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International Journal of Cardiology 119 (2007) 147–155

International Journal of Cardiology

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Efficacy of lifestyle intervention on peak exercise cardiac power output and reserve in premenopausal obese females: A randomised pilot study

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Received 28 March 2006; accepted 15 July 2006
Available online 26 January 2007

Abstract

Background: Clinically obese women have a two-fold increased risk for the development of heart failure. Among younger premenopausal females, obesity has been associated with cardiac remodelling and impaired resting systolic and diastolic function. However, few studies have evaluated cardiorespiratory and cardiac responses to maximal exertion among obese premenopausal females.
Design: A randomised pilot study was conducted to investigate the effects of a 3-month lifestyle intervention programme on weight management and maximal cardiorespiratory function in healthy clinically obese premenopausal females. Within this study, thirteen selected participants performed both graded and single-stage $\dot{V}O_{2peak}$ exercise tests, the latter integrating the non-invasive measurement of cardiac output (CO_2 rebreathing method), peak cardiac power output (CPO_{peak}) and physiological cardiac reserve. Six participants were randomly assigned to 3-months of lifestyle intervention and 7 served as waiting list controls.
Results: Trends were evident for improvement in the traditional weight-adjusted $\dot{V}O_{2peak}$ (ml kg^{-1} min^{-1}) measure among the lifestyle group compared with a modest reduction in the controls (test for interaction, $P=0.059$). CPO_{peak} showed a modest, non-significant increase in the lifestyle group and tended to decrease in the control (test for interaction, $P=0.166$). Physiological cardiac reserve also improved (2.63±0.54 to 2.92±0.43 W) in the lifestyle group and declined (2.69±0.24 to 2.56±0.28 W) in the control group (test for interaction, $P=0.091$). $\dot{V}O_{2peak}$ (ml min^{-1}) increased non-significantly on graded maximal exercise in the lifestyle group compared with control. The larger within group changes in the lifestyle group failed to achieve statistical significance (test for interaction, $P=0.131$).
Conclusions: In the absence of significant weight reduction, clinically obese premenopausal females derived modest benefits in maximal cardiorespiratory capacity and cardiac functional reserve from a 3-month lifestyle intervention incorporating supervised exercise.

Keywords: Exercise training; Dietary intervention; Cardiopulmonary exercise testing; CO_2 rebreathing technique; Randomised controlled trial

1. Introduction

Cardiovascular events represent the most important cause of morbidity and mortality associated with obesity. Vasan [1] has highlighted that recent reports have led to a paradigm shift in our understanding of the cardiomyopathy of obesity [2]. Seminal work in this area focused on resting cardiac dysfunction in the setting of morbid obesity [3–9]. Recently, younger premenopausal [13] overweight and obese females have been shown to exhibit a continuum of cardiovascular changes ranging from a hyperdynamic circulation [1,10] through to preclinical cardiac remodelling [11,12]. In some studies, early LV structural and load-independent functional abnormalities have been described [11–13] and associated with reduced exercise capacity [13]. Several reports [14–16], including obese females, have described an impaired cardiac function in response to graded exercise testing.

Maximum oxygen consumption ($\dot{V}O_2max$), the traditional measure of maximal cardiorespiratory function, is predictive of all-cause and cardiovascular disease mortality among women, independent of the level of body mass index

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doi:10.1016/j.ijcard.2006.07.099

[21]. The non-invasive indices of cardiac power and reserve as proposed by Tan and colleagues [17–19] have not previously been evaluated among obese subjects. Physiological cardiac reserve has been shown to be a reproducible and objective indicator of overall mechanical cardiac function [19]. Peak exercise cardiac power output (CPO_{peak}) has also been shown to be a major factor influencing peak oxygen consumption and exercise capacity among heterogeneous subjects [19]. Furthermore, it has been shown to be the most powerful predictor of prognosis among heart failure patients [20].

Randomised studies have shown that dietary advice combined with either structured aerobic exercise or lifestyle activity produces both short and long-term improvements in $\dot{V}O_2$max among overweight and obese females [22–26]. Studies examining the effects of lifestyle change have tended only to evaluate changes in resting cardiac function among sedentary obese participants [27,28]. Clinically obese women have been shown to have two-fold increased risk for the development of heart failure in contemporary studies [9]. Evaluation of CPO_{peak} and cardiac reserve may provide a useful index for directly quantifying the overall functional cardiac status and gain [29] attainable with lifestyle intervention in clinically obese participants.

2. Methods

2.1. Study population

Healthy premenopausal obese females older than 18 years of age were recruited to a multi-disciplinary weight management programme by local media advertisements and the e-mail servers of local government and the Metropolitan University in Leeds, UK. Advertisements specifically solicited obese females within the area willing to participate within a long-term programme. WHEEL (Weight, Healthy Eating and Exercise in Leeds) was a delayed-start, community-based RCT, comprising of supervised exercise and lifestyle physical activity, brief group cognitive behavioural therapy and educational classes on healthy eating and weight management. All study participants had to be healthy, clinically obese (BMI > 30.0 kg m^{-2}) and not previously diagnosed with cardiovascular disorders; a history of kidney, or liver disease and Type I or 2 diabetes mellitus. In addition, all participants were classified as sedentary, which was defined as reporting less than 30 min per day of moderate exercise on two days per week over the previous six months. Participants also had to be free of significant musculo-skeletal problems likely to interfere with increased physical exercise. The Leeds Teaching Hospital's Research Ethics Committee approved the study.

From 198 initial applicants, a total of 62 participants met the study inclusion criteria and were willing to undertake the study. The study protocol involved three months of intensive lifestyle intervention followed by nine months maintenance for all eligible participants. At the end of the orientation session, participants were randomly assigned (sequential opening of numbered envelopes) to 12 weeks of lifestyle intervention or waiting list control (delayed-start). Randomisation was restricted to achieve a balance of participants in the lifestyle intervention and control groups. Before treatment, participants completed an exploratory interview and participants weight and dieting histories, eating and exercise habits and psychological status were assessed. The waiting list control group was requested to maintain their current lifestyle habits and scheduled to begin intervention at the end of the 12-week period.

The weight management intervention was specifically designed in accordance with the principles of the Self-Determination psychological model of behaviour change [30]. The intervention strategy emphasised relatively individual approaches to physical activity and eating behaviour, in which health professionals provided a treatment rationale, but offered choice, minimised pressure and acknowledged participants' perspectives within the weight management process. The intensive phase consisted of 12 weeks of lifestyle intervention in which the participants were encouraged to undertake up to 4 h or more of physical activity of their choice per week. Participants negotiated to increase their regular walking and advised to accumulate at least 30 min of moderate physical activity on most, preferably all days of the week, in a manner consistent with their lifestyle and daily schedules. They were supported to progress towards overall physical activity goals in a manner suited to their level of competence and intrinsic motivation. The participants were encouraged to participate in at least two supervised exercise sessions weekly, from two circuit-training, one tai-chi and one aqua-aerobic class offered. Instruction in correct exercise techniques, monitoring of heart rate and ratings of perceived exertion during exercise was given within all of the supervised group sessions. Initial exercise intensities and the progression of all activities were consistent with the recommendations of the American College of Sports Medicine position statements [31,32]. The principal investigator and trained exercise instructors assisted participants in setting realistic physical activity goals, monitored their physical activity and provided opportunities for social interaction. Participants selected the activities they most enjoyed and individualised their physical activity and exercise programmes within overall project guidelines. Thus the intervention incorporated elements of both lifestyle physical activity and structured supervised aerobic exercise shown to offer long-term benefits in obese women.

Healthy eating and weight management education sessions were conducted weekly throughout the intervention period. A state-registered dietician delivered the healthy eating guidelines. All participants were provided with the same general dietary guidelines that did not put specific emphasis on calorie restriction. Participants were advised to consume a self-selected low saturated fat, high fibre diet, consistent with dietetic guidelines. Selected members of the lifestyle group also underwent a brief programme of group

cognitive behavioural therapy in which participants learned cognitive and behavioural strategies and techniques considered to be related to the initiation and maintenance of healthy eating behaviours.

2.2. Testing protocol

Of the eligible participants, 61 underwent baseline maximal exercise tests at the Leeds General Infirmary conducted according to a previously described methodology and validation study [19]. A smaller group of thirteen participants were selected to perform an additional single-stage symptom-limited treadmill exercise tests to allow the non-invasive measurement of cardiac output (CO_2 rebreathing method). This allowed the estimation of peak cardiac power output (CPO_{peak}) and cardiac reserve. The same investigators who were not blinded to the participant's group allocation performed the two-stage maximal exercise tests. The first stage consisted of a graded exercise test to volitional exhaustion. A total of nine 3-minute stages were used in which the speed and inclination were increased in an alternate fashion as follows: stage 1 (2.0 mph, 0%); stage 2 (2.0 mph, 6.0%); stage 3 (2.6 mph, 6.0%); stage 4 (2.6% mph, 10%); stage 5 (3.0 mph, 10%); stage 6 (3.0 mph, 13%); stage 7 (3.5 mph, 13.0%) and stage 8 (3.5 mph, 16.0%) and stage 9 (4.0 mph, 16.0%). Continuous breath-by-breath sampling of respiratory gases was carried out using the Medgraphics CardiO2 Cardiopulmonary Exercise Testing System (Medical Graphics Corporation, St Paul, Minnesota, US). Based on breath-by-breath samples and using a rolling average of eight breaths, the following respiratory data were assessed: $\dot{V}O_2$ (oxygen consumption, ml min^{-1} and ml kg^{-1} min^{-1}), $\dot{V}CO_2$ (carbon dioxide production, ml min^{-1}), RER (respiratory exchange ratio), $\dot{V}CO_2/\dot{V}O_2$, $P_{ET}co_2$ (end-tidal partial pressure of CO_2, mm Hg), VE (expired volume of gas, l min^{-1} BTPS) and Vt (tidal volume, ml BTPS). A 12 lead ECG was monitored throughout exercise testing. Heart rate responses were derived from the ECG.

Within one week of the graded exercise test, the participants re-attended the laboratory for the determination of resting and peak exercise cardiac output using CO_2 re-breathing techniques. The principle of rebreathing methods for determination of cardiac output is to cause the alveolar CO_2 level to increase until gas exchange ceases [33]. Alveolar CO_2 tension is then assumed to be equal to that in mixed venous blood. The end-tidal partial pressure of CO_2 ($P_{ET}co_2$) is used as a measure of arterial PCO_2. Cardiac output (Q) was estimated, using the indirect Fick principle, from CO_2 output and arterial and mixed venous contents, determined using appropriate CO_2 dissociation curves [19]. Three estimates of cardiac output were normally undertaken at rest. Resting estimates of cardiac output were made using the equilibrium CO_2 rebreathing method as described by Collier [33]. Following this, the participants completed a single-stage maximum workload test. The treadmill speed and incline were initially set to the level of the highest completed or nearly completed stage from the previous graded exercise protocol. The speed and incline of the treadmill were adjusted to enable the subject to sustain the exercise for at least 5 min and aim to attain a $\dot{V}O_2$ of at least 90% of the maximum attained during the graded test. At peak exercise, the exponential CO_2 rebreathing method of Defares [34] was employed in duplicate to estimate cardiac output. Independent investigators [35] have recommended the equilibrium method for the estimation of resting cardiac output and confirmed that automated curve fitting for the exponential method provides reproducible and valid results at peak exercise.

Cardiac power output (CPO) was calculated from the mean cardiac output and mean arterial pressure using the following equation [19]: $CPO = (Q \times MAP) \times K$, where CPO is in Watts (W), Q is cardiac output in l min^{-1}, MAP is mean arterial pressure in mm Hg and K is the conversion factor (2.22×10^{-3}). The physiological cardiac reserve is equal to the difference between CPO_{peak} and baseline resting CPO [19]. Systolic and diastolic blood pressures were obtained at rest and during each stage of treadmill exercise and peak exertion from the brachial artery using a sphygmomanometer. The peak mean arterial pressure (MAP_{peak}) was calculated as $SBP_{peak} + (2 \times DBP_{peak})/3$, where SBP_{peak} is peak systolic blood pressure and DBP_{peak} is peak diastolic blood pressure [19]. Systemic vascular resistance to blood flow (SVR) was estimated as MAP_{peak}/Q_{peak} and as per convention multiplied by a factor of 80 to convert units to dyn s cm^{-5}. Peak exercise arteriovenous O_2 content difference ($AVDO_{2peak}$), expressed as vol.%, was calculated as $(\dot{V}O_{2peak}/Q_{peak}) \times 100$.

2.3. Statistical analysis

Group data for each variable at rest and peak exercise are presented as mean ± SD. To assess the reproducibility of maximum oxygen consumption using the graded and single-stage treadmill protocols, Bland and Altman plots [36] were constructed. Baseline characteristics were compared between the groups using independent t-tests. Changes in variables across the intervention study, over time and between groups, were assessed using repeated measures analysis of variance models. Statistical comparisons between groups were made using all available data with participants grouped as originally randomised, regardless of the degree of intervention compliance. Statistical analyses were performed using SPSS software, Version 10. $P < 0.05$ was the accepted level of significance.

3. Results

The mean (±SD) age and anthropometric characteristics of the 13 premenopausal participants are presented in Table 1. The participants body mass index at baseline ranged from 28.9 to 50.4 kg m^{-2}. The resting and peak exercise metabolic and haemodynamic characteristics of all participants are also shown in Table 1. These variables were

Table 1
Baseline mean (SD) anthropometric and resting and peak graded exercise test characteristics in the study participants ($n=13$)

Age, years	40.9±6.8
Body mass, kg	104.7±21.8
Height, cm	162.4±5.9
Body mass index, kg m^{-2}	39.2±7.5
Maximum waist circumference, cm	128.4±16.8
Body fat content, %	34.9±9.9
Resting variables	
$\dot{V}O_2$, ml min^{-1}	429.2±84.3
$\dot{V}O_2$, ml kg^{-1} min^{-1}	4.2±0.6
Respiratory exchange ratio	0.86±0.07
Heart rate, beats min^{-1}	101±13
Systolic BP, mm Hg	132±20
Diastolic BP, mm Hg	86±9
Mean arterial pressure, mm Hg	103±12
Peak exercise variables	
$\dot{V}O_{2peak}$, ml min^{-1}	2244.0±338.5
$\dot{V}O_{2peak}$, ml kg^{-1} min^{-1}	21.8±2.78
RER, $\dot{V}O_2/\dot{V}CO_2$	1.11±0.05
Heart rate, beats min^{-1}	170±12
Systolic BP, mm Hg	176±19
Diastolic BP, mm Hg	79±10
Mean arterial pressure, mm Hg	111±10

not significantly different to the participants who did not undergo the two-stage maximal exercise testing protocol (data not shown). Among the 13 selected participants, the peak heart rate on the baseline graded exercise test was 170 (±12) beats min^{-1}. This represents 94.2%±5.3% of maximum predicted for age, with 10 subjects achieving >90% of maximum predicted heart rate. The mean respiratory exchange ratio (RER) on baseline graded testing was 1.11 (±0.05) with a range of 1.02 to 1.17.

The heart rate (but not mean arterial pressure) achieved at peak exercise was lower in the single stage versus the graded exercise test (170 versus 153 beats min^{-1}; $P=0.01$). $\dot{V}O_{2peak}$ was lower on the single-stage exercise test but attained 96.5% of the incremental test value (2244±338.5 versus 2165±357.1; $P=0.013$ respectively). $\dot{V}O_{2peak}$ values on the graded and single-stage exercise tests were correlated linearly ($r=0.962$; $P<0.001$). The typical error of the estimate was 96.5 ml min^{-1} or 4.9% as a coefficient of variation for log-transformed variables. Bland–Altman analysis revealed that mean $\dot{V}O_{2peak}$ (graded and single-stage tests)−$\dot{V}O_{2peak}$ (single stage) difference (bias) was equal to 78.7 ml min^{-1} with an SD (precision) of 97.6 ml min^{-1}. The 95% limits of agreement ranged −270.1 to 112.6 ml min^{-1}.

Resting heart rate and mean arterial pressure were significantly lower immediately prior to the single-stage as compared to the graded treadmill protocol (−16±13 beats min^{-1} and 4±6 mm Hg; $P=0.001$ and 0.036 respectively). Among all participants, the mean cardiac output at rest (Q_{rest}) was 5.8 l min^{-1} (±0.92) with a range of 4.2 to 7.5 l min^{-1}. Cardiac output increased to 15.8±1.9 l min^{-1} at peak exertion (Q_{peak}) with a range of 13.2 to 19.3 l min^{-1}. The mean cardiac power output at rest (CPO_{rest}) was 1.3 W (range 0.7 to 2.1 W) increasing to 4.0 W at peak exercise (CPO_{peak}; range 2.9 to 4.1 W). Accordingly, the physiological cardiac reserve, as represented by the difference between cardiac power output at rest and at maximum exercise, ranged almost two-fold with this group from 1.8 to 3.4 W. The association between haemodynamic variables measured at rest and peak oxygen uptake was generally poor (all $r<0.50$). Similarly, none of the variables measured at rest correlated with peak cardiac power output or cardiac reserve (data not shown).

Table 2
Baseline resting and peak exercise haemodynamic and metabolic measurements from the graded exercise test in the participants randomised to lifestyle intervention ($n=6$) and control groups ($n=7$)

	Standing at rest		Peak exercise	
	Intervention	Control	Intervention	Control
$\dot{V}O_2$, ml min^{-1}	460±90	403±76	2437±361	2159±375
$\dot{V}O_2$, ml kg^{-1} min^{-1}	4.03±0.49	4.25±0.66	20.64±2.90	22.80±2.43
RER	0.86±0.08	0.86±0.07	1.10±0.04	1.11±0.06
Heart rate, beats min^{-1}	99±16	102±11	165±12	174±10
Systolic BP, mm Hg	132±22	130±22	178±24	174±16
Diastolic BP, mm Hg	89±12	89±6	80±11	77±9
Mean arterial pressure, mm Hg	104±14	103±10	113±11	110±10

Table 2 shows the resting and peak exercise haemodynamic and metabolic measurements from the graded treadmill test in the participants randomly assigned to the lifestyle intervention and control groups. No significant between group differences were evident in peak exercise haemodynamic and metabolic measurements, although $\dot{V}O_{2peak}$ tended to be higher and peak heart rate lower in

Table 3
Baseline primary haemodynamic and metabolic measurements from the single-stage maximum workload test in the participants randomised to lifestyle intervention ($n=6$) and control groups ($n=7$)

	Sitting rest		Peak exercise	
	Intervention	Control	Intervention	Control
$\dot{V}O_2$, ml min^{-1}	416.2±74.9	348.1±86.6	2436.7±360.6	2158.9±374.8
$\dot{V}O_2$, ml kg^{-1} min^{-1}	3.64±0.19	3.64±0.65	20.27±2.82	21.58±2.71
Cardiac output, l min^{-1}	6.3±0.87	5.36±0.78	16.13±2.39	15.57±1.57
Stroke volume, ml $beat^{-1}$	74.9±5.5	64.3±8.6	103.2±8.6	104.2±6.5
Heart rate, beats min^{-1}	84.3±12.0	84.3±14.4	155.8±13.0	149.7±15.5
Systemic AVO_2 diff, vol.%	–	–	14.23±0.98	13.20±1.5
Systolic BP, mm Hg	130.5±21.1	129.3±21.9	180.8±24.0	177.1±12.2
Diastolic BP, mm Hg	82.5±14.8	85.7±11.7	78.3±10.3	81.4±14.6
Mean arterial pressure, mm Hg	98.5±16.9	100.1±14.7	112.5±14.0	113.3±13.5

Table 4
Pre- and post-intervention resting haemodynamic and metabolic measurements from the graded exercise test in the participants randomised to lifestyle intervention ($n=6$) and control ($n=7$) groups

	Lifestyle		Control		Main effect, time	Interaction effect
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	*P*-value	*P*-value
$\dot{V}O_2$, ml min^{-1}	459.5±90.4	399.5±65.2	403.3±75.5	336.7±90.4	0.003	NS
$\dot{V}O_2$, ml kg^{-1} min^{-1}	4.03±0.49	3.56±0.46	4.25±0.66	3.40±0.63	0.001	NS
RER	0.86±0.08	0.82±0.07	0.86±0.09	0.85±0.064	NS	NS
Heart rate, beats min^{-1}	98.8±16.3	89.5±20.5	101.9±11.4	88.6±15.6	0.001	NS
Systolic BP, mm Hg	131.7±21.6	127.0±21.9	130.4±21.9	131.0±19.0	NS	NS
Diastolic BP, mm Hg	89.2±12.0	83.3±16.6	88.6±6.3	82.9±11.1	0.013	NS
MAP, mm Hg	103.5±14.4	98.0±17.6	103.0±10.4	99.0±13.1	0.011	NS

the intervention group. Peak oxygen pulse tended to be higher in the intervention group (14.1±1.5 versus 12.4±1.6 ml min^{-1} beat^{-1}; $P=0.085$). The intervention group was non-significantly heavier than the control group (114.8±22.2 versus 96.1±18.5 kg; $P=0.126$).

Table 3 shows the single-stage treadmill test variables in the participants randomly assigned to the lifestyle intervention and control groups. Prior to the single-stage test, cardiovascular variables at rest were similar between the lifestyle and control groups, with the exception that cardiac output tended to be higher in the lifestyle group associated with a higher resting stroke volume ($P=0.025$). Cardiovascular responses at peak exertion on the single-stage test were generally not significantly different between the lifestyle and control groups. However, in terms of the single-stage test methodology, the control group participants tended to achieve a significantly higher proportion of the maximal heart rate achieved on the graded exercise test (94.5±4.7% versus 86.0±7.5%; $P=0.034$).

Of the 13 subjects selected, all participants completed the 3-month intervention. Adherence to the twice-weekly circuit training sessions was monitored. Mean adherence for these sessions was 70.0±31.5%. Of note, four participants within the intervention group failed to attend any of the supervised exercise classes. Repeated measures analysis of variance showed that there were no significant reductions in body weight in the lifestyle group compared with the control during the 3-month intervention period. Changes in resting and peak exercise haemodynamic and metabolic data obtained from the graded test are presented in Tables 4 and 5.

The graded exercise test results showed a trend towards an improved $\dot{V}O_{2peak}$ normalised for body weight among the lifestyle group (20.6 to 22.2 ml kg^{-1} min^{-1}) compared with no change (22.8 to 22.0 ml kg^{-1} min^{-1}) in the control group (test for interaction, $P=0.071$). Absolute $\dot{V}O_{2peak}$ non-significantly increased in the lifestyle group following the intervention period (2337.8 to 2436.7 ml min^{-1}) and remained unchanged (2163.6 to 2158.9 ml min^{-1}) in the control group (test for interaction, $P=0.167$). As shown in Table 5, there were no significant changes in peak exercise heart rate or peak RER achieved on graded exercise testing.

Changes in resting and peak exercise haemodynamic data obtained from the single-stage maximum workload test are presented in Table 6. Resting measures of cardiovascular function did not change significantly as a result of the intervention in either group. Consistent with the graded exercise test findings, there was a trend for an improvement in $\dot{V}O_{2peak}$ normalised for body weight among the lifestyle group compared with a modest reduction in the control group (test for interaction, $P=0.059$). In contrast, absolute $\dot{V}O_{2peak}$ on the single-stage test increased in both groups following the intervention period ($P=0.023$). The larger within group changes in the lifestyle group failed to achieve statistical significance (test for interaction, $P=0.131$).

The improvement in absolute $\dot{V}O_{2peak}$ after the intervention was associated with a lower peak heart rate in the lifestyle group compared to a higher peak heart rate in the control group (test for interaction, $P=0.093$). In contrast, both groups showed no significant changes in Q_{peak} and MAP_{peak}. Peak oxygen pulse increased significantly in the

Table 5
Pre- and post-intervention peak exercise haemodynamic and metabolic measurements from the graded exercise test in the participants randomised to lifestyle intervention ($n=6$) and control ($n=7$) groups

	Lifestyle ($n=6$)		Control ($n=7$)		Main effect, time	Interaction effect
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	*P*-value	*P*-value
VO_2, ml min^{-1}	2337.8±403.7	2463.7±360.6	2163.6±277.6	2158.7±374.8	NS	NS
VO_2, ml kg^{-1} min^{-1}	20.64±2.89	22.10±4.27	22.81±2.43	21.95±2.25	NS	0.071
RER	1.10±0.04	1.10±0.04	1.12±0.06	1.09±0.05	NS	NS
Heart rate, beats min^{-1}	164.8±12.4	166.0±8.0	174.1±10.1	169.9±6.2	NS	NS
Systolic BP, mm Hg	175.5±23.6	191.7±19.4	174.3±15.9	186.0±22.9	0.058	NS
Diastolic BP, mm Hg	80.0±11.4	79.2±14.3	77.3±9.0	76.6±10.3	NS	NS
MAP, mm Hg	112.5±11.8	116.7±14.2	109.6±9.9	113.1±13.9	NS	NS

Table 6
Pre- and post-intervention peak exercise haemodynamic and metabolic measurements from the single-stage maximum workload test in the participants randomised to lifestyle intervention ($n=6$) and control ($n=7$) groups

	Lifestyle ($n=6$)		Control ($n=7$)		Main effect, time	Interaction effect
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	*P*-value	*P*-value
VO_2, ml min^{-1}	2295.2±380.5	2489.2±296.4	2054.0±321.0	2099.4±353.8	0.023	NS
VO_2, ml kg^{-1} min^{-1}	20.27±2.81	22.45±3.90	22.58±2.70	21.29±1.72	NS	NS (0.059)
RER	1.11±0.03	1.15±0.13	1.04±0.04	1.12±0.07	NS	NS
Cardiac output, l min^{-1}	16.1±2.4	16.6±1.5	15.6±1.6	15.6±1.6	NS	NS
Heart rate, beats min^{-1}	155.8±13.0	151.3±9.1	149.7±15.6	159.7±12.0	NS	NS (0.093)
Stroke volume, ml $beat^{-1}$	103.2±8.6	109.6±10.2	104.2±6.5	102.0±14.9	NS	NS
Oxygen pulse, ml min^{-1} $beat^{-1}$	14.66±1.45	16.44±1.53	13.80±2.2	13.20±2.1	NS	0.003
Systolic BP, mm Hg	180.8±24.0	190.8±20.1	177.1±12.2	186.4±25.6	NS (0.092)	NS
Diastolic BP, mm Hg	78.3±10.4	79.1±14.3	81.4±14.6	73.6±12.2	NS	NS
MAP, mm Hg	112.5±14.0	116.2±15.0	113.3±13.5	111.1±15.3	NS	NS
$AVDO_{2peak}$, vol.%	14.2±0.98	15.0±0.91	13.2±1.5	13.0±1.7	NS	NS
SVR, dyn s^{-1} cm^{-5}	570.0±119.0	564.6±89.6	591.6±118.3	555.1±105.1	NS	NS

lifestyle group compared with controls (test for interaction $P=0.003$). In accordance with these observations, SV_{peak} tended to increase in the intervention group and decrease in the controls (test for interaction, $P=0.176$). CPO_{peak} showed some improvement in the lifestyle group (4.0 to 4.27 W), whereas it tended to decrease in the control group, 3.89 to 3.77 W (test for interaction $P=0.166$). Physiological cardiac reserve increased from 2.63 (±0.54) W to 2.92 (±0.43) W in the lifestyle group, whereas it declined (2.69±0.24 to 2.56± 0.28 W) in the control group (test for interaction, $P=0.091$).

4. Discussion

CPO determined non-invasively at rest and during peak exercise has not been previously described in sedentary obese middle-aged female participants. At baseline, the mean resting CPO among our obese participants (1.29± 0.35 W) was somewhat higher than previously reported estimates using similar methodologies. The mean resting CPO of a larger cohort of adult females ($n=103$) aged 20–70 years has been reported to be 0.8±0.35 W [41]. Our mean data are more consistent with values reported among asymptomatic females with mild hypertension and younger hypertensive adults with severe obesity (BMI ≥ 40.0), as evaluated by echocardiographic techniques [37]. Lower resting CPO values have been shown previously in overweight hypertensive adults and those with mild obesity. Inconsistencies may relate to differences in mean arterial blood pressure reflecting subject selection and methodological differences. The CPO_{peak} observed among obese premenopausal females in the present study (range 2.88 to 4.13 W) is comparable with mean values estimated among both pre- and postmenopausal subjects of varying levels of cardiorespiratory fitness [38–40]. Chantler et al. [41] reported a mean CPO_{peak} of 4.0±0.6 W among amongst apparently healthy adult women. Higher mean values have been observed among middle-aged and older female endurance athletes (CPO_{peak} 4.45 W) [42]. Paradoxical findings include the high CPO_{peak} (4.3 W) reported in 32 overweight unfit hypertensive female patients during graded cycle ergometry to exhaustion [39]. In this group a high mean arterial pressure (by invasive methods) at peak exercise was reported.

The findings of the present study demonstrated that lifestyle intervention tended to improve $\dot{V}O_{2peak}$ normalised to body weight, mean cardiac power output and cardiac reserve. However, the magnitude of these cardiorespiratory and haemodynamic adaptive responses was somewhat limited compared with earlier reports. Our improvement in $\dot{V}O_{2peak}$ normalised to body weight (11%) is lower than that reported among obese females following 16 weeks of dietary intervention plus lifestyle activity or programmed aerobic exercise (16.2–18.8%, respectively) [22] and the larger improvements associated with longer-term behavioural weight management programmes (16–24%). Jakicic et al. [26] reported mean $\dot{V}O_{2peak}$ changes ranging from 13.3 to 17.8% among overweight sedentary women undertaking moderate or vigorous intensity exercise (with moderate or high duration) for six months. Our findings are more consistent with the smaller increase reported in the moderate intensity and exercise duration group. However, 6 months of both intensive lifestyle and structured exercise interventions designed primarily to increase physical activity and cardiorespiratory fitness among sedentary overweight adults have reported similar small changes in $\dot{V}O_{2peak}$ normalised to body weight (adjusted mean changes of 1.58 to 3.46 ml kg^{-1} min^{-1}) [25].

The present study and others have documented modest improvements in absolute $\dot{V}O_{2peak}$ (ml min^{-1}) following short-term exercise training in premenopausal obese women. In contrast, considerably larger increases in $\dot{V}O_{2peak}$ (22–24%) were reported among 17 and 12 middle-aged obese females [22] in closely supervised trial of 14 weeks duration incorporating both exercise-induced weight loss and exercise without weight loss, respectively. Study differences in the absolute and body weight normalised $\dot{V}O_{2peak}$ changes are likely to be explained by differences in the selection of the participants, the mode,

intensity and dose of structured exercise training or lifestyle activity undertaken and the prearranged caloric intake and weight loss.

Our findings for maximal cardiac output are in contrast with some previous studies reporting significant increases following exercise training [43–45]. It has been shown that an improved cardiovascular response to maximal exercise after training, particularly among younger individuals, is mediated equally through increases in both Q_{peak} and maximal $AVDO_2$ [45–47]. Different subject characteristics and exercise training protocols employed may explain disparities within the literature. In the present study, maximal cardiac output remained unchanged and peak heart rate decreased on the single-stage treadmill exercise following intervention.

To our knowledge, the effects of exercise training on CPO_{peak} and cardiac reserve have not previously been reported among clinically obese subjects. The results of the present investigation indicate a trend towards improvements in overall cardiac function in obese middle-aged females. Notably, moderate increases in CPO_{peak} (8.7%) and physiological cardiac reserve (16.1%) were evident. Few investigators have presented data that allows for relevant comparison of maximal cardiac power output and responses to exercise training. Beere et al. [48] assessed the contribution of cardiac responses to 3 months of exercise training in a sample of 10 older and 13 younger males. Peak exercise cardiac output and MAP_{peak} (directly determined using thermodilution and brachial artery catheterisation techniques) were shown to be essentially unchanged following training in both older and younger groups, despite substantial increases in $\dot{V}O_{2peak}$ (17.8% and 20.2% respectively). In a 30-year longitudinal follow-up of the Dallas Bed Rest and Training Study, McGuire et al. [49] described cardiovascular adaptations to 6 months of progressive exercise training within five middle-aged overweight/obese male participants. Absolute $\dot{V}O_{2max}$ increased by 14% after exercise training with no significant changes evident in Q_{max} (derived using acetylene rebreathing technique) or peak mean arterial pressure (MAP_{peak}). Accordingly, no discernable training-induced changes were apparent for CPO_{peak} or cardiac reserve in these studies. In contrast, Marshall et al. [50] reported significant increases in CO_2 rebreathing-derived CPO_{peak} and cardiac reserve (16% and 21%, respectively) following unsupervised exercise training among nine middle-aged overweight participants. An 11% increase in peak exercise stroke volume provided the largest contribution to the improved cardiac function with lesser increments in peak heart rate and mean arterial pressure. By comparison, the present study revealed an 8% increase in peak exercise stroke volume compared with controls. It is notable that studies of training on cardiac power output have been largely confined to male participants. Spina et al. [51] previously showed that the mechanisms involved in the training-induced improvements may differ among men and women. Within older men and women, 9–12 month of endurance exercise increased $\dot{V}O_{2max}$ by 19% and 22% respectively. In the men, stroke volume during maximal exercise was 15% higher after training and this increase accounted for 66% of the increase in $\dot{V}O_{2max}$. In contrast, training resulted in no change in stroke volume in the women. The increase in $\dot{V}O_{2max}$ was accounted for entirely by a significantly higher $AVDO_{2peak}$ after or during maximal exercise.

Peak oxygen pulse (the quotient of the $\dot{V}O_{2peak}$ and heart rate) has been shown to be low among obese subjects [15]. In the present study, peak oxygen pulse on the single-stage exercise test increased significantly (16.5%) following intervention in the lifestyle group compared with control. This variable integrates the training induced changes in both stoke volume and arteriovenous oxygen difference ($AVDO_2$). Following 9 months of aerobic exercise, $\dot{V}O_{2peak}$ and peak oxygen pulse increased >10% in postmenopausal elderly women. As previously outlined [52–54], several plausible mechanisms have been described that could account for training-induced improvements in $AVDO_{2peak}$. Such changes may include conversion of muscle fibre-type characteristics, improvements in capillary density and motor unit recruitment and increases in the efficiency of distribution of CO to exercising tissues. The present study did not set out to address these specific mechanistic considerations.

There are several disadvantages to the non-invasive cardiac power method of assessing cardiac function. Our findings have re-emphasised some of the methodological issues associated with the estimation of cardiac output using the CO_2 rebreathing method [29]. Cardiac output was measured during a separate single-stage test at a work rate corresponding to the highest level achieved in the preceding graded treadmill protocol. Whilst this represents a high workload, oxygen consumption and heart rate are typically lower than those attained on graded exercise testing [19]. The present study has shown a systematic bias in oxygen uptake of approximately 4.0% between the graded and single-stage exercise test methodologies. Consequently, maximum cardiac power output may not be obtained. Furthermore, non-invasive CO_2 rebreathing method derives values for CO_2 concentration in arterial and mixed venous blood, respectively, from the end-tidal PCO_2 and the plateau value of CO_2 after rebreathing [29]. The key assumption [55] that $P_{ET}co_2$ relates to Pa CO_2 may not hold in disease states and the calculation of the arteriovenous CO_2 difference would be disturbed. More recently [56], it has been highlighted that during exercise, the widely accepted assumption that $PaCO_2$ is linearly related to CO_2 concentration in the blood over a broad physiological range may not hold. During heavy exercise acidosis has the effect of reducing the total CO_2 concentration at a given $PaCO_2$. The failure to take pH into consideration at high levels of exercise may cause cardiac output to be underestimated.

Consistent with the variability of blood pressure measurement using cuff manometry [57,58], it has been reported that the repeatability of cardiac power output is inferior to that of cardiac output [19]. Continuous monitoring of blood pressure and arterial pressure waveform during exercise with

photoplethysmography methods may improve the validity and reproducibility of non-invasive cardiac power output measurement [59].

In conclusion, we have shown that in small cohort of sedentary, obese premenopausal participants, lifestyle modification incorporating moderate-intensity supervised exercise training can modestly improve $\dot{V}O_{2peak}$ and provide some functional cardiac gains. These RCT findings also indicate that evaluation of peak oxygen pulse and physiological cardiac reserve may provide useful indices for directly quantifying the overall cardiac functional gain obtainable through lifestyle-based interventions. Further larger adequately powered RCT's of lifestyle activity and structured exercise are now required to confirm whether clinically obese patients can achieve similar improvements in cardiorespiratory fitness and cardiac reserve function.

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