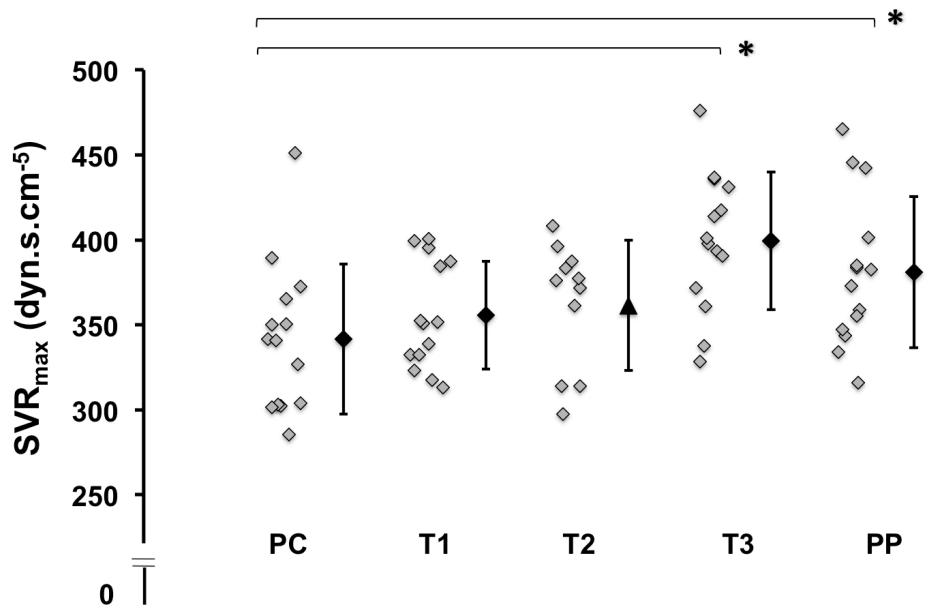
PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01

Figure 7.15 MAP$_{max}$ at pre-conception, through pregnancy and at post-partum



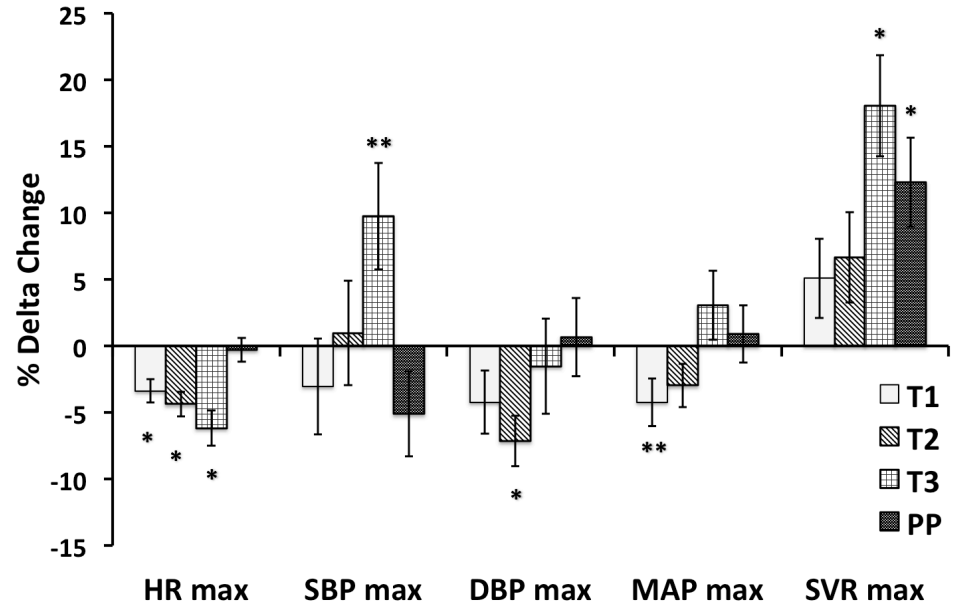
MAP: mean arterial blood pressure; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. **: p<0.05

Figure 7.16 SVR_{max} at pre-conception, through pregnancy and at post-partum



SVR: systemic vascular resistance; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01

Figure 7.17 Percentage changes of exercise variables at pre-conception, through pregnancy and at post-partum



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01; **: p<0.05.

7.5.4 Maximal cardiac function

Changes in longitudinal measures of maximal cardiac function from pre-conception, through pregnancy and in post-partum are shown in Figures 7.18 to 7.22 and Tables 7.7 to 7.10.

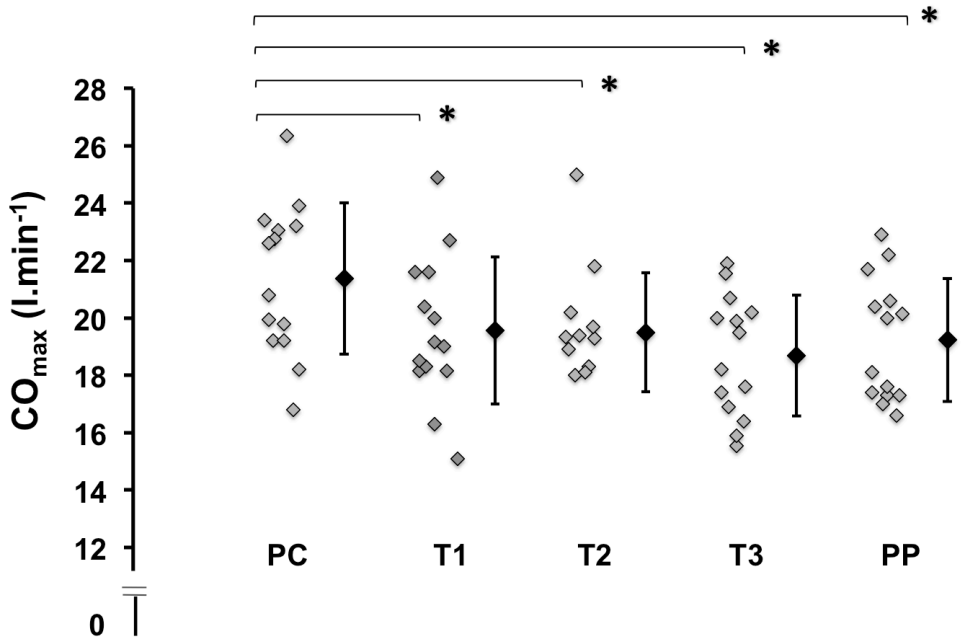
There was a significant reduction in maximal cardiac output in first trimester by 8% (p= 0.007). There was no significant change then seen through pregnancy (F ratio 1.62, p = 0.217), although there appeared to be a slight reduction. There was a non-significant rise of CO_{max} in post-partum, which remained significantly lower than pre-conception (p = 0.006).

There was a significant reduction in maximal cardiac power output in first trimester by 12% (p= 0.004). There was no significant change seen through pregnancy (F ratio 0.22, p = 0.801), although there appeared to be a slight increase. There was no change seen in post-partum, however this value was lower than pre-conception (p = 0.049).

There were no significant changes seen in maximal stroke volume throughout pregnancy from pre-conception, however SV_{max} appeared to remain non-significantly lower in post-partum by 9% (p = 0.06).

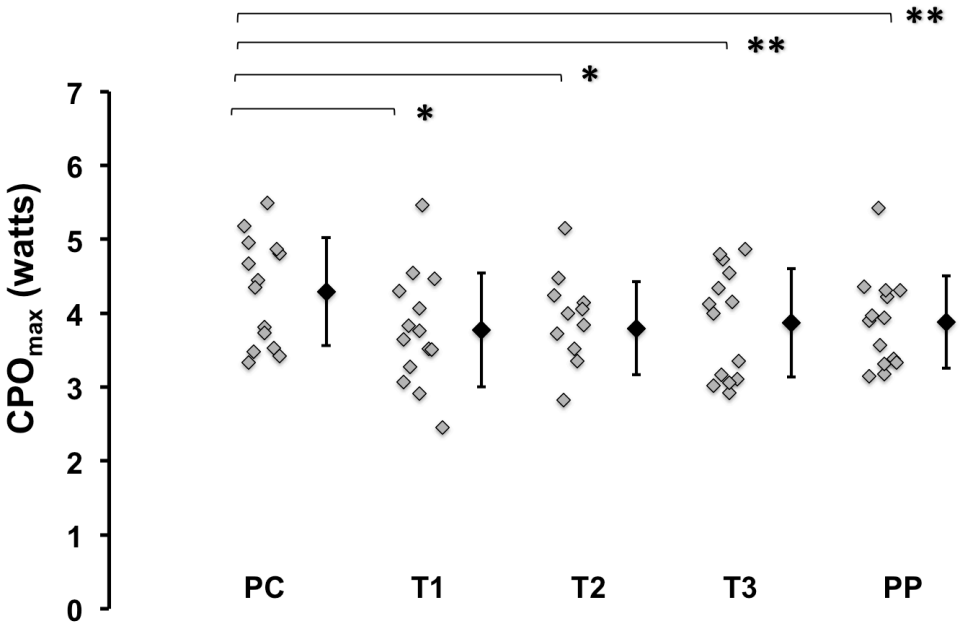
There appeared to be a non-significant reduction in maximal stroke work in the first trimester by 8% (p = 0.059). This remained low in the second trimester and was significantly lower than pre-conception by 7% (p = 0.022). However there was not a significant change in SW_{max} through pregnancy (F ratio 0.97, p = 0.392). Despite this there appeared to be a non-significant increase from the second to the third trimester. In post-partum there was a non-significant fall in $SW_{max.}$ This appeared to be non-significantly lower than pre-conception SW_{max} by 8% (p = 0.052).

Figure 7.18 Maximal cardiac output at pre-conception, through pregnancy and at post-partum



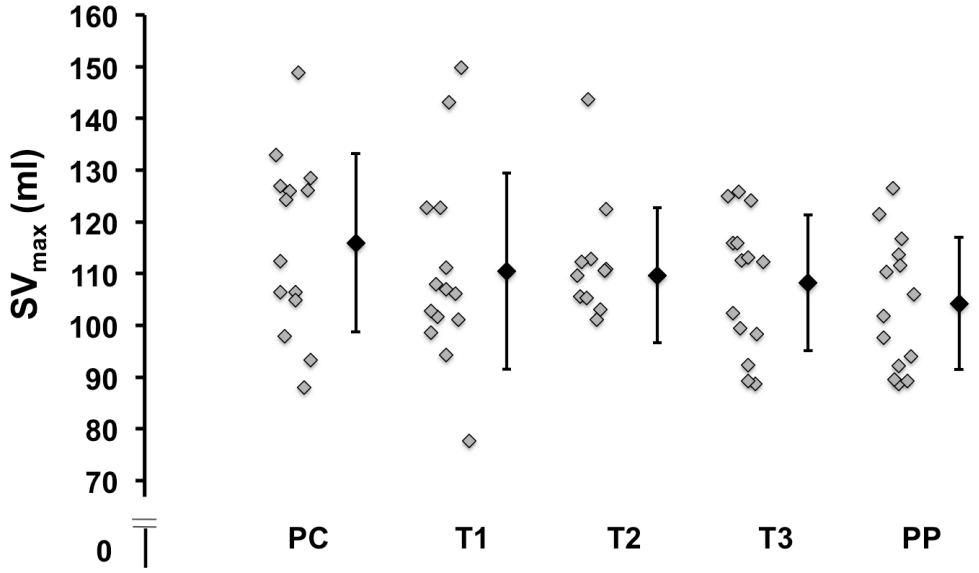
PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01.

Figure 7.19 CPO_{max} at pre-conception, through pregnancy and at post-partum



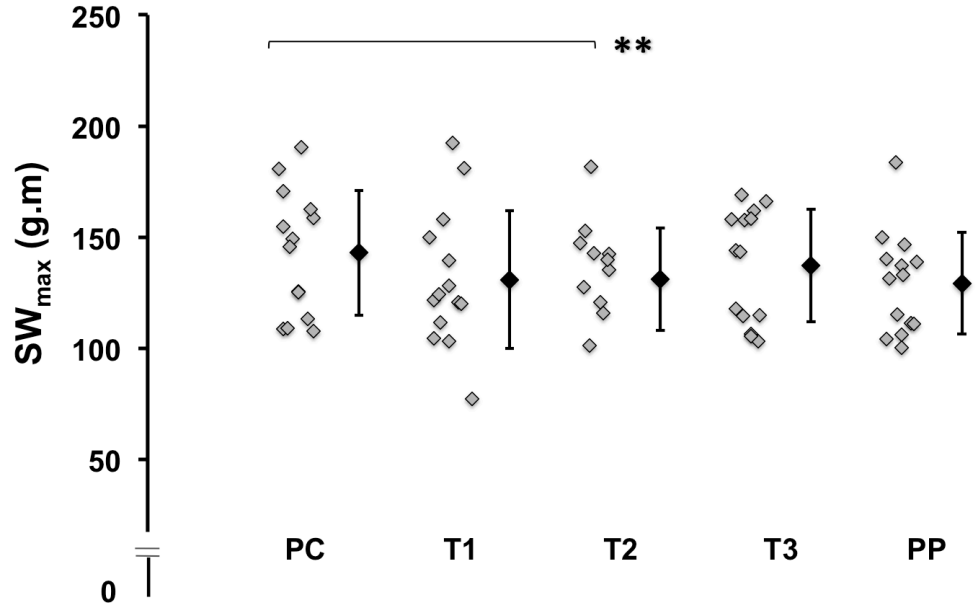
CPO: cardiac power output; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01; **: p<0.05.

Figure 7.20 Maximal stroke volume at pre-conception, through pregnancy and at post-partum



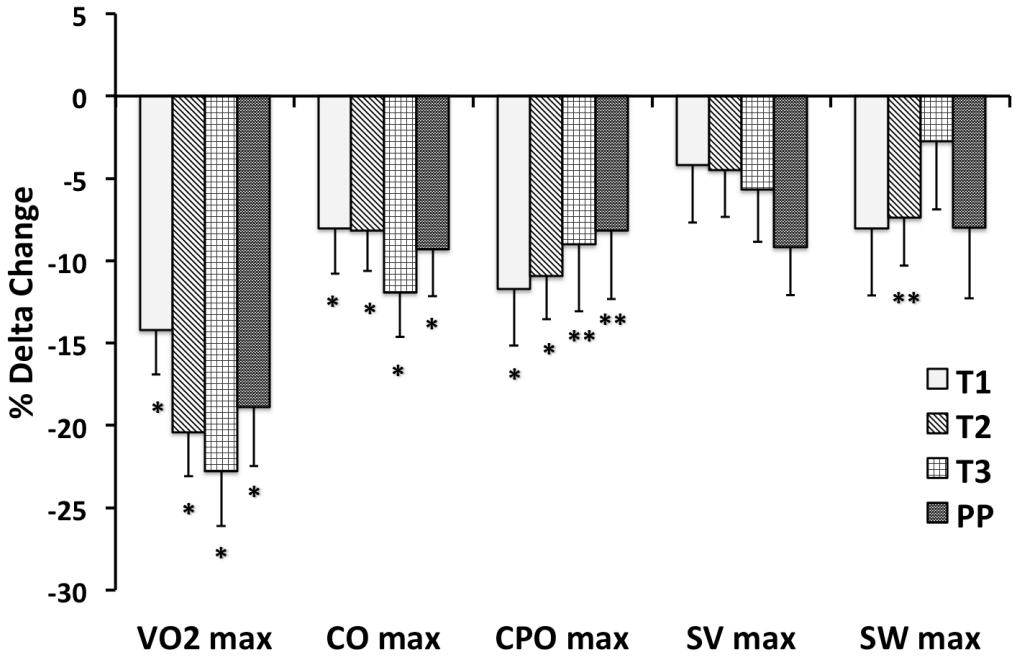
PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum.

Figure 7.21 Maximal stroke work at pre-conception, through pregnancy and at post-partum



PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. **: p<0.05.

Figure 7.22 Percentage changes of resting cardiac variables at pre-conception, through pregnancy and at post-partum



VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: $p<0.01$; **:$p<0.05$

7.5.5 Reserve haemodynamics

Changes in longitudinal reserve haemodynamic measures from pre-conception, through pregnancy and in post-partum are shown in Figures 7.23 to 7.28 and Tables 7.11 to 7.14.

Heart rate reserve significantly decreased initially in the first trimester by 14% ($p < 0.001$). There was a significant reduction in $HR_{reserve}$ throughout pregnancy (F ratio 15.51, $p < 0.001$). The greatest change was in the third trimester, where $HR_{reserve}$ was 26% lower than in pre-conception ($p < 0.001$). HR_{res} increased significantly in post-partum ($p = 0.003$) but remained significantly lower than pre-conception by 11% ($p < 0.001$)

Oxygen consumption reserve also significantly fell in the first trimester by 16% ($p < 0.001$). Again there was a significant reduction in $VO_{2\ reserve}$ throughout pregnancy (F ratio 9.2, $p = 0.001$). The greatest change was seen in the third trimester, where $VO_{2\ reserve}$ was 28% lower than pre-conception ($p < 0.001$). There was a non-significant rise in $VO_{2\ reserve}$ in post-partum ($p = 0.297$) and this value remained significantly 23% lower than pre-conception ($p < 0.001$).

Cardiac output reserve significantly fell in the first trimester by 11% ($p = 0.004$). This then appeared to reduce throughout pregnancy, however was not significant (F ratio 2.84, $p = 0.077$). The greatest change was seen in the third trimester with a 17% fall compared to pre-conception $CO_{reserve}$ ($p < 0.001$). There was a non-significant rise in $CO_{reserve}$ in post-partum ($p = 0.101$) and this value remained significantly 15% lower than pre-conception ($p = 0.001$).

Cardiac power output reserve significantly fell in the first trimester by 12% ($p = 0.005$). $CPO_{reserve}$ then did not change significantly throughout pregnancy (F ratio 0.05, $p = 0.956$). There was a slight non-significant rise in $CPO_{reserve}$ in post-partum ($p = 0.709$) and this value remained significantly 11% lower than pre-conception ($p = 0.023$).

Stroke volume reserve and stroke work reserve did not significantly change from pre-conception or throughout pregnancy. However both $SV_{reserve}$ and $SW_{reserve}$ significantly decreased in post-partum from the third trimester ($SV_{reserve}$: $p = 0.014$; $SW_{reserve}$: $p = 0.019$) and were also significantly lower than in pre-conception by 22% ($p < 0.001$) and 12% ($p = 0.031$) respectively.

Table 7.11 Reserve variables at pre-conception and through pregnancy and at post-partum

	PC Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	PP Mean (SD)
$HR_{reserve}$ (min^{-1})	121.2 (5.9)	105.5(13.8)	96.9 (11.7)	89.8 (13.6)	108.1 (9.5)
$VO_{2\ reserve}$ ($ml.min^{-1}$)	2527 (425)	2103 (357)	1918 (357)	1818 (403)	1911 (359)
$CO_{reserve}$ ($l.min^{-1}$)	18.3 (2.7)	16.2 (1.9)	15.8 (2.2)	14.9 (1.7)	15.5 (2.1)
$CPO_{reserve}$ (watts)	3.72 (0.71)	3.23 (0.65)	3.18 (0.62)	3.22 (0.64)	3.26 (0.61)
$SV_{reserve}$ (ml)	71.4 (14.6)	66.6 (13.8)	65.7 (14.3)	64.5 (8.6)	54.5 (12.0)
$SW_{reserve}$ (g.m)	92.2 (24.0)	87.8 (21.5)	86.7 (23.1)	91.6 (18.5)	79.2 (20.0)

Table 7.12 P values for difference between reserve variables at pre-conception and through pregnancy and post-partum

	PC v T1 P value	PC v T2 P value	PC v T3 P value	T3 v PP P value	PC v PP P value	T1 to T3 F ratio P value
$HR_{reserve}$ (min^{-1})	<0.001	<0.001	<0.001	0.003	<0.001	15.51 <0.001
$VO_{2\ reserve}$ ($ml.min^{-1}$)	<0.001	<0.001	<0.001	0.297	<0.001	9.20 0.001
$CO_{reserve}$ ($l.min^{-1}$)	0.004	0.001	<0.001	0.101	0.001	2.84 0.077
$CPO_{reserve}$ (watts)	0.005	<0.001	0.010	0.709	0.023	0.05 0.956
$SV_{reserve}$ (ml)	0.392	0.227	0.165	0.014	<0.001	0.09 0.875
$SW_{reserve}$ (g.m)	0.565	0.276	0.917	0.019	0.031	0.35 0.706

SD: standard deviation; HR: heart rate; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum

Table 7.13 Percentage changes between reserve variables at pre-conception and through pregnancy and at post-partum

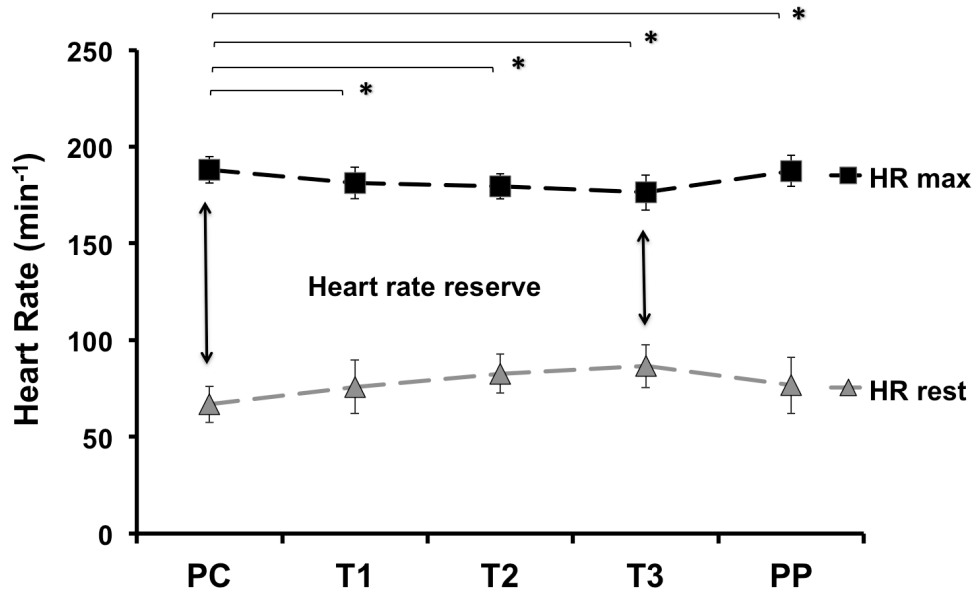
	Δ PC vs T1 Mean (SD) 95% CI	**Δ PC v T2** Mean (SD) 95% CI	**Δ PC v T3** Mean (SD) 95% CI	**Δ PC v PP** Mean (SD) 95% CI
$HR_{reserve}$ (min^{-1})	-15.7 (10.3) -21.1, -10.4	-24.4 (10.4) -29.8, -18.9	-31.4 (12.4) -37.9, -25.0	-13.1 (9.7) -18.2, -8.1
$VO_{2\ reserve}$ ($ml.min^{-1}$)	-424 (291) -577, -272	-609 (311) -772, -446	-708 (369) -901, -515	-616 (468) -861, -371
$CO_{reserve}$ ($l.min^{-1}$)	-2.2 (2.3) -3.4, -0.9	-2.5 (2.3) -3.7, -1.4	-3.4 (2.5) -4.7, -2.1	-2.8 (2.4) -4.1, -1.6
$CPO_{reserve}$ (watts)	-0.49 (0.55) -0.78, -0.20	-0.53 (0.43) -0.76, -0.31	-0.50 (0.62) -0.82, -0.18	-0.46 (0.66) -0.81, -0.11
$SV_{reserve}$ (ml)	-4.9 (20.6) -15.7, 5.9	-5.8 (17.0) -14.7, 3.1	-7.0 (17.7) -16.2, 2.3	-17.0 (13.3) -23.9, -10.0
$SW_{reserve}$ (g.m)	-4.5 (28.3) -19.3, 10.3	-5.5 (18.2) -15.1, 4.0	-0.7 (22.9) -12.6, 11.3	-13.0 (20.1) -23.5, -2.5

Table 7.14 Percentage changes between reserve variables at pre-conception and through pregnancy and post-partum

	%Δ PC v T1 Mean (SD) 95% CI	**%Δ PC v T2** Mean (SD) 95% CI	**%Δ PC v T3** Mean (SD) 95% CI	**%Δ PC v PP** Mean (SD) 95% CI
$HR_{reserve}$ (min^{-1})	-13.2 (8.6) -17.7, -8.6	-20.1 (8.6) -24.6, -15.6	-26.0 (10.0) -31.2, -20.7	-10.8 (7.6) -14.7, -6.8
$VO_{2\ reserve}$ ($ml.min^{-1}$)	-16.2 (10.2) -21.6, -10.9	-23.7 (10.6) -29.2, -18.1	-27.7 (12.9) -34.4, -21.0	-23.1 (16.0) -31.5, -14.8
$CO_{reserve}$ ($l.min^{-1}$)	-10.6 (13.1) -17.5, -3.8	-12.9 (12.2) -19.3, -6.5	-17.4 (12.4) -23.9, -10.9	-14.6 (12.1) -21.0, -8.3
$CPO_{reserve}$ (watts)	-12.2 (15.0) -20.1, -4.4	-13.7 (11.3) -19.6, -7.8	-12.4 (15.4) -20.4, -4.3	-10.8 (16.4) -19.4, -2.3
$SV_{reserve}$ (ml)	-2.4 (30.4) -18.3, 13.5	-4.8 (27.0) -18.9, 9.4	-5.2 (27.1) -19.5, 9.0	-22.3 (17.4) -31.4, -13.2
$SW_{reserve}$ (g.m)	1.0 (34.4) -17.0, 19.0	-3.0 (26.8) -17.1, 11.0	4.2 (27.9) -10.4, 18.8	-11.7 (19.5) -21.9, -1.4

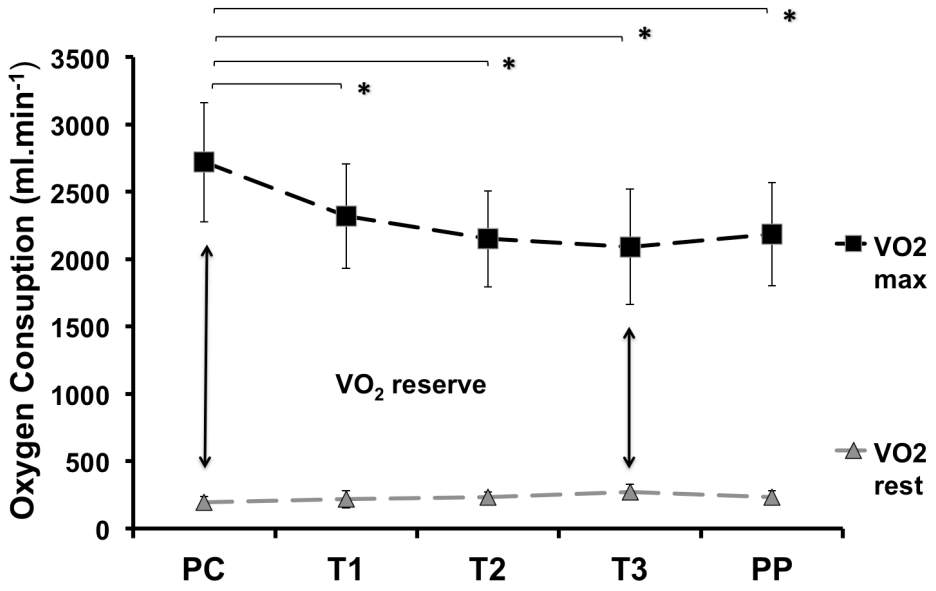
SD: standard deviation; CI: confidence intervals; HR: heart rate; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum

Figure 7.23 Heart rate reserve at pre-conception, through pregnancy and at post-partum



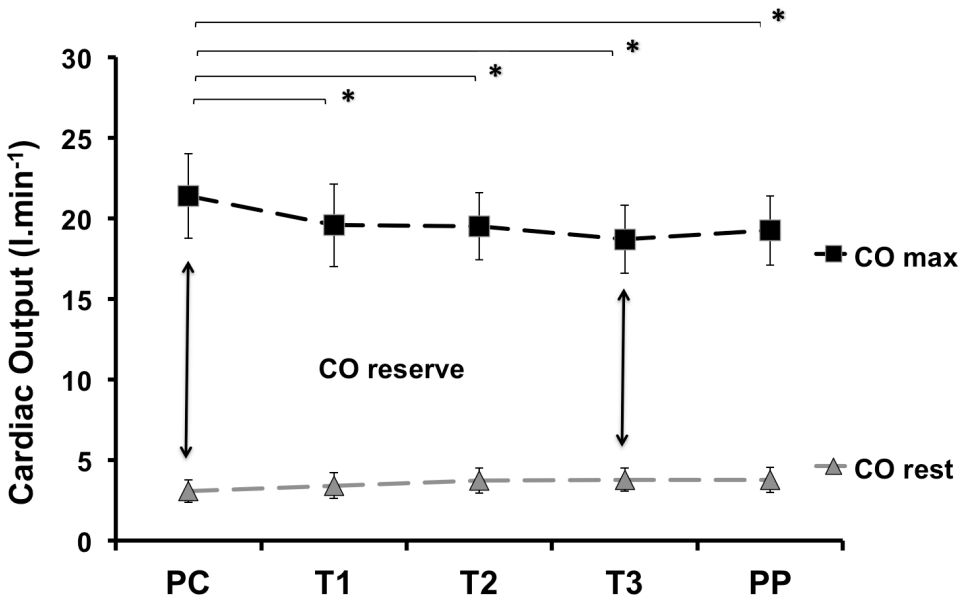
HR: heart rate; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01.

Figure 7.24 VO_2 reserve at pre-conception, through pregnancy and at post-partum



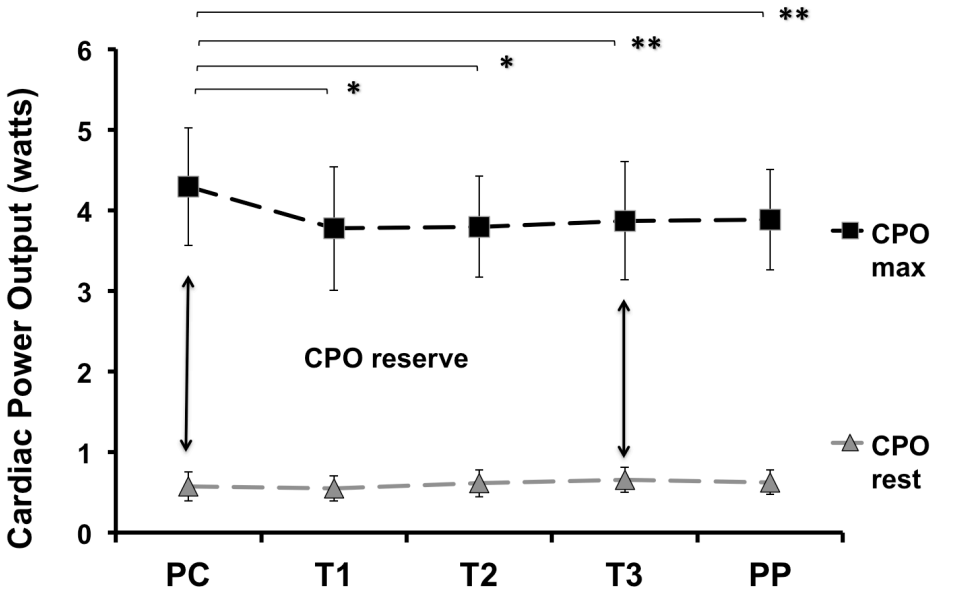
VO_2: oxygen consumption; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01.

Figure 7.25 Cardiac output reserve at pre-conception, through pregnancy and at post-partum



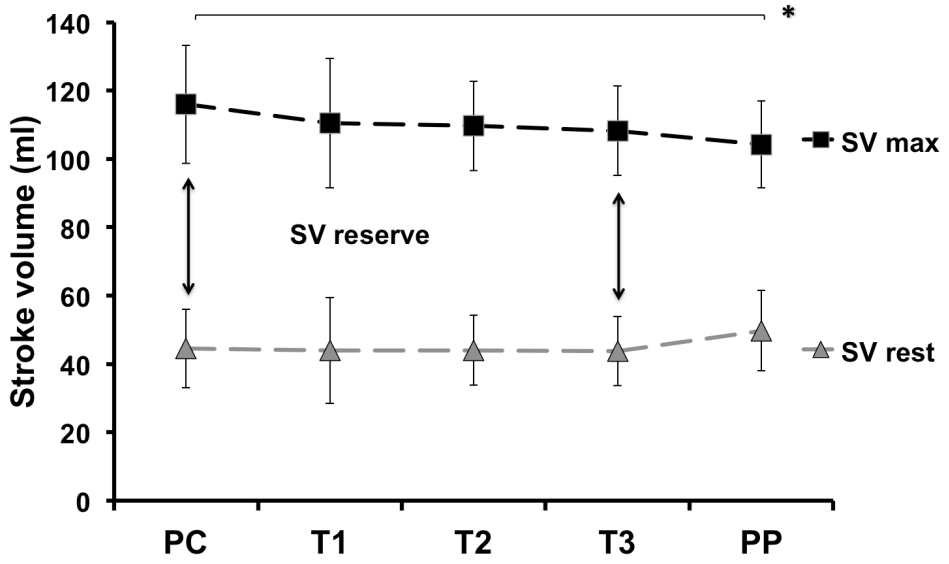
CO: cardiac output; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01.

Figure 7.26 CPO reserve at pre-conception, through pregnancy and at post-partum



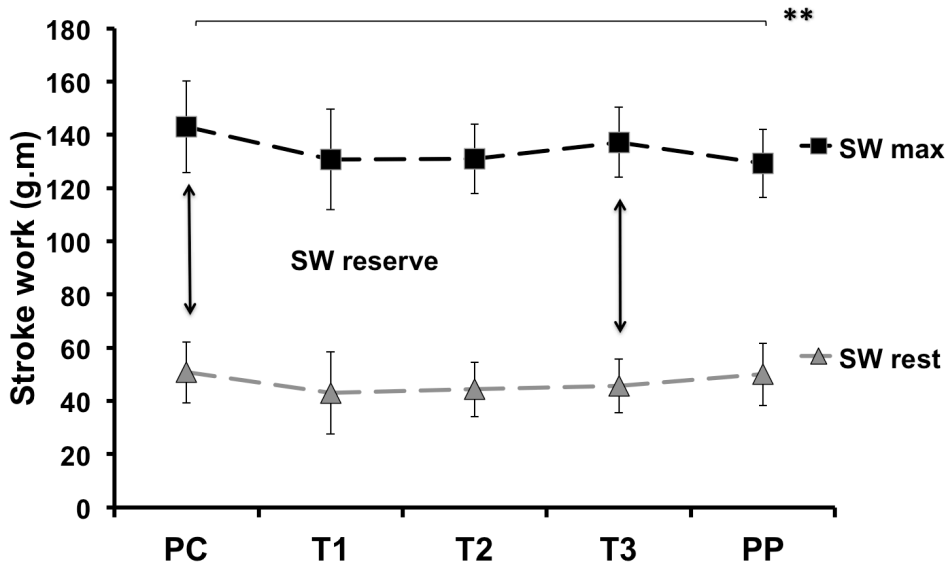
CPO: cardiac power output; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01; **:p<0.05

Figure 7.27 Stroke volume reserve at pre-conception, through pregnancy and at post-partum



SV: stroke volume; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01.

Figure 7.28 Stroke work reserve at pre-conception, through pregnancy and at post-partum



SW: stroke work; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01; **:p<0.05

7.5.6 Symptom scores (SF-36v2)

Changes in longitudinal symptom scores from pre-conception, through pregnancy and in post-partum are shown in Figure 7.29 and Tables 7.15 and 7.16. SF-36v2 scores were compared as a total score and split into domains of physical health and mental health.

Physical health in all individuals was well within the normal range in pre-conception (mean: 85.2, SD: 6.3). There was a significant fall in score in the first trimester by 11.6 ($p = 0.002$). Through pregnancy there was a significant fall in scores (F ratio 25.8, $p < 0.001$). The greatest change was seen in the third trimester, where the score fell by 27.1 ($p < 0.001$). The score then significantly improved in post-partum ($p <0.001$) to levels similar to that seen in pre-conception.

Mental health in all individuals was well within the normal range in pre-conception (mean: 80.3, SD: 8.5). There was a significant fall in score in the first trimester by 5.5 ($p = 0.030$). Scores did not significantly change throughout pregnancy (F ratio 3.1, $p = 0.065$), however the greatest difference in score was seen in the third trimester, where there was decrease by 10.8 ($p = 0.014$). Scores then non-significantly improved in post-partum by 5.1 ($p = 0.109$) and remained significantly lower than pre-conception scores by 5.7 ($p = 0.048$).

Overall SF-36v2 scores in all participants was well within normal range in pre-conception (mean: 85.3, SD: 6.3).There was a significant decrease in score in the first trimester by 7.9 ($p = 0.009$). Through pregnancy there was a significant fall in scores (F ratio 25.1, $p < 0.001$). The greatest difference in scores was seen in the third trimester, where there was a decrease of 21.1 ($p < 0.001$). Score in post-partum then significantly increased by 16.8 ($p < 0.001$) to levels non-significantly slightly below scores seen in pre-conception (mean: 81.0, SD: 10.1).

Table 7.15 Symptom scores through pregnancy and at post-partum and changes from pre-conception

	Physical health Mean (SD)	**Mental health** Mean (SD)	**SF-36 Score** Mean (SD)	**Δ SF-36 (v PC)** Mean (SD) 95% CI	**%Δ SF-36 (v PC)** Mean (SD) 95% CI
PC	85.2 (6.3)	80.3 (8.5)	85.3 (6.9)		
T1	73.6 (10.5)	74.8 (8.0)	77.4 (9.2)	-7.8 (9.2) -12.8, -2.9	-8.9 (11.2) -15.0, -2.8
T2	68.3 (10.6)	74.7 (7.2)	72.8 (9.2)	-12.5 (11.0) -18.5, -6.5	-14.1 (13.7) -21.5, -6.6
T3	58.1 (14.2)	69.5 (14.2)	64.2 (14.2)	-21.0 (14.7) -29.0, -13.1	-24.4 (17.9) -34.1, -14.6
PP	81.8 (8.6)	74.6 (12.6)	81.0 (10.1)	-4.3 (8.6) -8.9, 0.4	-4.9 (10.4) -10.5, 0.8

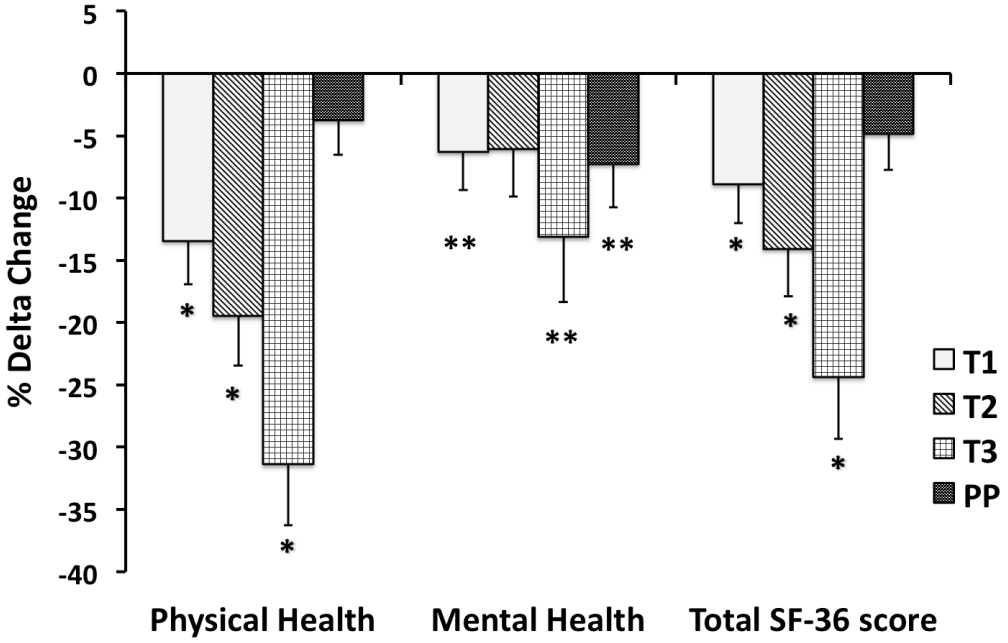
SD: standard deviation; CI: confidence intervals; PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum

Table 7.16 P values for difference between symptom scores through pregnancy and at post-partum and changes from pre-conception

	PC v T1 P value	**PC v T2** P value	**PC v T3** P value	**T3 v PP** P value	**PC v PP** P value	**T1 to T3** F ratio P value
Physical health	0.002	<0.001	<0.001	<0.001	0.155	25.8 <0.001
Mental health	0.030	0.071	0.014	0.109	0.048	3.1 0.065
SF-36 Score	0.009	0.002	<0.001	<0.001	0.109	25.1 <0.001

PC: pre-conception; T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum

Figure 7.29 Percentage changes in symptoms scores from pre-conception



T1: first trimester; T2: second trimester; T3: third trimester; PP: post-partum. *: p<0.01; **:p<0.05

7.6 Discussion

Study VII examined the physical and cardiac effects of longitudinally from pre-conception, throughout pregnancy to 3 months post-partum. This is the first study to examine the longitudinal changes in CO_{max}, CPO_{max} and VO_{2max} before, during and after pregnancy.

Initial changes were analysed between pre-conception and the first trimester. There were significant decreases in VO_{2max} by 14%, $VO_{2max/kg}$ by 14%, HR_{max} by 3.5%, MAP_{max} by 4%, CO_{max} by 8% and CPO_{max} by 12%. Importantly this is despite no change in exercise duration. No significant changes were also identified in SBP_{max}, DBP_{max}, SVR_{max}, SV_{max} and SW_{max}. At rest we identified significantly increases in HR_{rest}, VO_{2rest} and CO_{rest} by 14%. There were significant decreases in DBP_{rest} by 18%, MAP_{rest} by 12% and SVR_{rest} by 21%. No significant change was seen in SBP_{rest}, CPO_{rest}, SV_{rest} and SW_{rest}. As a result of the changes at rest and exercise, we calculated that there were significant decreases in $HR_{reserve}$ by 14%, $VO_{2reserve}$ by 16%, $CO_{reserve}$ by 11% and $CPO_{reserve}$ by 12%. $SV_{reserve}$ and $SW_{reserve}$ did not significantly change from pre-conception.

This study firstly agrees with the current literature, which states that resting HR and CO increase, whilst blood pressure and SVR decrease in the first trimester [Robson *et al* 1989, Desai et al 2004, Mahendru *et al* 2014]. Changes in CPO_{rest} have not been previously reported, but we have shown that this does not significantly change. At maximal exercise, there was a significant decrease in CO_{max}, CPO_{max} and VO_{2max}, despite preserved exercise duration. Moreover, $HR_{reserve}$, $VO_{2reserve}$, $CO_{reserve}$ and $CPO_{reserve}$ all decreased and so, this suggests a real reduction in cardiac performance in early pregnancy, that has not been previously identified. Changes in resting cardiac output in early pregnancy have been attributed to an increase in blood volume, neurohormonal activation, increase in left ventricular wall muscle mass and contractility [Robson *et al* 1989, Mabie *et al* 1994, Desai *et al* 2004]. However, despite these physiological changes, it appears that the heart does not have the ability to sustain the same peak performance in early pregnancy. As a result of the enhanced resting cardiac function, cardiac reserve inevitably reduces.

Changes in cardiovascular parameters between trimesters were then analysed. There were significant decreases in exercise duration, VO_{2max} and $VO_{2max/kg}$. There were significant increases in SBP_{max}, MAP_{max}, and SVR_{max}. However, there were no significant changes in HR_{max}, DBP_{max}, $CircP_{max}$, CO_{max}, CPO_{max}, SV_{max}, and SW_{max}. At rest, there were significant increases in HR_{rest} and VO_{2rest}. There were no significant changes in SBP_{rest}, DBP_{rest}, MAP_{rest}, SVR_{rest}, CO_{rest}, CPO_{rest}, SV_{rest}, and SW_{rest}. Therefore, there were significant decreases in $HR_{reserve}$ and $VO_{2reserve}$, but no significant changes in $CO_{reserve}$, $CPO_{reserve}$, $SV_{reserve}$, and $SW_{reserve}$. These changes seen at rest are again consistent with previous reports [Robson *et al* 1989, Mabie *et al* 1994, Desai *et al* 2004]. Although we did not report a significant change between repeated measures of CO_{rest}, we did actually see a peak rise in CO_{rest} in the second trimester and maintenance of this in the third trimester. The lack of significance may be because of the low number of subjects or because we used an analysis of repeated measures throughout pregnancy to compare a difference across measures. We also identified that CPO_{rest} continues to rise progressively from the first trimester to the third trimester, although again was not statistically different overall between three trimesters. The same response was seen in HR_{rest} and VO_{2rest}, although both of these were statistically significant. The changes in direct and indirect markers of cardiac function at rest suggest that the cardiovascular system adapts to meet the demands of the growing foetus and increasing weight carriage.

In contrast to the only published longitudinal study examining VO_{2max} at peak exercise throughout pregnancy, the present study showed a significant decrease in VO_{2max}, associated with a significant reduction in exercise duration (using the same treadmill protocol). Lotgering *et al* [Lotgering *et al* 1991] performed a longitudinal study using treadmill exercise, whilst at the same gestation also compared the differences with cycle exercise, in all three trimesters and post-partum. He found no significant difference in VO_{2max} between trimesters and post-partum and no difference between exercise methods. In our experience women became more symptomatic of pregnancy as gestation increased and therefore became less able to perform the same workload. In addition to reduced HR_{max} and VO_{2max}, we also showed that $HR_{reserve}$ and $VO_{2reserve}$ both significantly fell throughout pregnancy. It therefore appears that HR_{max} and $HR_{reserve}$ may be a reasonable surrogate for VO_{2max} and $VO_{2reserve}$ when assessing women in pregnancy.

This is also the first study to report the longitudinal changes throughout pregnancy in CO_{max} and CPO_{max} with maximal treadmill testing. Despite the significant reduction in exercise duration and VO_{2max}, we showed no significant difference in both direct makers of cardiac performance (CPO_{max}), and surrogate markers ($CircP_{max}$, CO_{max}, SV_{max} and SW_{max}). The mean CPO_{max} values in each trimester appear to show an increase from the first trimester to the third, however this failed to reach significance. The cardiovascular reserve measured both directly ($CPO_{reserve}$) and indirectly ($CO_{reserve}$, $SV_{reserve}$ and $SW_{reserve}$) also showed no deterioration throughout pregnancy. Importantly this showed preservation in peak cardiac performance throughout pregnancy. As we did not calculate absolute work load, which has to incorporate both the stage of exercise, but also the weight change, it is difficult to be absolutely certain if cardiac performance has increased for the level of work performed.

Next, cardiovascular physiological changes between the third trimester and post-partum (3 months) were analysed. There were significant increases in exercise duration, $VO_{2max/kg}$ and HR_{max} and a significant reduction in SBP_{max} in post-partum. There were no significant changes in VO_{2max}, DBP_{max}, MAP_{max}, SVR_{max}, $CircP_{max}$, CO_{max}, CPO_{max}, SV_{max}, and SW_{max}. At rest, there were significant decreases in HR_{rest}, VO_{2rest} and SBP_{rest} in post-partum. However, there were no significant changes in DBP_{rest}, MAP_{rest}, SVR_{rest}, CO_{rest}, CPO_{rest}, SV_{rest}, and SW_{rest}. Consequently, there was a significant increase in $HR_{reserve}$ and there were significant decreases in $SV_{reserve}$, $SW_{reserve}$, but no change in $VO_{2reserve}$, $CO_{reserve}$ and $CPO_{reserve}$. Interestingly, this analysis agreed with the maximal treadmill exercise study by Lotgering *et al* [Lotgering *et al* 1991]. Both studies showed no significant

changes in VO_{2max} between the third trimester and post-partum. This is also in agreement with others who used maximal cycle exercise [Spinnewijn *et al* 1996, Heenan *et al* 1996]. The present study also agrees with the longitudinal study by Sady *et al* [Sady *et al* 1990]., which both saw no change in VO_{2max}, but lower $VO_{2max/kg}$ in the third trimester. This suggests that scaling VO_{2max} by body mass, potentially leads to a false interpretation of reduced aerobic capacity. The only other study examining CO_{max} was performed by Sady *et al*, using an acetylene re-breathing technique during maximal cycle exercise. They found that CO_{max} was higher in the third trimester than 8 weeks post-partum, but showed no change in HR_{max}. Therefore, they attributed the change in cardiac flow to an increase in SV_{max}. The present study had a lower HR_{max} and no change in either CO_{max} or SV_{max} in the third trimester. Notably, both studies have different methods, especially the difference in weight bearing exercise. Our present study had lower maximal heart rates and therefore suggests that the third trimester exercise test may not have been tolerated as well and so may not have been as maximal as the post-partum test. Symptom scores between tests were marginally different: RER 1.11 in the third trimester and RER 1.15 in post-partum however, peak ventilation capacity was unchanged. Hence one can at least say that there is no evidence of deterioration in CO_{max} in the third trimester compared to post-partum.

Furthermore this is the first study to report that there was no change in CPO_{max} or $CPO_{reserve}$ despite a significant reduction in exercise ability in the third trimester compared to 3 months post-partum. Both the flow and pressure generating capacities of the heart were maintained.

The physiological changes were then examined between pre-conception and the third trimester. Besides changes already described between the third trimester and post-partum, the study showed significantly higher VO_{2max}, $CircP_{max}$, CO_{max}, and CPO_{max} and lower SVR_{max} in pre-conception. At rest we additionally identified lower CO_{rest} and higher DBP_{rest} and SVR_{rest}, but no change in SBP_{rest} in pre-conception. As a conclusion, $HR_{reserve}$ $VO_{2reserve}$, $CO_{reserve}$ and $CPO_{reserve}$ were all significantly lower in the third trimester compared to pre-conception.

7.61 Study Limitations

The study was again limited by the inability to measure cardiac output and blood pressure continuously, using non-invasive methods, during exercise. The time frame in which subjects became pregnant after the pre-conception test was not

equal and it was not possible to control for variability in weight and cardiovascular fitness levels during that time. The study was further limited by the low number of subjects however, it was very difficult to control for this in the timeframe of the study, as women either did not become pregnant or pulled out because of unwillingness to continue in the study. The population studied were therefore biased by those who were self motivated to continue with the study. Equally all, bar one woman, were Caucasian and 7 of the 14 regularly performed regular exercise prior to pregnancy. This is therefore a relatively selective population, and so further study to confirm these findings in other populations.

7.7 Conclusions

Importantly, this study highlights the weakness in using post-partum as a surrogate for pre-conception. The present study is the first to show that there is an initial fall in both cardiac performance and cardiac reserve in pregnancy. After this there is maintenance of cardiac performance and reserve throughout pregnancy, despite deterioration in symptoms and fall in exercise ability and aerobic capacity. The initial changes in cardiac performance are independent of weight, however as gestation increases maintenance of cardiac performance may be related to the increased weight carriage. Again direct measurement of CPO_{max} was necessary to determine changes in cardiac performance in pregnancy, rather than surrogate measures.

Chapter 8

Cardiovascular physiological effects of inert weight carriage in obesity

Chapter 8

Study VIII: Cross sectional study to determine the cardiovascular effects of obesity

8.1 Introduction

Obesity is a growing epidemic worldwide. In England, obesity prevalence has risen from 16% in 1993 to 26% in 2011, in female adults [HSCIC 2011]. The effect of different degrees of obesity on cardiovascular and overall prognosis are areas of debate, however severe obesity (Class III, BMI> 40kg.m^{-2}) is associated with a poor prognosis [Lavie *et al* 2015; Flegal *et al* 2013]. One problem with using BMI alone to categorize individuals and ascribe risk is that BMI is a crude tool used to estimate body fat percentage and does not account for the natural variation in body geometry [Rothman 2008]. Moreover, poor cardiopulmonary fitness and cardiac performance is commonly predicted to be poor in obese individuals, as they regularly complain of exercise limitation, breathlessness, fatigue and joint pains. It is sometimes necessary to make an attempt to establish cardiac function in obese patients, either to aid decisions with treatment or risk stratification. However, assessing cardiac function accurately in obese individuals can be difficult, due to the limitation in techniques used to assess function, primarily using imaging [Poirier *et al* 2006]. One way to overcome this is to measure CPO at rest and maximal exercise, which would then allow calculation of cardiac reserve.

A study by Alexander [Alexander 1964] showed that at varying grades of moderate treadmill exercise, CO and oxygen consumption were much greater in obese individuals than subjects with ideal body weight. However, at high workloads (> 5 times baseline), CO decreased to a low-normal level [Alexander *et al* 1998b]. Kaltman *et al* [Kaltman *et al* 1976] also reported normal or high resting CO with high oxygen consumption appropriate to body weight in 12 severely obese individuals. During exercise (passive leg raises) there was a consistent rise in stroke volume. Stroke work and central blood volume were also uniformly increased, consistent with a hyperdynamic and hypervolaemic state. More recently the effects of weight loss after bariatric surgery have shown significant incremental improvements in relative, but not the absolute aerobic capacity at 6 and then 12 months post surgery [De Souza *et al* 2010; Wilms *et al* 2013]. Although there appeared to be an increase in oxygen consumption with weight loss, this was only when the absolute values

were scaled per kilogram. One has to be cautious when interpreting data using oxygen consumption scaled by body mass in obese patients. Hothi showed that the mean $VO_{2max/kg}$ was lower in obese patients with heart failure compared to lean heart failure patients, however the absolute VO_{2max} and CPO_{max} was significantly higher in obese patients [Hothi *et al* 2015].

Study IV and V showed that additional acute inert weight loading resulted in a significant reduction in exercise duration and O_2 consumption with a divergent improvement in CPO_{max} during maximal treadmill exercise. It is uncertain whether the same cardiovascular response occurs in chronic perfused weight carriage.

8.2 Purpose and hypothesis of the study

The purpose of this study was to determine the differences in cardiovascular physiology, at rest and maximal exercise, between females with significant excess weight (BMI > 35 $kg.m^{-2}$) and lean females (BMI < 26 $kg.m^{-2}$).

The hypotheses tested in this investigation were

(i) Aerobic capacity ($VO_{2max/kg}$) will be significantly reduced in obese individuals in comparison to lean individuals.

(ii) Absolute VO_{2max} will increase as the severity of obesity (BMI) rises, due to the increased metabolic demands.

(iii) There will be a significant increase in peak cardiac performance in obese individuals in comparison to lean individuals.

(iv) Cardiac function at rest will be associated with an increase in pressure and flow generating capacity in obese subjects in comparison to lean individuals.

(v) There will be a more significant reduction in peak cardiac performance and cardiac reserve with age, in obese individuals compared to lean individuals.

(vi) Peak cardiac performance will not improve as the severity of obesity (BMI) increases.

(vii) Conventional indirect indicators of cardiac function are unreliable as measures of overall cardiac function during exercise stress testing in obesity.

8.4 Methods

This was a prospective observational cross sectional study aimed at comparing the physiological cardiovascular changes seen in obesity with age and sex matched healthy individuals.

8.4.1 Study participants

Females patients with morbid obesity (BMI >35) were enrolled from the obesity clinic at Leeds Teaching Hospitals NHS Trust. These patients had been referred by their general practitioners for obesity management, and were primarily being considered for bariatric surgery. They had an initial assessment with the lead obesity dietician, to assess suitability for surgical obesity management. They were then discussed in an Obesity Management multi-disciplinary meeting to determine management plan and if appropriate were then seen by to one of three bariatric surgeons. The patients being considered for surgery were then referred to the cardiology department for specific cardiac pre-operative assessment and physiological testing.

8.4.2 Healthy controls

The physiological data from controls used for comparison were obtained from previous studies performed by our research group, using the same equipment and methods. These healthy controls were both male and female with ages ranging from 20 to 80 years. They were previously recruited in an observational study of healthy sedentary individuals to determine the changes in cardiac function over time [Chantler *et al* 2006]. These data have provided our lab with our local normal values and are routinely used in clinical practice to plot variance of patient test results from the norm. Complete physiological data, weight, height, BMI and body surface area were available for comparison.

8.4.3 Clinical cardiac assessment

Patients attended the cardiology department initially in a clinic setting, and were assessed where possible by Professor Tan, Professor of Cardiology. This assessment included a full clinical history and examination, to delineate any cardiac symptoms or signs suggestive of cardiac disease and establish their previous

medical history and active medical problems and limitations. NYHA functional class was determined through enquiry about daily activities and exercise.

Patients then underwent cardiopulmonary exercise testing to determine their aerobic capacity and cardiac reserve and also had a transthoracic echocardiogram to identify those with structural heart disease. If they gave a history of angina or history suggestive of symptomatic coronary artery disease, they also underwent either functional testing to look for cardiac ischaemia or a coronary angiogram to identify coronary artery disease, as per NICE guidelines [NICE CG126 2011].

Following testing and full clinical assessment, a clinical recommendation was made to the bariatric surgeon, to state whether they had adequate cardiac reserve and coronary perfusion where necessary to undergo surgery.

8.4.4 Cardiopulmonary exercise testing

An initial symptom-limited maximal treadmill exercise test was performed with the Medgraphic Ultima metabolic cart (Medgraphics Corporation, St. Paul, Minnesota, USA) and continuous ECG monitoring, to measure and monitor breath-by-breath rates of ventilation, O_2 consumption (VO_2), CO_2 production (VCO_2), beat-by-beat heart rate (HR) and exercise duration. Manual cuff sphygmomanometry was used to measure systolic and diastolic blood pressures (SBP and DBP) in mm Hg. The standard protocols used within the department are either a modified Bruce or Bruce protocol however, the starting speed and inclines were too severe for the majority of obese patients and could lead to them stopping within the first one to two minutes and not completing a meaningful level of exercise. Therefore, I designed a specific ramp protocol for these patients, called the "*Lewis protocol"* (Table 8.1). This had the advantage of starting with a very slow 2 minute walk and so allowing the patient to adjust to walking on a treadmill, followed by gradual increments in speed and gradient each minute. In practice, it was found that patients with marked exercise limitation tolerated this protocol much better and in the end performed an overall higher workload. When patient limitation was not as marked, the modified Bruce or Bruce protocols were used. A second peak single-stage exercise test was performed after 45 minutes rest to target the peak workload attained during the prior incremental test and enable measurement of cardiac output using the CO_2 re-breathing technique [Vanhees *et al* 2000]. Detailed explanation of the testing procedure and equipment used is outlined in Chapter 2.

Table 8.1 Lewis treadmill protocol

Time (mins)	**Speed** (mph)	**Gradient** (%)
0 to 2	1	0
2 to 3	1.2	1
3 to 4	1.4	2
4 to 5	1.6	3
5 to 6	1.8	4
6 to 7	2.0	5
7 to 8	2.2	6
8 to 9	2.4	7
9 to 10	2.6	8
10 to 11	2.8	9
11 to 12	3.0	10
Continue to raise speed by 0.2 mph and gradient by 1% every minute		

8.4.5 Transthoracic echocardiogram

Patients underwent a transthoracic echocardiogram, performed by a trained sonographer (British society of echocardiography certified) in the cardiology department at Leeds General Infirmary. A variety of machines were used, including GE Vivid 7, GE Vivid 9, Philips IE33.

Standard echocardiogram protocol (British Society of Echocardiogram guidelines) was used where possible [Wharton *et al* 2012] however, due to the population being scanned, many images were not available or suitable for analysis. The study was performed in the left lateral position, with ECG gating, in a dedicated darkened room. Particular focus was to assess both chamber sizes of left ventricle, right ventricle and atria. Where possible LV wall thickness was measured, as was mitral valve forward flow and filling pattern.

8.4.6 Statistics

All data were analysed using SPSS. Data are presented as mean and standard deviation. Delta measures and percentage change in measures between obese and non-obese subjects are also displayed as a mean and standard deviation with 95%

confidence intervals. Statistical comparisons were made with Student's paired, two-tailed t test. A *P* value of < 0.05 was considered to be statistically significant.

8.5 Results

8.5.1 Study population baseline characteristics

A total of 90 obese female (BMI > 35) patients were recruited and compared to 130 age matched healthy female controls (BMI < 30). Differences in weight and body mass index are shown below in Figures 8.1 and 8.2 and Table 8.3. There were highly significant differences in weight across all ages with a mean difference of 68 kg ($p < 0.001$). The same pattern was seen with differences in BMI, with mean difference of 26 $k.m^{-2}$ ($p < 0.001$).

Two obese patients were excluded because of severe limiting heart disease (Moderate - severe left ventricular systolic dysfunction; Severe coronary artery disease with limiting angina). A further seven obese patients were excluded because of their inability to perform exercise, due to excessive leg or joint pain. This left 81 obese patients available for analysis.

All healthy subjects were fit and healthy and taking no regular medications. They had no impediments to exercise and either regularly performed no or moderate level exercise at most.

Many of the obese patients had co-morbidities, the commonest of which are shown in Table 8.2. 12 patients had a previous history of cardiac problems, which at the time of assessment was of negligible functional significance. 8 had confirmed or suspected coronary artery disease (*2 had previous small myocardial infarctions; 2 had previous elective percutaneous coronary intervention; 4 had a history of well controlled angina*); 1 had moderate aortic stenosis; 2 had atrial fibrillation; 1 had Wolf Parkinson White syndrome and 1 had previous myocarditis, with no deterioration in cardiac function on echocardiography.

70 of the patients had been referred for cardiac assessment pre-bariatric surgery and at the time of analysis 60 had so far undergone surgery. 2 had been referred for assessment prior to other abdominal surgery and the other 9 patients were recruited from general cardiology and medical obesity clinics.

72 of the patients underwent transthoracic echocardiography either at the same first clinical visit or a few weeks prior to the assessment. 67 had good left ventricular systolic function; 5 had mild left ventricular systolic dysfunction and 1 had impaired right ventricular systolic dysfunction. 1 had moderate aortic stenosis and the other 71 had no significant valve dysfunction. Electrocardiograms showed that 79 patients were in sinus rhythm and 2 in atrial fibrillation.

All patients and controls underwent exercise testing without complications. Obese patients were more symptomatic with a mean NYHA 1.3 ± 0.5, compared to no exertional symptoms in the control group. There was a significant difference between RER_{max} at peak exercise (Obese: 0.865 ± 0.12; Control: 1.19 ± 0.11, $p < 0.001$).

Table 8.2 Co-morbidities present in obese subjects

	Number	Percent (%)
Hypertension	25	31.3
Asthma or COPD	29	36.7
OSA	19	24.4
Diabetes	22	27.8
Depression	30	38.5
OA or Joint problems	38	48.7
GORD	13	16.5
Hypothyroidism	6	7.7
Cardiac disease	12	15.6

COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnoea; OA: osteoarthritis; GORD: gastro-oesophageal reflux disease.

Figure 8.1 Differences in weight between healthy and obese subjects

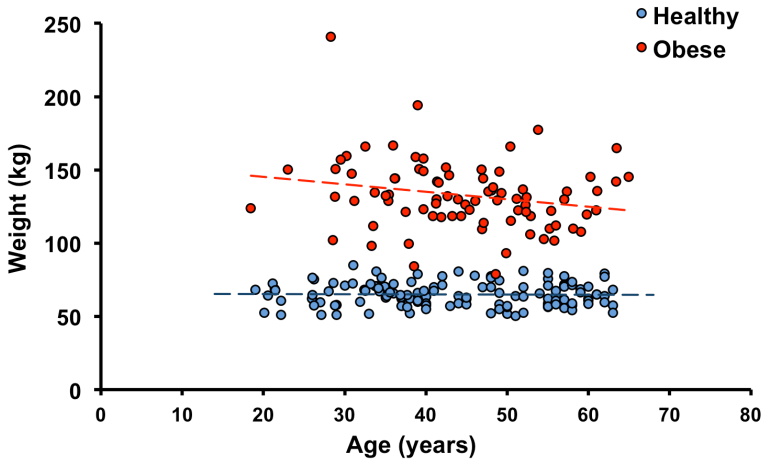


Figure 8.2 Differences in BMI between healthy and obese subjects

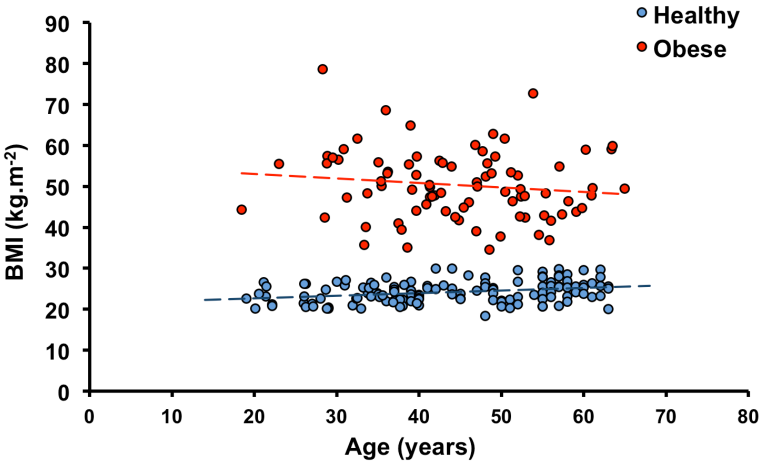


Table 8.3 Differences in demographics between healthy and obese subjects

	Age (years) Mean (SD)	Weight (kg) Mean (SD)	Height (cm) Mean (SD)	BMI (kg.m^{-2}) Mean (SD)	BSA (m^2) Mean (SD)
Healthy	44.0 (11.5)	64.9 (8.0)	163.9 (6.5)	24.1 (2.6)	1.70 (0.12)
Obese	44.7 (10.2)	132.6 (23.9)	162.3 (6.5)	50.3 (8.4)	2.29 (0.20)
P value	0.640	<0.001	0.090	<0.001	<0.001
∆Mean (SED)	0.7 (1.5)	67.8 (2.3)	-1.5 (0.9)	26.2 (0.9)	0.59 (0.02)
95% CI	-2.3, 3.7	63.3, 72.3	-3.3, 0.2	24.3, 28.1	0.54, 0.63

SD: standard deviation; SED: standard error of difference; CI: confidence intervals; BMI: body mass index; BSA: body surface area.

8.5.2 Differences in resting variables between healthy and obese subjects

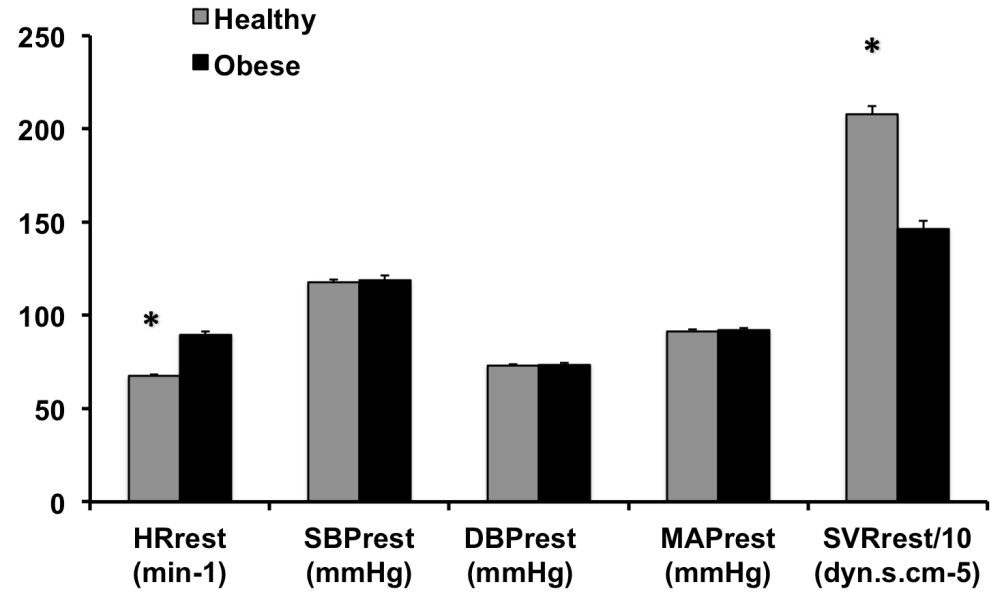
Cross-sectional differences resting variables in healthy and obese subjects are shown in Figures 8.3 and 8.4 and Table 8.4. At rest there was a significantly higher mean heart rate seen in the obese patients ($p < 0.001$) with a 33% difference between means. There were no significant differences in mean blood pressures, however systemic vascular resistance was significantly lower in obese patients ($p < 0.001$) with a 30% difference. There were significant differences in all markers of cardiac function measured ($p < 0.001$) with a 55% increase in $VO_{2\ rest}$, 45% increase in CO_{rest}, 45% increase in CPO_{rest}, 20% increase in SV_{rest} and 19% increase in SW_{rest} in obese patients.

Table 8.4 Differences between resting variables in healthy and obese subjects

	Healthy Mean (SD)	**Obese** Mean (SD)	**P value**	Δ Mean (SED) 95% CI	% Δ means
HR_{rest} (min^{-1})	67.3 (9.5)	89.6 (16.7)	<0.001	22.3 (2.0) 18.3, 26.3	32.9
SBP_{rest} (mmHg)	117.8 (13.5)	118.8 (22.4)	0.709	1.0 (2.7) -4.3, 6.4	0.8
DBP_{rest} (mmHg)	72.9 (7.8)	73.4 (11.0)	0.677	0.6 (1.4) -2.2, 3.3	0.6
MAP_{rest} (mmHg)	91.3 (9.4)	91.9 (11.9)	0.697	0.6 (1.5) -2.3, 3.5	0.5
SVR_{rest} ($dyn.s.cm^{-5}$)	2072 (490)	1463 (408)	<0.001	-610 (65) -737, -482	-29.6
$VO_{2\ rest}$ ($ml.min^{-1}$)	224 (43)	347.5 (98.5)	<0.001	124 (11) 101, 146	55.4
CO_{rest} ($l.min^{-1}$)	3.70 (0.87)	5.36 (1.42)	<0.001	1.65 (0.17) 1.31, 2.00	44.9
CPO_{rest} (watts)	0.75 (0.20)	1.09 (0.33)	<0.001	0.34 (0.04) 0.26, 0.42	45.4
SV_{rest} (ml)	55.5 (13.1)	66.1 (21.4)	<0.001	10.6 (2.7) 5.4, 15.9	19.6
SW_{rest} (g.m)	69.2 (17.2)	82.1 (26.7)	<0.001	12.9 (3.4) 6.2, 19.7	18.9

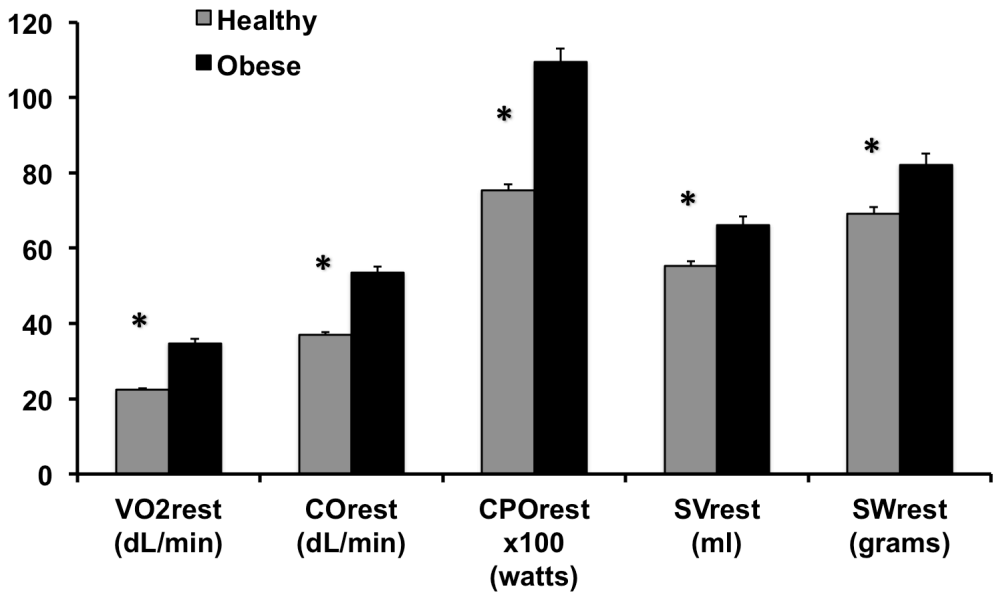
SD: standard deviation; SED: standard error of difference; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Figure 8.3 Differences between resting variables in healthy and obese subjects



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. *: p<0.01

Figure 8.4 Differences between resting cardiac variables in healthy and obese subjects



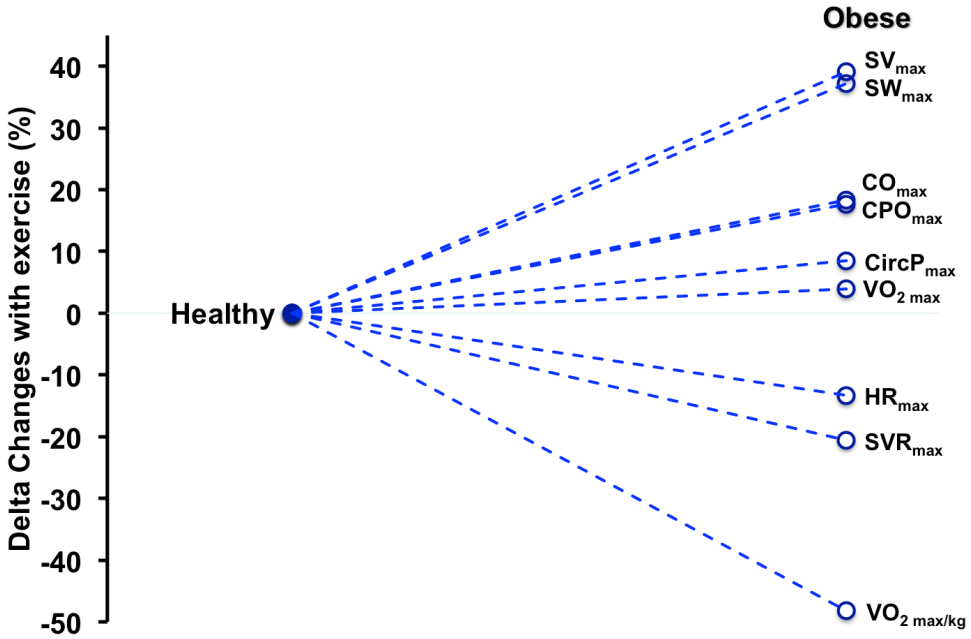
VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

8.5.3 Differences in exercise variables between healthy and obese subjects

Cross-sectional differences in maximal exercise haemodynamic variables in healthy and obese subjects are shown in Figures 8.5, 8.6 and 8.7 and Table 8.5. At maximal exercise there were significantly lower mean heart rates in obese subjects ($p < 0.001$) with 13% difference. Mean arterial pressure did not significantly change, however systolic pressures were significantly lower ($p = 0.003$) and diastolic pressures significantly higher ($p = 0.002$) with an 8% and 7% difference between means seen respectively. Systemic vascular resistance was also significantly lower in obese subjects ($p < 0.001$) with a 21% difference in means.

There was no significant difference seen in $VO_{2\ max}$ however, there were significantly lower $VO_{2\ max/kg}$ values in obese subjects ($p < 0.001$) with a 48% difference in means. The remainder of the cardiac measures were significantly greater in obese patients. There was an 18% increase in CO_{rest} ($p < 0.001$), 18% increase in CPO_{rest} ($p < 0.001$), 9% increase in $CircP_{max}$, ($p = 0.023$), 39% increase in SV_{rest} ($p < 0.001$) and a 37% increase in SW_{rest} ($p < 0.001$).

Figure 8.5 Percentage difference in means of maximal exercise variables in healthy and obese subjects



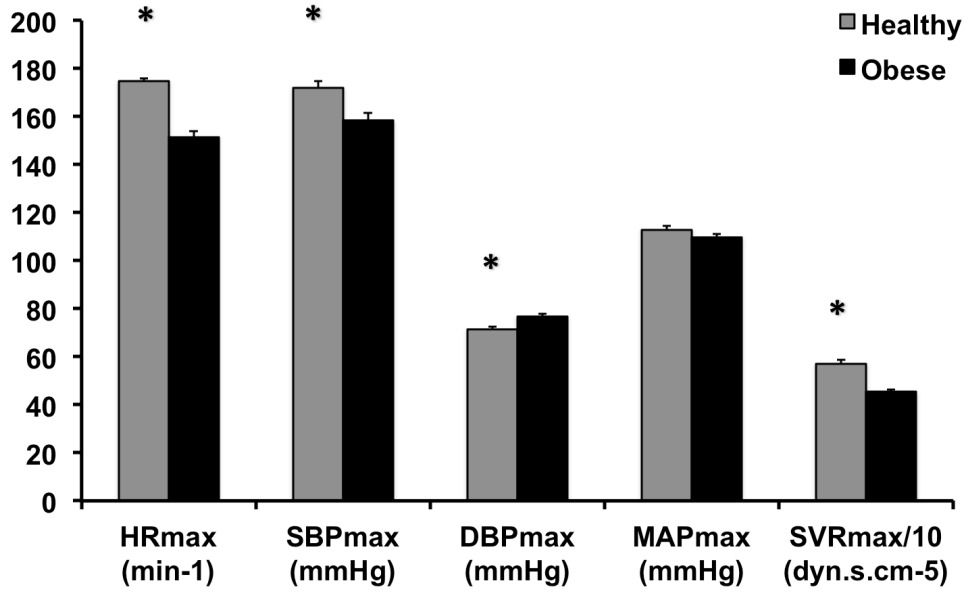
SV: stroke volume, SW: stroke work, CO: cardiac output, CPO: cardiac power output, VO_2: oxygen consumption, CircP: circulatory power, HR: heart rate, SVR: systemic vascular resistance.

Table 8.5 Differences between maximal exercise variables in healthy and obese subjects

	Healthy Mean (SD)	**Obese** Mean (SD)	**P value**	∆Mean (SED) 95% CI	% ∆ means
HR_{max} (min^{-1})	174.6 (12.1)	151.5 (21.7)	<0.001	-23.1 (2.6) -28.3, -18.0	-13.3
SBP_{max} (mmHg)	171.8 (32.5)	158.4 (28.8)	0.003	-13.4 (4.4) -22.0, -5.0	-7.9
DBP_{max} (mmHg)	71.4 (12.1)	76.7 (12.0)	0.002	5.3 (1.7) 2.0, 8.7	7.2
MAP_{max} (mmHg)	112.7 (18.6)	109.7 (13.0)	0.167	-3.0 (2.2) -7.3, 1.3	-2.8
SVR_{max} ($dyn.s.cm^{-5}$)	571 (175)	453.5 (89.0)	<0.001	-118 (21) -158, -77	-20.6
VO_{2max} ($ml.min^{-1}$)	2000 (488)	2081 (439)	0.225	80 (66) -50, 210	3.9
$VO_{2max/kg}$ ($ml.min^{-1}.kg^{-1}$)	30.9 (6.9)	16.0 (3.6)	<0.001	-14.9 (0.7) -16.3, -13.5	-48.2
CO_{max} ($l.min^{-1}$)	16.7 (3.3)	19.8 (3.0)	<0.001	3.1 (0.4) 2.2, 4.0	18.3
CPO_{max} (watts)	4.10 (0.64)	4.82 (0.89)	<0.001	0.74 (0.11) 0.52, 0.96	17.7
$CircP_{max}$ ($mmHg.ml\ O_2.min^{-1}$)	302 (70)	329 (89.5)	0.023	26.6 (11.6) 3.7, 49.5	8.5
SV_{max} (ml)	96.2 (17.4)	133.9 (23.5)	<0.001	37.8 (3.0) 31.8, 43.7	39.1
SW_{max} (g.m)	145.1 (25.5)	199.6 (41.9)	<0.001	54.5 (5.1) 44.4, 64.6	37.2

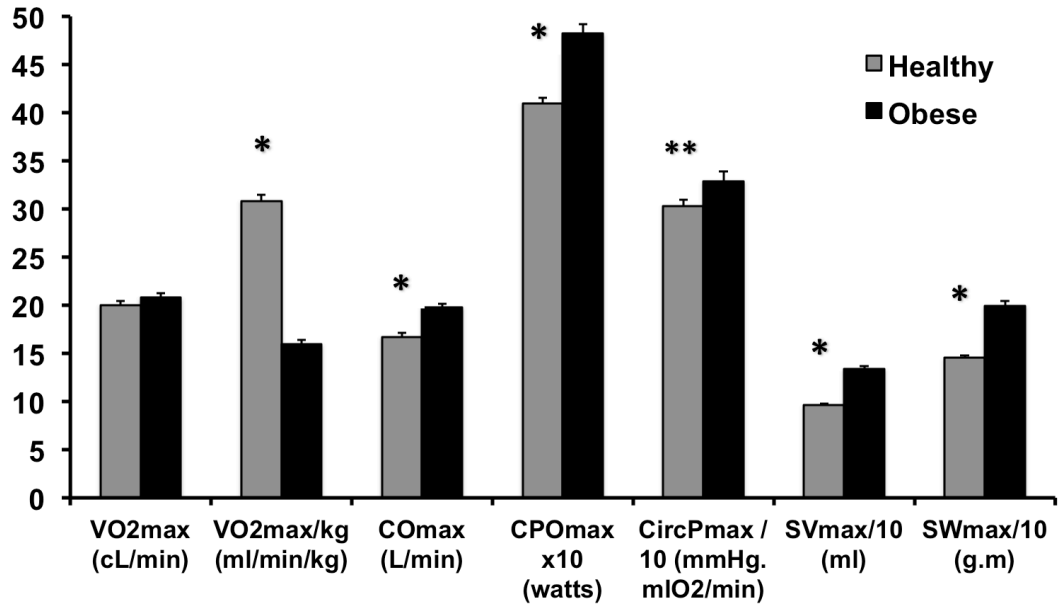
SD: standard deviation; SED: standard error of difference; CI: confidence intervals; HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: circulatory power; SV: stroke volume; SW: stroke work.

Figure 8.6 Differences between maximal exercise variables in healthy and obese subjects



HR: heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial blood pressure; SVR: systemic vascular resistance. *: p<0.01

Figure 8.7 Differences between maximal exercise cardiac variables in healthy and obese subjects



Ex Dur: exercise duration; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; CircP: Circulatory power; SV: stroke volume; SW: stroke work. *: p<0.01; **: p<0.05

8.5.3.1 Changes in exercise haemodynamics with age in healthy and obese subjects

Differences and changes with age for individual haemodynamic measures are shown in Figures 8.8 to 8.17. Changes in maximal heart rate decreased simultaneously with age in both healthy and obese individuals, with a marked lower heart rate seen in obese subjects throughout. Maximal mean arterial pressure did not change with age however, there appeared to be an increase in MAP_{max} in healthy subjects with age. Overall there were not significant differences between both groups. Systemic vascular resistance at maximal exercise only slightly increased in obese patients with age, however there was a marked increase in SVR_{max} in the healthy group leading to significant differences in means between groups.

VO_{2max} remained similar between groups and showed simultaneous reduction in values with age. However when VO_{2max} was scaled per kilogram, values were significantly lower in obese subjects. The difference in values was more marked at younger ages, due to the difference in regression lines between groups. CO_{max} was significantly higher in obese subjects and had very similar regression line to healthy subjects, showing a decrease in values with age. CPO_{max} showed a slight fall in values with age in obese subjects, however remained preserved with age in healthy subjects. This lead to larger differences in CPO_{max} between young healthy and obese subjects. When CPO_{max} was charted against $VO_{2\ max/kg}$ it was evident that obese subjects achieved much higher CPO_{max} values at much lower $VO_{2max/kg}$ than in healthy subjects.

SV_{max} values were preserved with age in obese subjects, as opposed to healthy subjects, who showed a fall in values with age. This lead to larger differences in SV_{max} in older subjects. SW_{max} was consistently higher in obese subjects and simultaneously showed a slight increase with age, as seen in healthy subjects.

Figure 8.8 Changes in HR_{max} with age in healthy and obese subjects

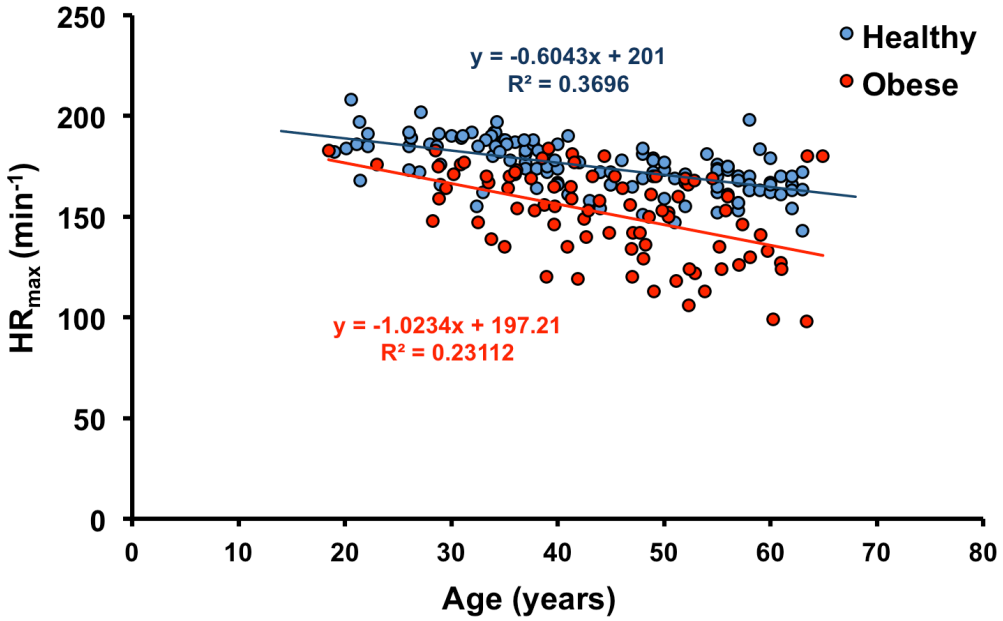


Figure 8.9 Changes in MAP_{max} with age in healthy and obese subjects

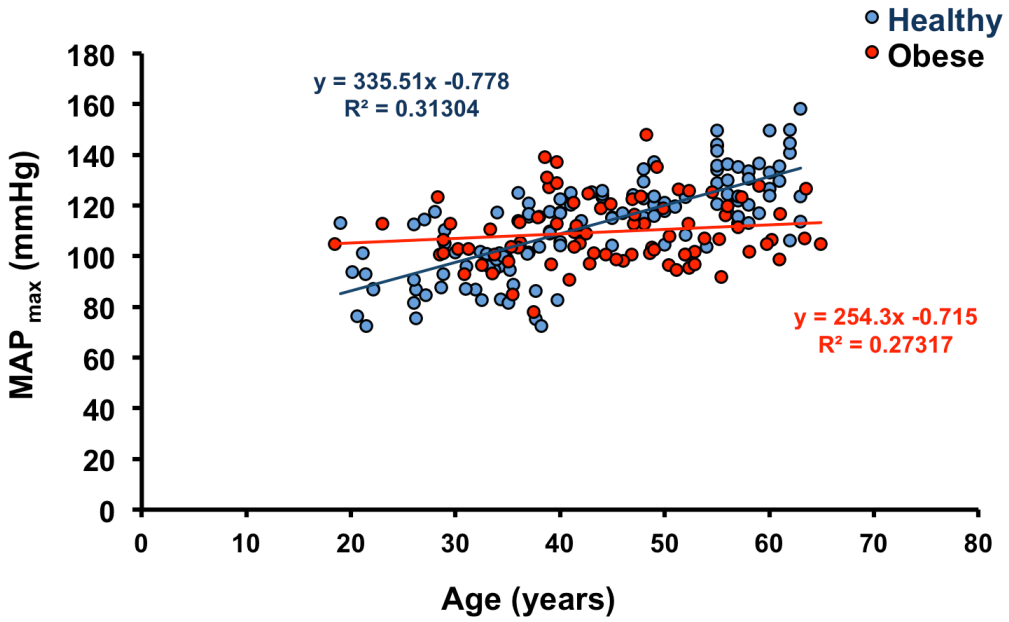


Figure 8.10 Changes in SVR_{max} with age in healthy and obese subjects

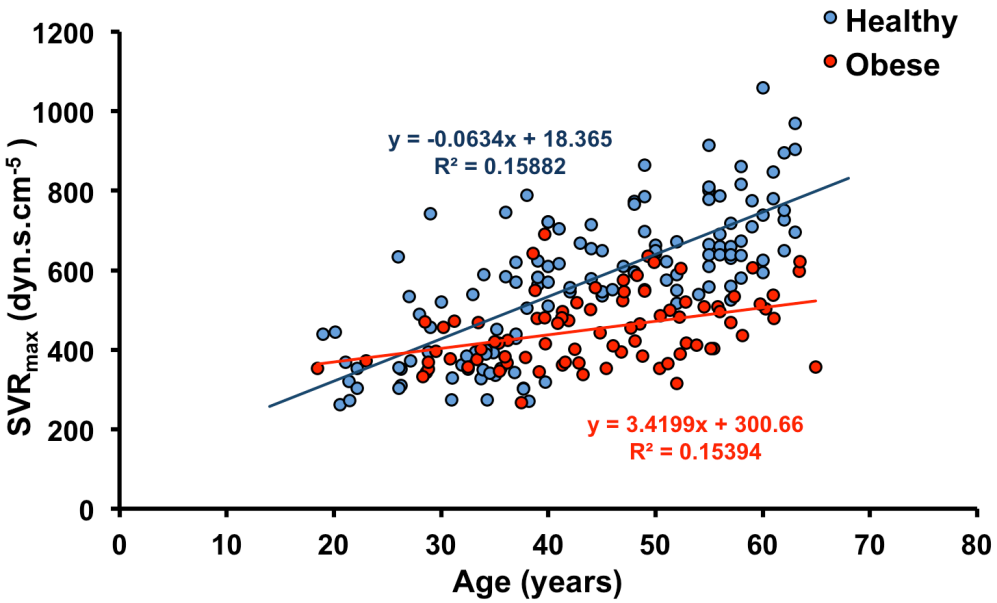


Figure 8.11 Changes in $VO_{2\ max}$ with age in healthy and obese subjects

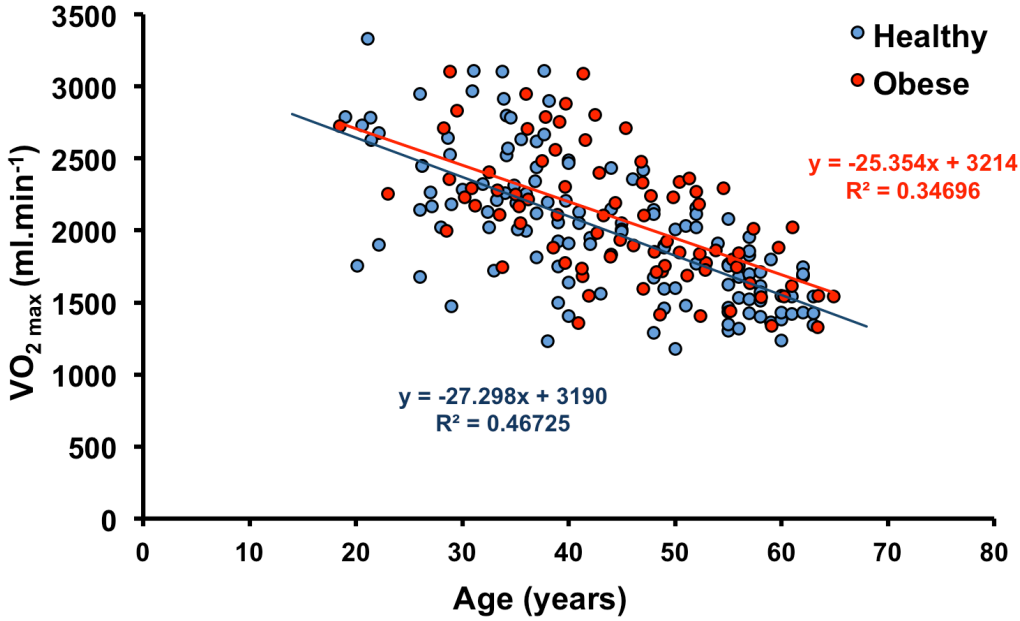


Figure 8.12 Changes in $VO_{2\ max/kg}$ with age in healthy and obese subjects

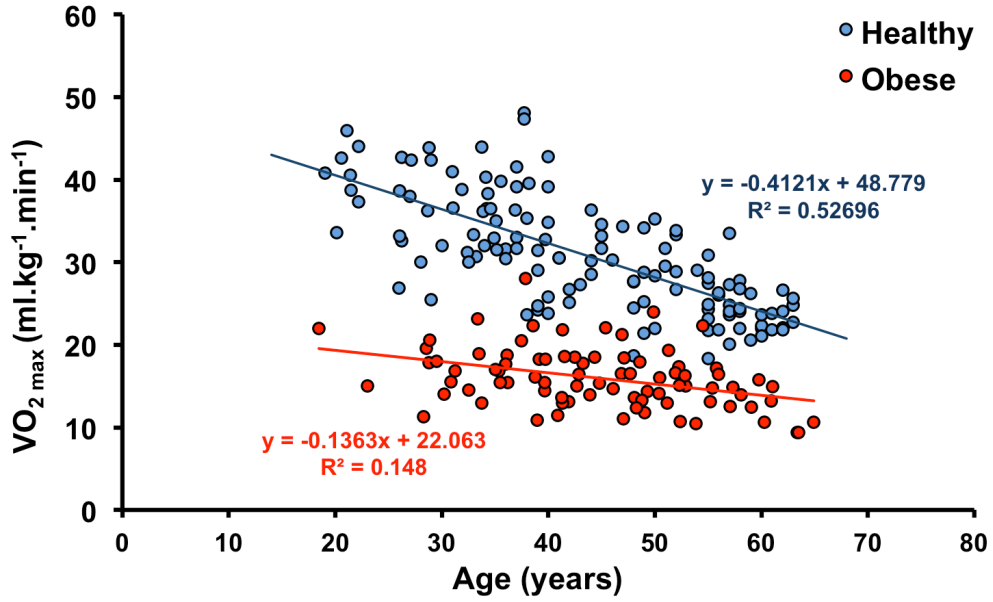


Figure 8.13 Changes in CO_{max} with age in healthy and obese subjects

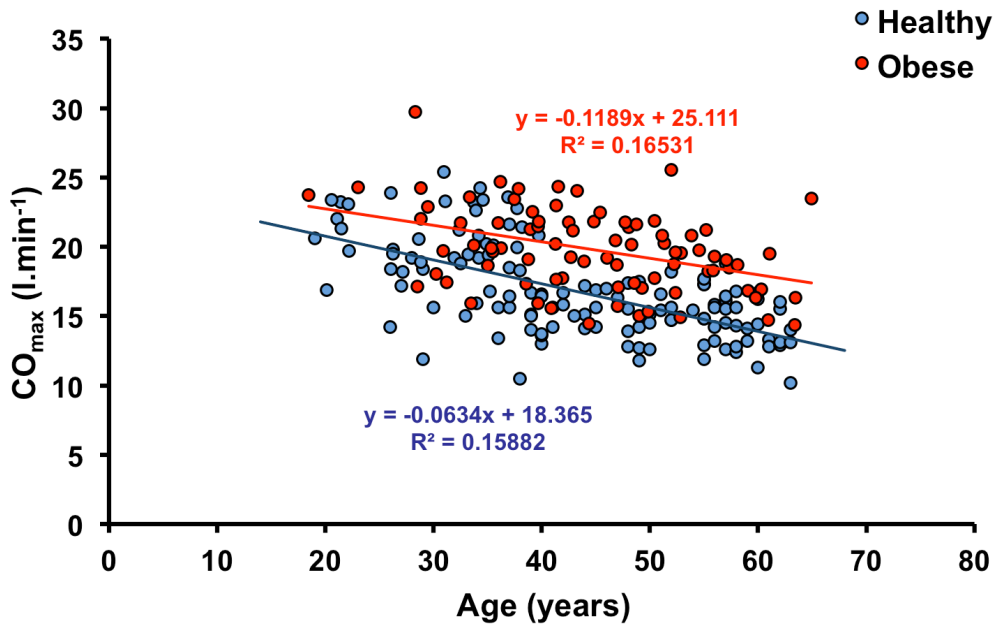


Figure 8.14 Changes in CPO_{max} with age in healthy and obese subjects

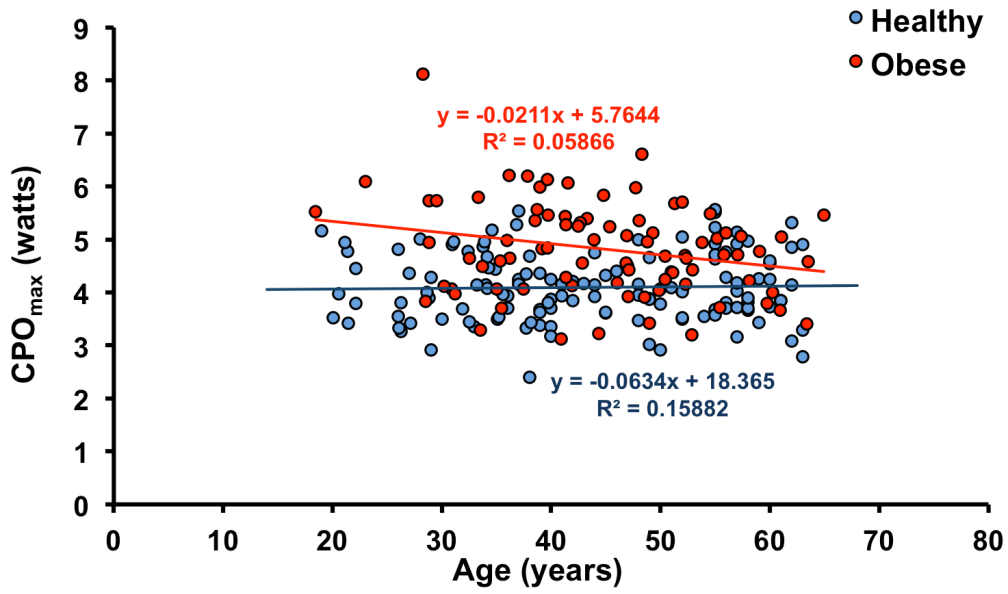


Figure 8.15 Changes in CPO_{max} and $VO_{2\ max/kg}$ in healthy and obese subjects

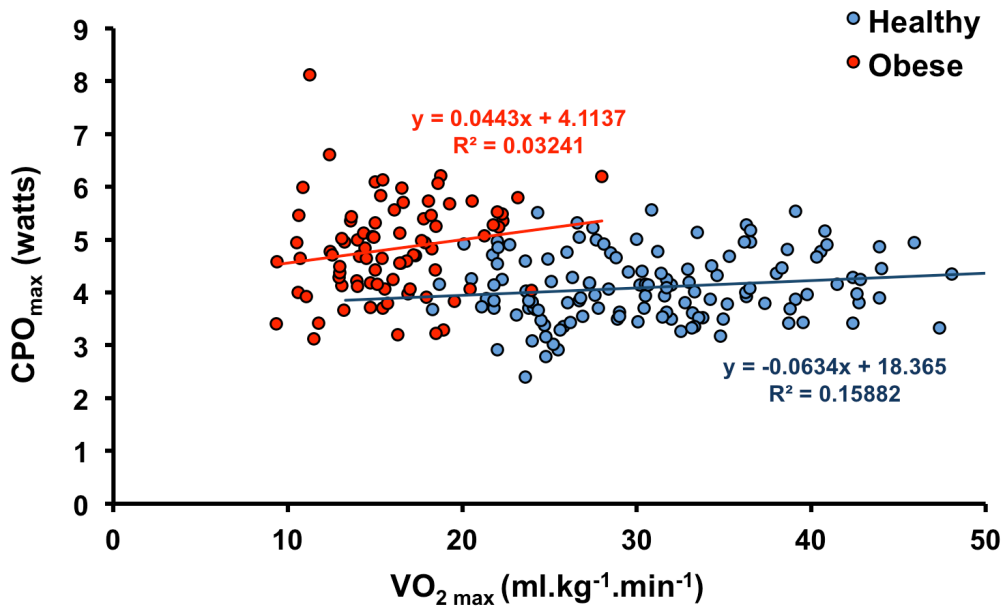


Figure 8.16 Changes in SV_{max} with age in healthy and obese subjects

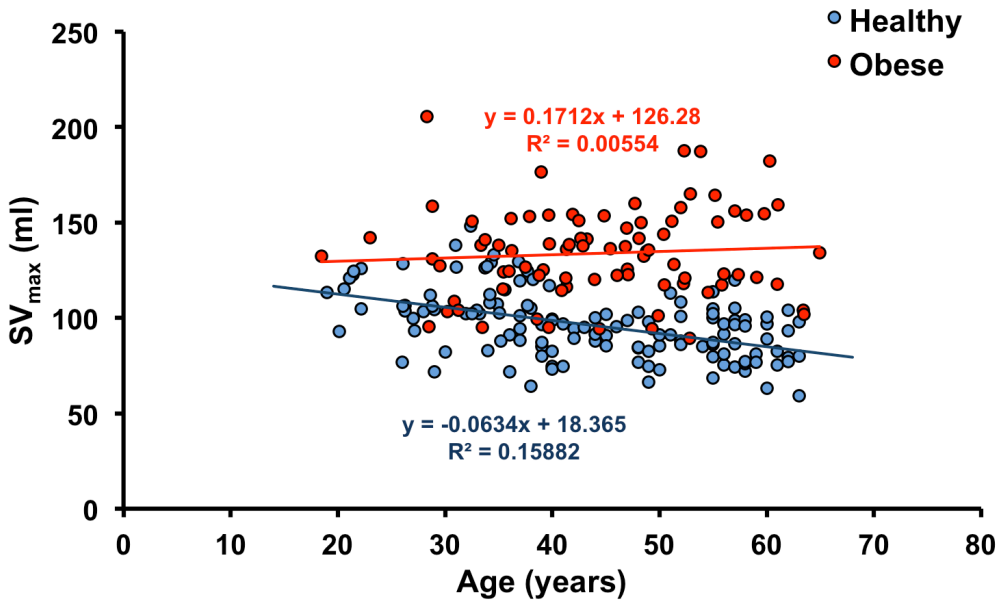
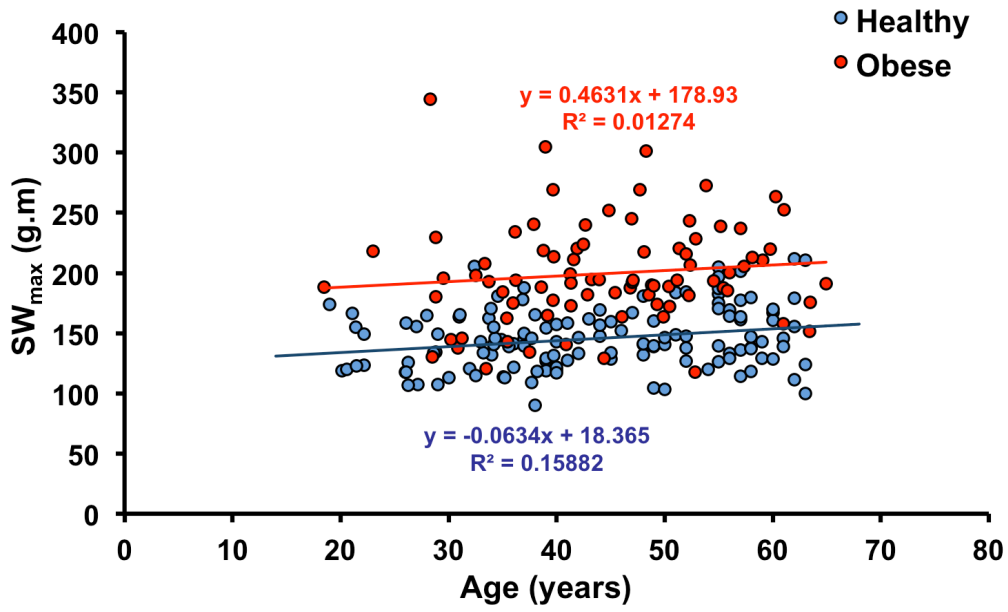


Figure 8.17 Changes in SW_{max} with age in healthy and obese subjects



8.5.3.2 Changes in exercise variables with BMI in healthy and obese subjects

Differences and changes with BMI for individual haemodynamic measures are shown in Figures 8.18 to 8.25. There were no significant differences in mean MAP_{max} between groups however, there was increase in MAP_{max} with BMI seen in healthy subjects, whereas MAP_{max} remained unchanged with BMI in obese subjects. SVR_{max} increases with BMI in healthy subjects, however reduces with BMI in obese subjects. $VO_{2\ max}$ shows a similar rate of increase with BMI in both obese and healthy subjects however, when $VO_{2max/kg}$ decreases with BMI in both groups, with a steeper rate of decrease seen in healthy subjects.

CO_{max} and SV_{max} do not change with BMI in healthy subjects however, show a steady increase with BMI in obese subjects. CPO_{max} and SW_{max} both show steady increases in values with BMI in both healthy and obese subjects.

Figure 8.18 Changes in MAP_{max} with BMI in healthy and obese subjects

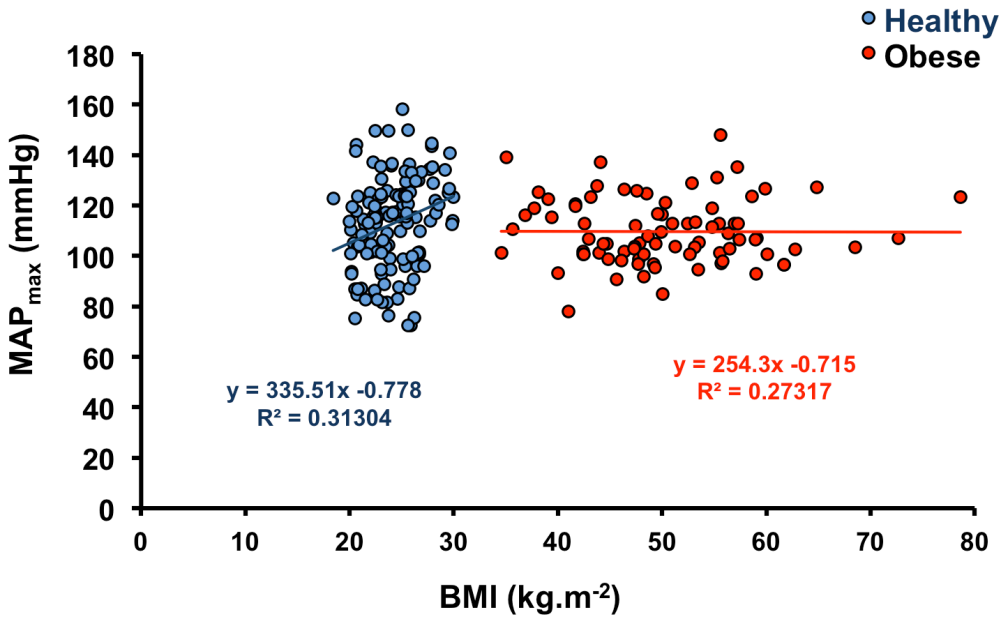


Figure 8.19 Changes in SVR_{max} with BMI in healthy and obese subjects

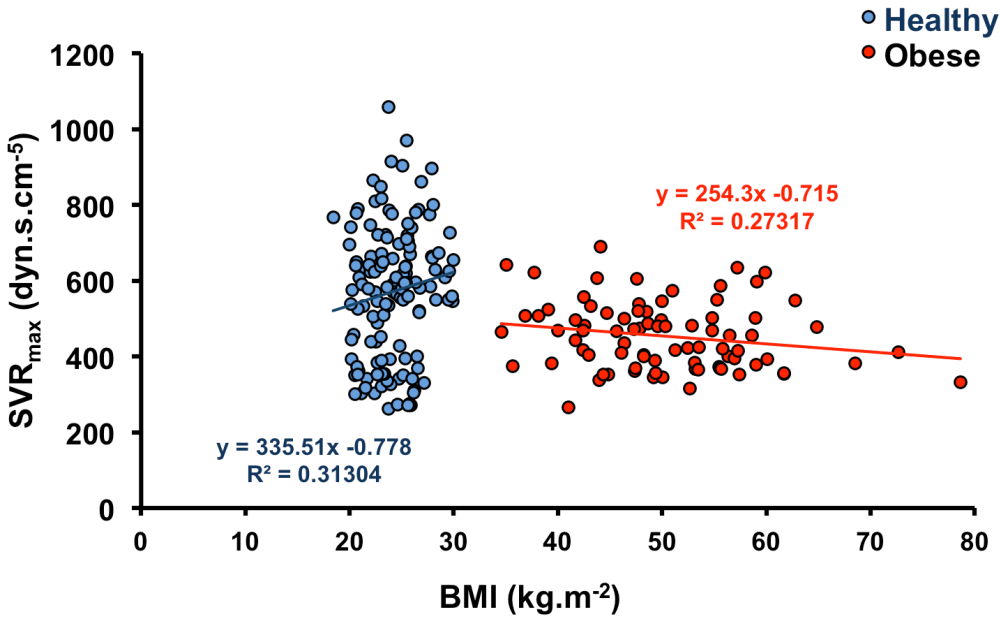


Figure 8.20 Changes in $VO_{2\ max}$ with BMI in healthy and obese subjects

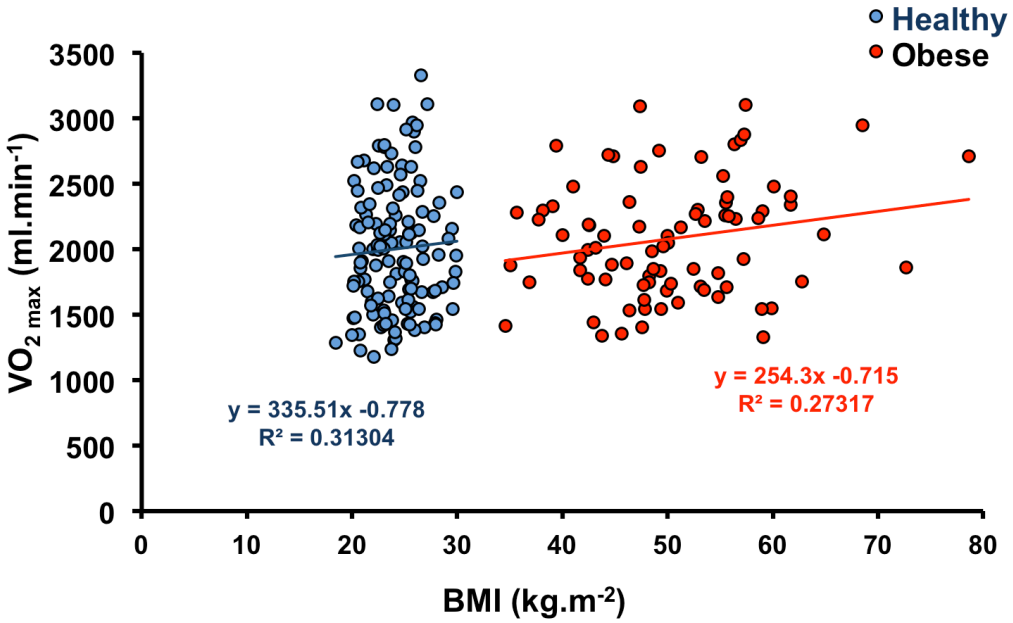


Figure 8.21 Changes in $VO_{2\ max/kg}$ with BMI in healthy and obese subjects

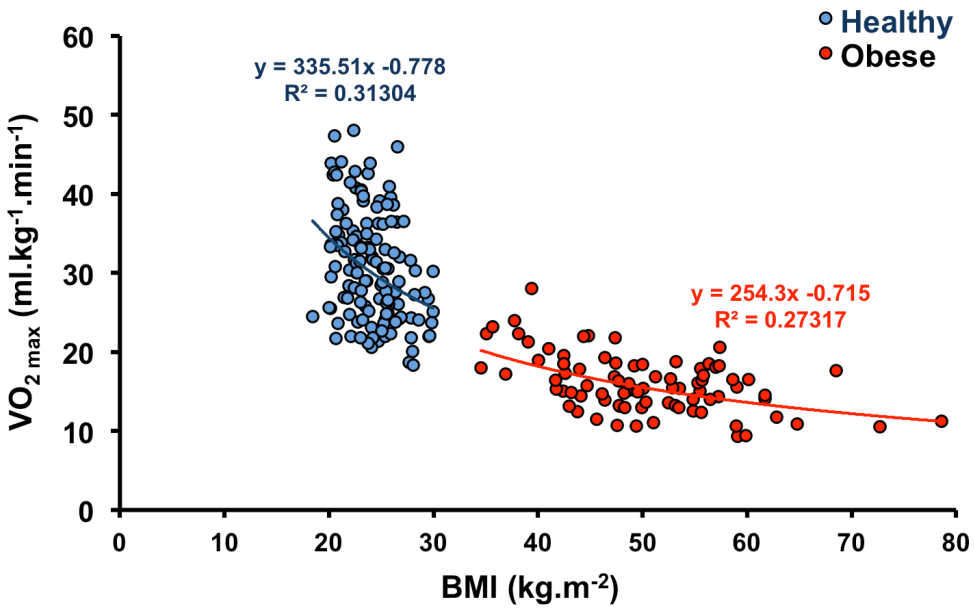


Figure 8.22 Changes in CO_{max} with BMI in healthy and obese subjects

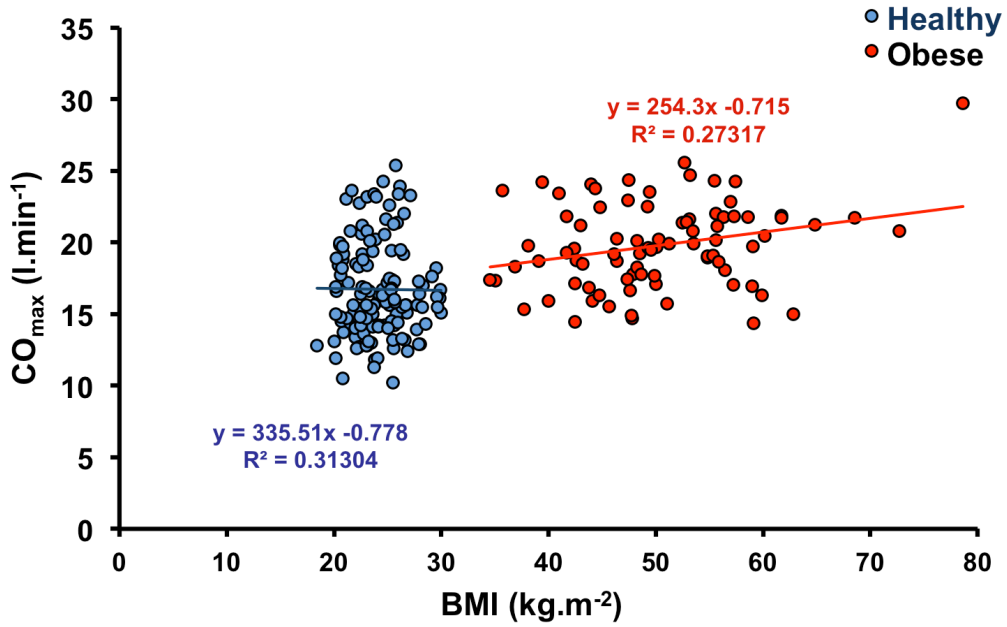


Figure 8.23 Changes in SV_{max} with BMI in healthy and obese subjects

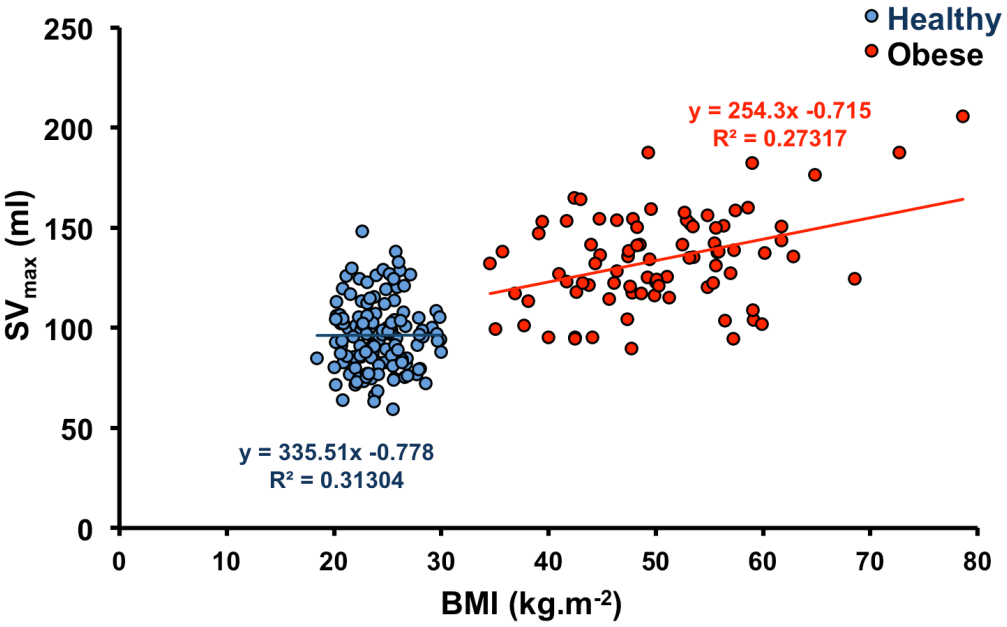


Figure 8.24 Changes in CPO_{max} with BMI in healthy and obese subjects

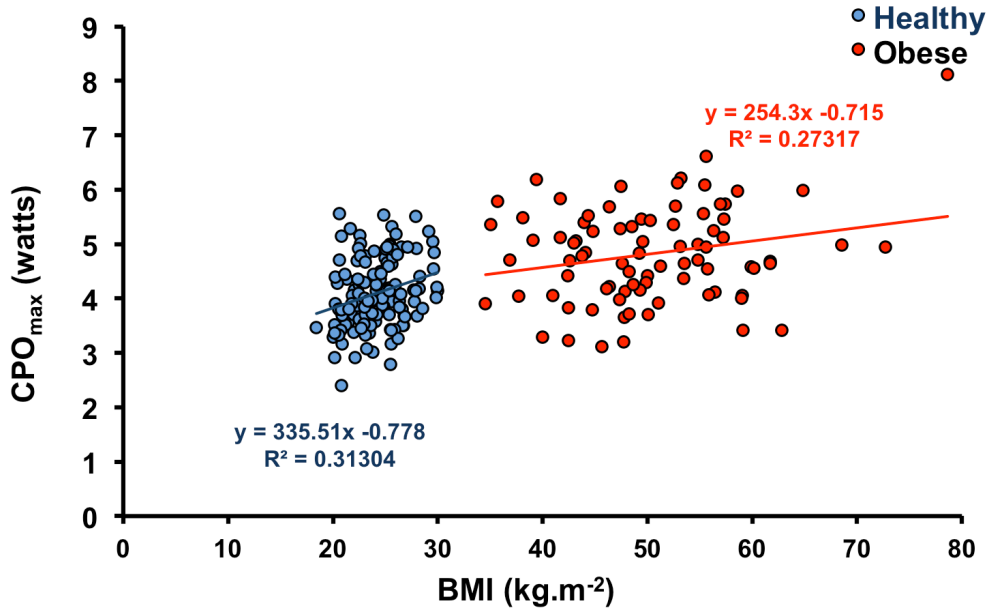
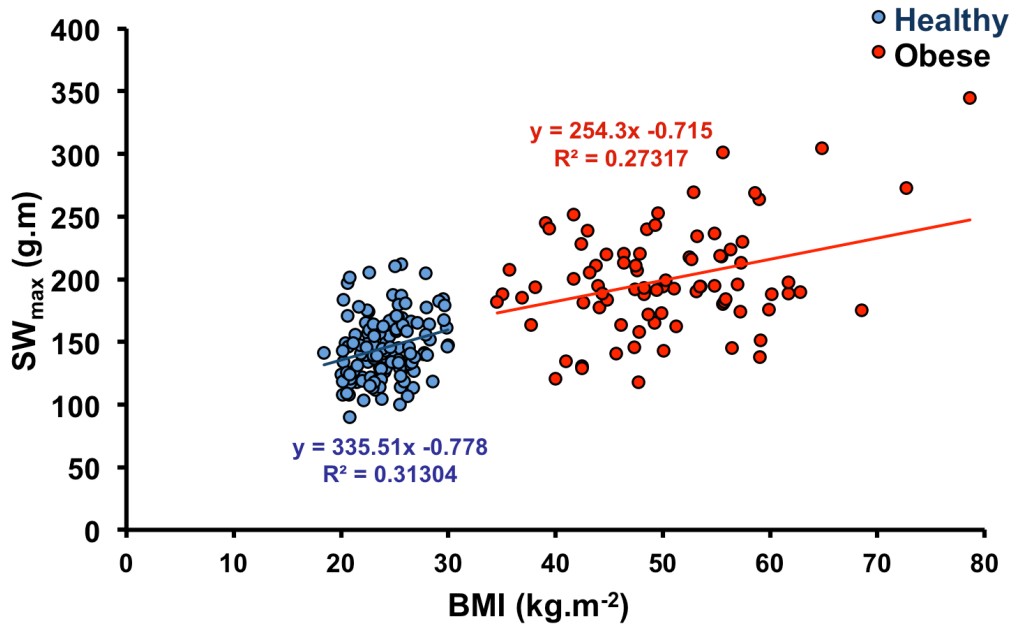


Figure 8.25 Changes in SW_{max} with BMI in healthy and obese subjects



8.5.4 Differences in reserve variables between healthy and obese subjects

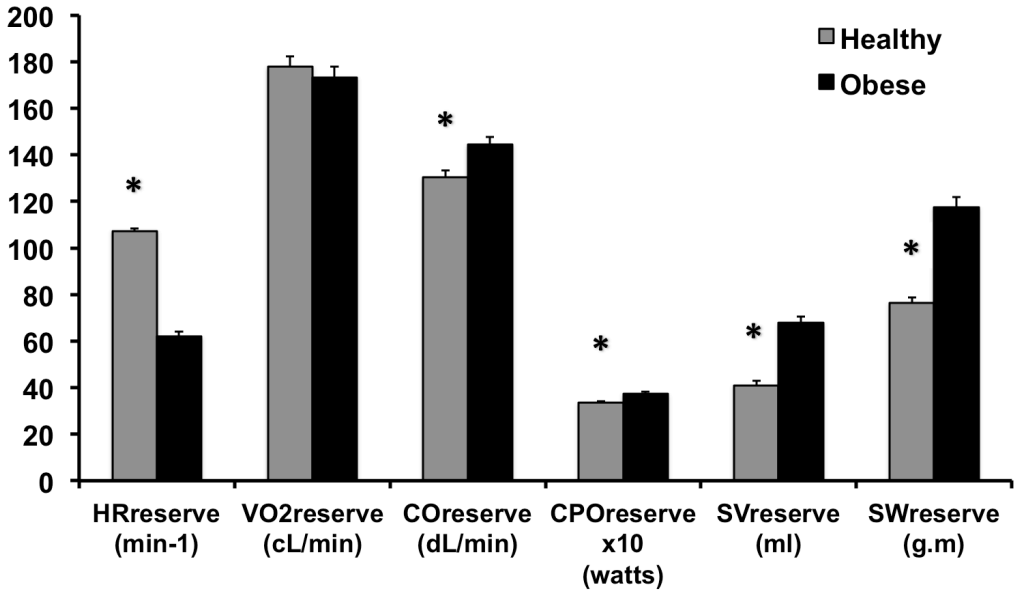
Cross-sectional differences in reserve haemodynamic variables in healthy and obese subjects are shown in Figures 9.26 and Table 9.6. There was a significant lower heart rate reserve seen in obese patients ($p < 0.001$) with a 42% difference in means. There was no significant difference in $VO_{2reserve}$ however, the other measures of functional cardiac reserve were significantly higher in obese subjects ($p < 0.01$). Differences in means were by an increase of 11% in $CO_{reserve}$, 11% in $CPO_{reserve}$, 66% in $SV_{reserve}$ and 54% in $SW_{reserve}$.

Table 8.6 Differences in reserve variables between healthy and obese subjects

	Healthy Mean (SD)	**Obese** Mean (SD)	**P value**	ΔMean (SED) 95% CI	% Δ means
$HR_{reserve}$ (min^{-1})	107.3 (12.5)	61.9 (19.5)	<0.001	-41.8 (2.4) -46.5, -37.1	-42.3
$VO_{2\ reserve}$ ($ml.min^{-1}$)	1776 (497)	1733 (421)	0.512	-43.2 (65.8) -173.0, 86.6	-2.5
$CO_{reserve}$ ($l.min^{-1}$)	13.0 (3.6)	14.4 (2.9)	0.001	1.4 (0.4) 0.6, 2.3	10.8
$CPO_{reserve}$ (watts)	3.33 (0.64)	3.73 (0.81)	<0.001	0.40 (0.10) 0.19, 0.60	11.4
$SV_{reserve}$ (ml)	40.7 (22.6)	67.8 (24.7)	<0.001	27.1 (3.3) 20.6, 33.6	65.5
$SW_{reserve}$ (g.m)	75.9 (25.9)	117.5 (40.2)	<0.001	41.6 (5.0) 31.8, 51.4	53.7

SD: standard deviation; SED: standard error of difference; CI: confidence intervals; HR: heart rate; VO_2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work.

Figure 8.26 Differences in reserve variables between healthy and obese subjects



HR: heart rate; VO2: oxygen consumption; CO: cardiac output; CPO: cardiac power output; SV: stroke volume; SW: stroke work. *: p<0.01.

8.6 Discussion

This study is the first to determine the differences in peak cardiac performance between obese females (BMI > 35 $kg.m^{-2}$), without known cardiac dysfunction and lean healthy females (BMI < 26 $kg.m^{-2}$), using maximal treadmill exercise. The results show that individuals who chronically carry excess perfused weight (Obesity) have 13% significantly lower HR_{max} ($P < 0.001$) and 48% lower $VO_{2max/kg}$ ($P < 0.001$) than lean individuals. Exercise duration was not compared, due to the differences in exercise protocols used. These observations support our first hypothesis that the chronic carriage of excess weight would result in a reduction in aerobic capacity. However, one has to be cautious when interpreting data using oxygen consumption scaled by body mass in obese patients. This is highlighted by the figures which compare both VO_{2max} and $VO_{2max/kg}$ between groups with age and BMI (Figures 8.11, 8.12, 8.20, 8.21). Absolute VO_{2max} values were not different between groups across all ages however, $VO_{2max/kg}$ in the obese group was significantly lower, particularly at a younger age. This could potentially discriminate against younger individuals when using this data, particularly for commencing treatment or considering cardiac transplantation. In addition, as BMI increases there appears to be an associated decrease in $VO_{2max/kg}$, whereas absolute VO_{2max} either stays the same or increases in both groups. However, the metabolic demands during maximal exercise in the obese group only appear to increase slightly with increasing BMI. This is probably because the difference in body composition between obese patients is likely to be fat mass, rather than muscle. At rest VO_{2rest} was higher in the obese group, but overall the $VO_{2reserve}$ did not differ between groups. This shows that the metabolic demands of chronic weight carriage are higher at rest and exercise.

We can therefore say that scaling VO_2 by body mass in obese subjects will lead to misinterpretation. The best way to scale haemodynamic parameters is to scale by lean body mass (LBM), which requires calculation of LBM [Chantler *et al* 2005]. Body composition assessment would require either a dual-energy X-ray absorptiometry scanner or use of a three compartment model, using body density by air displacement plethysmography and total body water by $H_2{}^{18}O$ dilution [Das et al 2003]. Neither of these models were available to us and therefore we can not utilise oxygen consumption as an indirect measure of cardiac performance with any confidence.

The results did conclusively show that peak cardiac performance (CPO_{max}) and cardiac reserve ($CPO_{reserve}$) was significantly higher by 17% and 11% respectively

($P < 0.001$) in the obese group. This increase appears to be driven by the increased flow generating capacity, with a 39% higher SV_{max} ($P < 0.001$) and was not associated with a higher pressure generating capacity, with no difference in MAP_{max} between groups. These are in agreement with previous reports that also showed a hyperdynamic increase in SV and CO [Alexander 1964; Kaltman *et al* 1976], but disagree with the finding by Alexander that CO decreased to a low-normal level at high work loads [Alexander *et al* 1998b]. Moreover, these changes are the reverse of the changes associated with acute inert weight carriage, which saw an increase in pressure, but not flow generating capacity of the heart. This difference is likely to be secondary to the adaptive physiological responses that have taken place with chronic weight carriage. We know that blood volume increases, as well as cardiac chamber size and myocardial wall thickness. This inevitably leads to a larger left ventricular diastolic volume, increased contractility and hence larger stroke volume. At rest, we saw the same pattern with a significantly higher CPO_{rest} by 45% ($P < 0.001$) and SV_{rest} by 19% ($P < 0.001$), although HR_{rest} was also significantly elevated by 33% ($P < 0.001$) in the obese group. Again there was no significant difference in pressure generating capacity.

With advancing age, there appeared to be a gradual downward decline in cardiac performance in the obese group. However, this did not ever fall below levels seen in lean healthy group ($R^2 = 0.06$). With increased severity of obesity (BMI) cardiac function appeared to show a gradual increase in cardiac function ($R^2 = 0.27$) down to level. These observations supports the concept that cardiac function adapts to obesity through an increase in central blood volume, stroke volume and cardiac output. However, with time (i.e. as individuals get older) the chronic volume loaded state leads to increased LV wall stress and hypertrophy and eventual diastolic or systolic dysfunction and LV failure. The group we studied excluded any individuals with known LV dysfunction or heart failure and therefore further study looking at longitudinal long term follow up of individuals without LV dysfunction is needed to establish if any or all have progressive loss of cardiac performance with prolonged obesity.

Once again the responses of CPO_{max} and VO_{2max} differ with weight carriage and reinforces the necessity to directly measure cardiac function when assessing individuals carrying any form of weight.

8.61 Study Limitations

The study was again limited by the inability to measure cardiac output and blood pressure continuously, using non-invasive methods, during exercise. The major limitation is the cross sectional design, which enables comparison of means, but does not allow us to infer causality to the changes seen in cardiovascular haemodynamics with absolute certainty. One would have to study patients who were lean and then became obese, or study those who lost weight. The difficulty with the former concept is that this would be a very difficult study to recruit to and complete, due to volunteers generally not wanting to become obese. The challenge with the latter concept would be to try and establish whether chronic weight carriage leads to reversible changes in cardiovascular pathophysiology that can be identified after weight loss and if not, determine what changes are irreversible.

The obese patients also had a mixture of co-morbidities and many were taking predominantly anti-hypertensive or diabetic medication, although did not have known cardiac dysfunction. Therefore, without controlling for these factors, which was not possible due to the small numbers tested, we can not again infer causality purely to weight carriage alone. There was also a significant difference in the measures of effort at maximal exercise between groups. The obese group on average had lower respiratory exchange ratios and peak heart rates than the healthy lean group. Although the motivation in the obese group was generally good, the majority did not perform regular exercise like the healthy group, and so their ability to cope with exercise was less well tolerated. This factor is not easy to control for, but despite that we still saw significantly improved cardiac performance in the obese group.

8.7 Conclusions

Chronic weight loading in morbidly obeses females resulted in significantly lower relative, but not absolute peak oxygen consumption, than healthy lean controls during maximal treadmill exercise. Peak cardiac performance and cardiac reserve was significantly higher in obese patients, with an increase in the flow, but not pressure generating capacity of the heart.

Importantly, this study highlights the problem of scaling oxygen consumption by body mass in obese patients, due to the under estimation of physical performance. Again direct measurement of CPO_{max} is preferable to determine changes in cardiac performance in obesity, rather than with surrogate measures.

Chapter 9

General Discussion

Chapter 9

General Discussion

The plan of this thesis was to determine what effects pregnancy and separately the weight loading in pregnancy have on cardiovascular physiology. In order to answer this question, subjects were studied longitudinally (acting as their own controls) in the pre-conception, pregnant and post-partum states. Based on prior considerations, it was important from the outset to determine serial changes in both physical and cardiac performance, as well as changes at rest, to establish reserve capacity. This approach has the theoretical, but potentially major, advantage of identifying a subject's ability to respond to additional stresses in pregnancy, which most notably will include labour. It was also recognised at the outset that the major body of literature, studying cardiovascular physiological changes in pregnancy, has used post-partum as a surrogate for the prior non-pregnant state (pre-conception) [Gammeltoft 1926; Burwell *et al* 1938; Palmer and Walker 1949; Adams 1954; Roy *et al* 1966; Walters *et al* 1966; Ueland *et al* 1969; Katz *et al* 1978; Caton *et al* 1987; Atkins *et al* 1981; Davies *et al* 1986; Clark *et al* 1989; Sady 1989; Pivarnik 1990; Easterling *et al* 1990; Lotgering 1991; McMurray *et al* 1991; Spinnewijn *et al* 1996]. Clearly such an approach, while practical, may be fundamentally flawed.
In addition to directly studying the effects of pregnancy in healthy women, attempts were made to deconstruct the possible confounding effects of weight gain during pregnancy. Creation of a model for simulated pregnancy with use of the "*Empathy Belly*" and also of a physiological model of weight carriage – were an attempt to establish the normal response to weight loading. This was to allow comparison with the overall effects of pregnancy, which also include neuro-hormonal changes.

The approach used to assess cardiac performance and reserve has been extensively studied and validated. However, there was an opportunity to further evaluate this method, in the context of new researchers, updated equipment and the availability of new alternative technology. The purpose of this was to establish that the CO_2 rebreathing was the most valid and appropriate technique to be used in pregnant subjects. Traditionally invasive techniques were used to measure cardiovascular haemodynamics [Swan *et al* 1970] however, it is not justifiable to use this approach in healthy individuals. Consequently, non-invasive techniques have been routinely adopted. Contradictory studies examining CO in pregnancy

have been reported in the literature and relate in part to the methods used to measure cardiac output [Atkins *et al* 1981; Robson *et al* 1989]. The most commonly reported method utilised Doppler echocardiography. Unfortunately this is generally best performed at rest thereby restricting its use as a means of assessing effects during exercise. Other non-invasive methods have been used, most notably the re-breathing techniques [Knuttgen and Emerson 1974; Pivarnik *et al* 1993; Khodiguian *et al* 1996].

In study I, two rebreathing methods (IGR and CO_2 rebreathing) were directly compared with Doppler echocardiography at rest. There was observed to be no overall agreement across all three methods, indicating that they cannot be considered to be interchangeable. There was agreement between each rebreathing method and the Doppler measurements based on Bland Altman analysis. However, this also demonstrated a slight difference in absolute values for cardiac output. This may be seen as a calibration effect. Each method was internally consistent and reproducible and so can used to compare serial changes.

In study II, there were significant differences in measures of CO between rebreathing methods (IGR and CO2 rebreathing) at submaximal exercise. These results were highly consistent between subjects and therefore are likely to be real. This is in disagreement with the only other direct comparison of these two methods performed at exercise by Jakovlejevic *et al*, who found no difference in CO between methods at rest or peak exercise [Jakovlejevic *et al* 2008]. We failed to achieve adequate reliability from the IGR method at peak exercise, despite support from the manufacturer, and so the two studies can not be directly compared. One therefore must also be very cautious comparing similar measures between research groups, as it is likely that research methods will vary and machines may be calibrated to different normals.

In study III, when CO was measured by the CO_2 rebreathing method, there was good reproducibility and therefore we had confidence that this was the vaild method to be used for the remainder of the thesis to establish both peak cardiac performance and cardiac reserve.

Study IV is the first to measure the effects of weight loading, in the form of an "*Empathy Belly",* on physical and cardiac performance. This simulation was chosen to mimic the weight carriage experienced in the latter stages of pregnancy. It was found that weight loading directly enhances cardiac performance during maximal treadmill exercise, despite a reduction in exercise duration and fall in VO_{2max}. The improvement in cardiac performance was through an increase in the pressure

generating capacity of the heart without a change in cardiac output. This observation is typical of the response seen during pure isometric exercise e.g. hand grip exercise [Laird *et al* 1979]. Maximum cardiac output and stroke volume remained constant, most probably as a result of similar overall workload, despite different exercise duration. There was a clearly divergent response in the direct marker of cardiac function, CPO_{max}, as compared to an indirect marker, VO_{2max}. This brings into question the reliability of use of VO_{2max} in interpretation of cardiac function, when inert weight is being carried. Importantly, this highlights a discrepancy that has not previously been fully appreciated.

Study V is the first to examine the incremental physical and cardiac effects of inert weight loading in healthy females of child-bearing age. Additional loading resulted in a further reduction in exercise duration and VO_{2max}. Furthermore, incremental inert load carriage led to an increase in CPO_{rest} however, did not result in a significant stepwise increase in cardiac performance or blood pressure during maximal treadmill testing. Previously reported studies have examined the effects of incremental weight carriage at submaximal exercise and found significant increases in HR, blood pressure and CO, but no change in SV. [Bhambhani *et al* 1997; Bhambhani & 2000; Sagiv *et al* 1994; Sagiv *et al* 2002]. In the present study heart rate did not change between loading conditions, because both were maximal tests. Therefore, we are likely to have measured an estimation of the peak cardiac performance. The lack of significant increase in cardiac performance suggests there is a limit to cardiac pumping capability, which is not fully achieved with unloaded exercise testing. Again the divergent observations seen with VO_{2max} and CPO_{max} were seen. This emphasizes the value of measuring cardiac function directly.

Study VI examined the physical and cardiac effects of pregnancy, in each trimester and compared them longitudinally to the post-partum state, which was used as a surrogate for pre-conception. This is also the first study to assess differences in longitudinal effects on CPO_{max} and VO_{2max} between pre-conception and post-partum. In the first trimester, DBP_{rest} and VO_{2rest}, HR_{max}, $HR_{reserve}$ and exercise duration were significantly reduced compared to post-partum. In the second trimester, DBP_{rest}, MAP_{rest}, SVR_{rest}, HR_{max}, $HR_{reserve,}$ exercise duration, VO_{2max}, $VO_{2reserve}$ and $CircP_{max}$ were all significantly reduced. Finally in the third trimester, HR_{max}, $HR_{reserve,}$ exercise duration, VO_{2max}, $VO_{2reserve}$ and $CO_{reserve}$ were all significantly reduced. No significant change in CPO_{max} or $CPO_{reserve}$ was seen throughout pregnancy.

Based on these findings and using post-partum as a surrogate for pre-conception, we have shown that markers of physical function, including HR_{max}, $HR_{reserve,}$ exercise duration, VO_{2max}, $VO_{2reserve}$ all reduce in pregnancy. Although no comparison was made between trimesters, due to the different numbers studied, the physical function appeared to progressively worsen as gestation advanced. Despite the physiological lowering of blood pressure and systemic vascular resistance in the early stages of pregnancy due to hormonal effects, cardiac performance and cardiac reserve remained unchanged. This suggests a protective and adaptive mechanism has occured, whereby the increase in blood volume that occurs early in pregnancy, improves CO_{rest} and maintains CO_{max}. As pregnancy advances and more weight is carried, blood pressure returns to normal, and CO is maintained, maintaining overall cardiac reserve. It is likely that the blood pressure recovery in the latter stages of pregnancy is in part due to the chronic isometric exercise of carrying the foetus.

Importantly, study VI also showed that 3 months post-partum was a poor surrogate of pre-conception and highlighted that the cardiovascular physiological changes that have occurred in pregnancy have not returned to baseline at 3 months. Other studies have also concluded that physiological changes are not completely reversed by 3 months post-partum [Capeless 1991; Sady 1990; Robson *et al* 1987], whilst some suggest resting changes do return to baseline by 14-17 weeks post-partum [Mahendru et al 2014]. One therefore has to interpret changes compared to post-partum with caution and where possible compare changes to pre-conception to understand the true physiological responses.

Study VII examined the longitudinal physical and cardiac effects of pregnancy from pre-conception, throughout pregnancy, to 3 months post-partum. This is the first study to examine the longitudinal changes in CPO_{max} and VO_{2max} before, during and after pregnancy. Initial changes were analysed between pre-conception and the first trimester. These data agree with findings from other studies that show that resting HR and CO increase, whilst blood pressure and SVR decrease in the first trimester [Robson *et al* 1989; Desai et al 2004; Mahendru *et al* 2014]. Changes in CPO_{rest} have not been previously reported, and so we are the first to show that this does not significantly change. At maximal exercise, there was a significant decrease in CO_{max} and CPO_{max} coinciding with a decrease in VO_{2max}, despite preserved exercise duration. Moreover $HR_{reserve}$, $VO_{2reserve}$, $CO_{reserve}$ and $CPO_{reserve}$ all decreased and so, this suggests a real reduction in cardiac performance that has not been previously identified.

Changes in cardiac output in early pregnancy at rest have been attributed to increasing blood flow, neurohormonal activation and an increase in left ventricular wall muscle mass and contractility [Robson *et al* 1989; Mabie *et al* 1994; Desai *et al* 2004]. However, despite these physiological changes, it appears that the heart does not have the ability to sustain the same peak performance in early pregnancy. As a result of the enhanced resting cardiac function, cardiac reserve inevitably reduces.

Changes between trimesters were then analysed. Our data at rest are again consistent with previous reports showing a gradual increase in HR_{rest}, blood pressure and CO_{rest} [Robson *et al* 1989; Mabie *et al* 1994; Desai *et al* 2004]. Although we did not report a significant change between repeated measures of CO_{rest}, we did actually see a peak rise in CO_{rest} in the second trimester and maintenance of this in the third trimester. The reason for not showing significance was because we used an analysis of repeated measures throughout pregnancy to compare a difference across measures, rather than comparing change at each time point. We also identified that CPO_{rest} continues to rise progressively from the first trimester to the third trimester, although again this was not statistically different overall across all three trimesters. However, VO_{2rest} did show a statistically significant increase across trimesters. These changes in resting direct and indirect markers of cardiac function suggest that the cardiovascular system adapts to meet the demands of the growing foetus and increasing weight carriage.

In contrast to the only published longitudinal study examining VO_{2max} at peak exercise throughout pregnancy, the present study showed a significant decrease in VO_{2max}, associated with a significant reduction in exercise duration (using the same treadmill protocol). Lotgering *et al* [Lotgering *et al* 1991] performed a longitudinal study, using treadmill exercise, whilst at the same gestation also comparing differences with cycle exercise in all three trimesters and post-partum. They found no significant difference in VO_{2max} between trimesters and post-partum and no difference between exercise methods. In our experience women became more symptomatic of pregnancy as pregnancy progressed and therefore became less able to perform the same workload. In addition to reduced HR_{max} and VO_{2max}, we also showed that $HR_{reserve}$ and $VO_{2reserve}$ both significantly fell throughout pregnancy.

This is the first study to report the longitudinal change throughout pregnancy in both CO_{max} and CPO_{max} with maximal treadmill testing. Despite the significant reduction in exercise duration and VO_{2max}, we showed no significant difference in both direct makers of cardiac performance, namely CPO_{max}, and surrogate markers - $CircP_{max}$,

CO_{max}, SV_{max} and SW_{max}. The mean CPO_{max} values in each trimester appear to show an increase from the first trimester to the third, however this fails to reach statistical significance. The cardiac reserve measured both directly ($CPO_{reserve}$) and indirectly ($CO_{reserve}$, $SV_{reserve}$ and $SW_{reserve}$) also showed no deterioration throughout pregnancy. Importantly, this shows preservation of cardiac reserve throughout pregnancy, after the inital fall from pre-conception. Although we were not able to accurately calculate absolute work load performed, which has to incorporate both the stage of treadmill exercise protocol, but also the weight of the indvidual, it is probable that the cardiac performance had increased for the level of work performed. The overall maintenance in cardiac performance appears to be driven by an increase in pressure generating capacity and is likely in part to be due to the increase in weight carriage, as is seen in inert weight carriage.

Then changes between the third trimester and 3 months post-partum were analysed. There were significant increases in exercise duration, $VO_{2max/kg}$ and HR_{max} in post-partum. However, there were no significant changes in VO_{2max} or CO_{max}. The only other study examining CO, by Sady using an acetylene re-breathing technique during maximal cycle exercise, found that CO_{max} was higher in the third trimester than 8 weeks post-partum. The main difference in studies was the type of exercise, but also that the present study had lower HR_{max} in the third trimester, whereas Sady showed no difference between HR_{max}. This suggests that in our study, exercise was not tolerated as well in the the third trimester and potentially is related to the exercise being weight bearing.

This is also the first study to report that there was no change in CPO_{max} or $CPO_{reserve}$ despite a significant reduction in exercise ability in the third trimester compared to 3 months post-partum. Both the flow and pressure generating capacities of the heart were unchanged, which is likely to be because the haemodynamic changes have not completely reversed.

When changes between the third trimester and post-partum were compared to changes between the third trimester and pre-conception, we highlighted additional differences. Besides changes seen in post-partum, we showed significantly higher VO_{2max}, $CircP_{max}$, CO_{max}, and CPO_{max} and lower SVR_{max} pre-conception. At rest we additionally identified lower CO_{rest} and higher DBP_{rest}, SVR_{rest}, but no change in SBP_{rest}. As a conclusion, $HR_{reserve}$ $VO_{2reserve}$, $CO_{reserve}$ and $CPO_{reserve}$ were all significantly higher pre-conception, than in the third trimester. Importantly this study highlights the flaw of using post-partum as a surrogate for pre-conception. The present study provided invaluable evidence that there is an initial fall in both cardiac

performance and cardiac reserve in pregnancy. After this there is maintenance of cardiac performance and reserve throughout pregnancy, despite a fall in exercise ability and aerobic capacity.

Study VIII is the first to determine the differences in peak cardiac performance between obese females (BMI > 35 $kg.m^{-2}$), without known cardiac dysfunction and lean healthy females (BMI < 26 $kg.m^{-2}$), using maximal treadmill exercise. We showed that chronic carriage of excess weight, that occurs in obese females, results in a reduction in aerobic capacity and physical performance, as evidence by lower $VO_{2max/kg}$ and HR_{max} compared to lean individuals. However, absolute VO_{2max} values does not differ between groups across all ages. Whereas, $VO_{2max/kg}$ in the obese group is particularly lower at a younger age. Moreover, as BMI increases there appears to be an associated decrease in $VO_{2max/kg}$, whereas absolute VO_{2max} either stays the same or increases in both groups. The metabolic demands during maximal exercise in the obese group only appear to increase slightly with increasing BMI. This is probably because the difference in body composition between obese patients is likely to be fat mass, rather than muscle. At rest VO_{2rest} was higher in the obese group, but overall the $VO_{2reserve}$ did not differ between groups. This shows that the metabolic demands of chronic weight carriage are higher at rest and exercise. We can therefore say that scaling VO_2 by body mass in obese subjects will lead to misinterpretation of overall physical performance and aeobic capacity.

Study VIII conclusively showed that peak cardiac performance (CPO_{max}) and cardiac reserve ($CPO_{reserve}$) was significantly higher with chronic weight carriage. This increase appears to be driven by the increased flow generating capacity and was not associated with a higher pressure generating capacity. These findings are in agreement with previous reports that described a hyperdynamic increase in SV and CO [Alexander 1964; Kaltman *et al* 1976], but disagree with the finding by Alexander, that CO decreased to a low-normal level at high work loads [Alexander *et al* 1998b]. Moreover, these changes are the reverse of the changes associated with acute inert weight carriage, which saw an increase in pressure, but not flow generating capacity of the heart. This difference is likely to be secondary to the adaptive physiological responses that have taken place with chronic weight carriage. We know that blood volume increases, as well as cardiac chamber size and myocardial wall thickness [Alpert *et al* 2014]. This inevitably leads to a larger left ventricular diastolic volume, increased contractility and hence larger stroke volume.

At rest, we saw the same pattern with a significantly higher CPO_{rest} and SV_{rest}, although HR_{rest} was also significantly elevated. Once again, the responses of CPO_{max} and VO_{2max} differ with weight carriage and reinforces the necessity to directly measure cardiac function when assessing individuals carrying any form of weight.

When we examine the effects of weight on physical and cardiac performance using the different models of weight carriage: inert ("*Empathy Belly"*); additional inert weight carriage ("*Empathy Belly" and rucksack*); Pregnancy, compared to post-partum; Pregnancy compared to pre-conception; and Obesity compared to lean controls, we can identify both similarities and distinct difference (shown in Table 9.1). Weight uniformally appears to be associated with a reduction in physical performance, as evidence by the worsening of symptoms (NYHA), the reduction in exercise capacity and aerobic capacity. Though the effect of weight on cardiac function appears to differ, depending on the model of loading. Acute inert weight loading results in an increase in the pressure generating capacity, but no change in flow generating capacity. Additional inert weight carriage does not result in a further rise, suggesting that peak cardiac function had already been demonstrated and achieved.

The effect of pregnancy on cardiac performance differs depending on the timing of the non-pregnant baseline function (i.e. post-partum or pre-conception). When cardiac performance in pregnancy is compared to post-partum, there is no change, whereas when it is compared to pre-conception, cardiac performance is lower in pregnancy. The fact that weight does not significantly differ between pre-conception and post-partum, shows pregnancy itself has a direct and independent effect on peak cardiac function, that persists up to 3 months post-partum. The overall detrimental effect appears to be a reduction in the peak flow generating capacity of the heart. However, as described earlier the pressure generating capacity does increase with gestation and therefore in part is likely to be secondary to weight gain.

Chronic weight carriage, in the form of obesity, results in an increase in cardiac performance by increasing the flow generating capacity of the heart with no change in pressure generation. This is rather suprising, as many obese patients develop hypertension and one might have expected a similar response to that seen in acute weight carriage with a more sustained isometric response.

Table 9.1 Effects of different forms of weight carriage on peak physical and cardiac performance.

	NYHA	ExDur	VO_{2max}	$VO_{2max/kg}$	CPO_{max}	CO_{max}	MAP_{max}
Inert weight (Belly)	N/A	↓	↓	↓	↑	↔	↑
Additional Inert weight (Sack)	N/A	↓	↓	↓	↔	↔	↔
Pregnancy (T3 v PP)	↑	↓	↓	↓	↔	↓	↔
Pregnancy (T3 v PC)	↑	↓	↓	↓	↓	↓	↔
Obesity	↑	(↓)	↔	↓	↑	↑	↔

NYHA: New York Heart Association symptomatic class; ExDur: exercise duration; VO_2: oxygen consumption; CPO: cardiac power output; CO: cardiac output; MAP: mean arterial pressure; Belly: *Empathy Bell;* Sack: rucksack and *Empathy Belly*; T3: third trimester; PP: post-partum; PC: pre-conception; ↑: increase; ↓: decrease; ↔: no change; (↓): likely decrease, although not compared.

9.1 Future directions of study

This study has provided new evidence of how pregnancy affects cardiac function at rest and maximal exercise in healthy women. One therefore could apply this knowledge to study women in pregnancy with cardiovascular disease to gain a better understanding of how different cardiac diseases, and how the severity of cardiac disease, responds during pregnancy. This, in time, could lead to studies to establish risk modeling to know when to intervene in pregnancy and achieve better maternal and fetal outcomes.

In addition, this study has shown how cardiac function responds to acute and chronic weight carriage. Further study could examine how cardiac function responds to significant weight loss in obese individuals, as seen in bariatric surgery and also how cardiac performance changes over time with sustained excess weight carriage. This can futher be applied to obese individuals with cardiovascular disease to determine if absolute CPO_{max} is a strong prognostic marker in morbidly obese patients with heart failure and thereby, in part, explain the obesity paradox.

9.2 Conclusions

Inert weight loading, weight carriage in pregnancy and non-physiological weight gain in obesity in the non-pregnant state, reduce physical performance. Both inert weight carriage and weight carriage in association with obesity increase cardiac performance. Acute weight loading induces an increase in pressure generating capacity, whilst chronic weight carriage leads to an increase in flow generating capacity.

For the first time, I have shown that peak cardiac performance reduces in pregnancy, although this then gradually improves throughout pregnancy and is likely to be, in part, caused by an increase in weight gain. This important finding shows that testing cardiac reserve pre-conception is not necessarily an accurate reflection of how a patient with cardiac disease may respond in pregnancy. Therefore, perhaps peak cardiac performance, rather than indirect measures of cardiac function, should be established in pregnancy to aid management decisions in patients with established cardiac disease.

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Appendix A

Leeds (West) Research Ethics Committee

A/B Floor, Old Site

Leeds General Infirmary

Great George Street

Leeds

LS1 3EX

Tel: 0113 392 6788

18th December 2006

Professor Lip-Bun Tan

Room 35/OB/009

Old Nurses Home

Leeds General Infirmary

Dear Professor Tan,

Study title:	**A study investigating the effects of pregnancy on the Functional REServe of the Heart in women with and without heart disease- the FRESH Pregnancy Study.**
REC reference:	**03/121**
Protocol number:	**Tan / Barker March 2004**

Amendment number:	Tan / Lewis Amendment
Amendment date:	**7th November 2006**

The above amendment was reviewed at the meeting of the Leeds (West) Sub-Committee of the Research Ethics Committee held on 14th December 2006.

Ethical opinion

General recruitment email to be sent out across the Leeds Teaching Hospitals NHS Trust; Regional press advertisement (TV, radio and newspaper; advertisement in GP surgeries and local health clubs.

Echocardiography assessments to be performed at each visit.

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

- *Notification of Substantial Amendment, dated 7th December 2006.*
- *Email to be sent across hospital.*
- *Poster, undated.*
- *Consent Form, Version 3, dated 6th December 2006.*
- *Leaflet, undated.*
- *Project Proposal, version 4, dated December 2006.*

Membership of the Committee

The members of the Ethics Committee who were present at the meeting were Dr John Puntis, Chair and Mrs Rhona Bratt, Committee Member.

Research governance approval

All investigators and research collaborators in the NHS should notify the R&D Department for the relevant NHS care organisation of this amendment and check whether it affects research governance approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

03/121: Please quote this number on all correspondence

Yours sincerely

Laura Sawiuk

Committee Co-ordinator

E-mail: laura.sawiuk@leedsth.nhs.uk

Appendix B

THE BORG SCALE - Leg Fatigue

0	Nothing at all
0.5	Very, very little tired
1	Very little tired
2	A little tired
3	Moderately tired
4	Rather tired
5	Tired
6	
7	Very tired
8	
9	
10	Extremely tired

THE BORG SCALE - Shortness of Breath

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

Appendix C

The SF-36v2™ Health Survey

Your Health in General

In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

2. **Compared to one year ago, how would you rate your health in general now?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
○	○	○	○	○

3. **The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?**

	Yes, limited a lot	**Yes, limited a little**	**No, not limited at all**
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○	○	○
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
c) Lifting or carrying groceries	○	○	○
d) Climbing **several** flights of stairs	○	○	○
e) Climbing **one** flight of stairs	○	○	○
f) Bending, kneeling, or stooping	○	○	○
g) Walking **more than a kilometre**	○	○	○
h) Walking **several hundred metres**	○	○	○
i) Walking **one hundred metres**	○	○	○
j) Bathing or dressing yourself	○	○	○

4. **During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	○	○	○	○	○
b) **Accomplished less** than you would like	○	○	○	○	○
c) Were limited in the **kind** of work or other activities	○	○	○	○	○
d) Had **difficulty** performing the work or other activities (for example, it took extra effort)	○	○	○	○	○

5. **During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	○	○	○	○	○
b) **Accomplished less** than you would like	○	○	○	○	○
c) Did work or other activities **less carefully than usual**	○	○	○	○	○

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
○	○	○	○	○

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
○	○	○	○	○	○

8. **During the past <u>4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) did you feel full of life?	○	○	○	○	○
b) have you been very nervous?	○	○	○	○	○
c) have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○
d) have you felt calm and peaceful?	○	○	○	○	○
e) did you have a lot of energy?	○	○	○	○	○
f) have you felt downhearted and depressed?	○	○	○	○	○
g) did you feel worn out?	○	○	○	○	○
h) have you been happy?	○	○	○	○	○
i) did you feel tired?	○	○	○	○	○

10. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?**

All of the time	Most of the Time	Some of the time	A little of the time	None of the time
○	○	○	○	○

11. **How TRUE or FALSE is each of the following statements for you?**

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	○	○	○	○	○
b) I am as healthy as anybody I know	○	○	○	○	○
c) I expect my health to get worse	○	○	○	○	○
d) My health is excellent	○	○	○	○	○

***THANK YOU* FOR COMPLETING THIS QUESTIONNAIRE!**

Appendix D

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Letter to the Editor

Discordant changes in peak O_2 consumption and peak cardiac power during weight loaded treadmill exercise

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Clinicians recognise that heart failure (HF) patients suffer from exercise intolerance to varying degrees, and those with the worst organ failure such as cardiogenic shock have the greatest limitation. Exercise duration has been shown to correlate well with cardiac pump dysfunction [1]. Nowadays, exercise intolerance is usually quantified as aerobic exercise capacity measured as peak O_2 consumption (VO_{2max}) during cardiopulmonary exercise testing (CPX), previously introduced into cardiology by Weber and colleagues as a tool to evaluate patients with HF [2]. The authors described it as "an objective, reproducible and safe non-invasive method for characterizing cardiac reserve and functional status in patients with chronic cardiac failure". This association and in terms of clinical use, perceived equivalence with cardiac reserve led to the finding that VO_{2max}/kg is a strong predictor of HF prognosis [3] and this has subsequently been adopted as a key selection criterion for cardiac transplantation [4–6]. Subsequently, direct methods of measuring cardiac reserve and pumping capability became available [7,8], and whenever entered into multivariate analyses together with VO_{2max}, peak cardiac power (CPO_{max}) emerged consistently as the stronger predictor of HF prognosis [9,10]. These findings are unsurprising since CPO_{max} is a direct representation of cardiac organ pump function in maintaining the circulation [11]. In cross-sectional studies in healthy subjects [12] and HF patients [13], *instantaneous* comparisons of VO_{2max} and CPO_{max} have also been found to be significantly correlated as shown in Fig. 1a.

Following from the above developments, the next relevant question is: can VO_{2max} be generally assumed to be a reliable, unequivocal, indirect indicator of cardiac dysfunction? One necessary criterion to establish that VO_{2max} is a generally good surrogate for cardiac functional reserve is that any *longitudinal* change in VO_{2max} must be accompanied by a concordant change in CPO_{max} irrespective of how the change was brought about. In other words, a decrease in VO_{2max} will always occur together with a decrease (not an increase) in CPO_{max}. In order to test the hypothesis that the two variables, VO_{2max} and CPO_{max}, fulfil this criterion of concordant changes, we recruited healthy volunteers to perform maximal treadmill exercises with and without carriage of an inert mass which simulates body mass increments that are seen during development of obesity or pregnancy.

Twenty-five healthy female volunteers within the child-bearing age (mean age 22.74 ± 3.43 (SD) year; range 18.3 to 31.9 years), free from any cardiorespiratory diseases or other significant medical disorders, body mass of 63.1 ± 6.1 kg and BMI of 22.22 ± 1.75 $kg \cdot m^{-2}$, were recruited and performed symptom-limited treadmill CPX in the absence (C, control test) and presence of a weighted device (Empathy Belly, Birthways, Inc., Vashon Island, USA) plus a standard rucksack (L, loaded test). The study was approved by the Leeds (West) Ethics Committee. The mean weight of the load carried was 22.1 ± 2.33 kg, equivalent to 35.0 ± 1.7% of the body mass of the participants (Fig. 1b). Non-invasive haemodynamic measurements, CO_2-rebreathing and standard respiratory gas analyses as described previously [8,14] enabled recording of resting and exertional haemodynamic parameters and measurements of peak oxygen consumption (VO_{2max}) and peak cardiac power output (CPO_{max}). All subjects exercised beyond a respiratory exchange ratio (RER) of 1.05 and reached their cardiopulmonary limits.

Weight-loading resulted in reduced exercise duration (C: 14.5 ± 2.6, L: 11.9 ± 2.0 min, $P < 0.001$) and VO_{2max} (C: 2.90 ± 0.39, L: 2.65 ± 0.42 $L \cdot min^{-1}$, $P < 0.001$). The reduction was even more marked when peak O_2 uptake was corrected for body mass (VO_{2max}/kg) (C: 46.4 ± 7.9, L: 32.2 ± 6.7 $mL \cdot min^{-1} \cdot kg^{-1}$, $P < 0.001$). The percentage reductions from baseline values for these indicators of exercise capacity were 17.4 ± 7.9% for exercise duration, 8.6 ± 7.9% for VO_{2max} and 30.5 ± 8.3% for VO_{2max}/kg, as shown in Fig. 1b. However, these significant reductions in exercise duration, VO_{2max} and VO_{2max}/kg, contrasted

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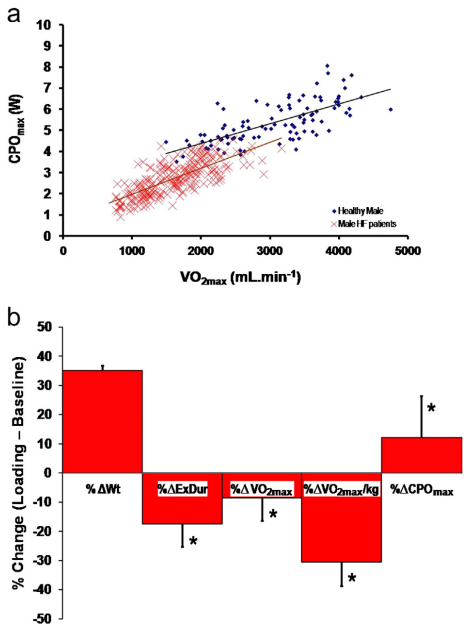

Fig. 1. a. Cross-sectional studies indicating good correlation between VO_{2max} and CPO_{max} in a cohort of healthy male volunteers [12] and of heart failure patients [13]. **b**. Percentage changes (Δ = Loading − Baseline) during CPX with inert mass loading vs. baseline CPX without loading, in total mass (ΔWt), exercise duration (ExDur), peak O_2 consumption (VO_{2max}), peak VO_{2max} normalised for the combined weight (VO_{2max}/kg), and in peak cardiac power output (CPO_{max}). *P < 0.001.

with a significant increase in the directly measured peak cardiac power, CPO_{max} (C: 4.38 ± 0.70, L: 4.87 ± 0.75 W, P < 0.001). Compared to baseline, the percentage increase in CPO_{max} was 12.2 ± 14.1% (95% CI: 6.6–17.7%). The systemic vascular resistance was not as low at peak weight-loaded CPX compared to baseline (C: 316 ± 42, L: 341 ± 50 dyn·s·cm^{-5}, P = 0.011).

Using the model of inert weight carriage to simulate body mass increments with the development of obesity during maximal treadmill CPX, the experimental data showed that both VO_{2max} and CPO_{max} were changed simultaneously but not in accordance with our stated hypothesis, as the changes in these variables were in opposite directions. It is evident that the significant correlation between these two variables observed in cross-sectional studies, as shown in Fig. 1, is not borne out on more stringent testing with a longitudinal study where the two variables fail to produce concordant changes. The conventional concept that VO_{2max} is a good surrogate indicator of cardiac functional reserve cannot be generalised to all possible scenarios encountered in clinical practice. Caution should be exercised particularly in conditions of significant weight alterations such as in the contexts of cachexia, obesity and pregnancy.

In conclusion, we can infer that a lowering of VO_{2max} should not be assumed to indicate a definite worsening of cardiac dysfunction. Without comprehending the biomedical circumstances, changes in VO_{2max} should not be crudely assumed to be a universally reliable indirect indicator of parallel changes in cardiac functional capacity. The corollary is also true, that CPO_{max} (had it been the more easily measured variable) is not necessarily a good surrogate indicator of VO_{2max}. A helpful clinical implication is that, to gauge how good the cardiac pump is, the most reliable and generally applicable method is to measure *directly* how well the heart can generate and impart hydraulic energy to meet the most demanding physiological stresses that can be imposed on the circulation.

Conflict of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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