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Original Scientific Paper

The effects of exercise training on insulin resistance in patients with coronary artery disease

Neville G. Suskin[a], George Heigenhauser[b], Rizwan Afzal[b], Diane Finegood[c], Hertzel C. Gerstein[b] and Robert S. McKelvie[b]

[a]University of Western Ontario, London, [b]McMaster University, Hamilton, Ontario and [c]Simon Fraser University, Vancouver, British Columbia, Canada

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Background **It is unclear whether the beneficial effects of habitual exercise on insulin resistance are due to concomitant weight loss, changes in diet or whether they are simply related to the transient effects of the last bout of exercise. Moreover, patients with coronary artery disease (CAD) have not been studied.**

Design **Randomized controlled trial.**

Methods **To determine the effects of exercise training on insulin resistance (i.e. low insulin sensitivity) in CAD patients without diabetes independent of changes in weight, diet or the effect of acute exercise, 29 patients were randomized to 12 weeks of supervised exercise training and 26 to usual activity. Insulin sensitivity was determined at 72 h following their last bout of exercise using the minimal model technique. Weight was held constant by adjusting caloric intake.**

Results **Following the intervention, peak oxygen uptake increased by 0.18 ± 0.14 l/min in the exercise training group, which was significantly higher ($P < 0.0001$) than that in the usual activity group (0.02 ± 0.14 l/min). Insulin sensitivity did not change significantly within or between groups during the study [exercise training $-0.24 \pm 1.15 \times 10^4$/min and usual activity $0.06 \pm 0.67 \times 10^4$/min/(μU/ml)].**

Conclusions **Twelve weeks of moderate exercise training in the absence of weight loss did not result in significant change in insulin resistance in patients with CAD.** ***Eur J Cardiovasc Prev Rehabil*** **14:803–808 © 2007 The European Society of Cardiology**

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Introduction

Dysglycemia and insulin resistance (low insulin sensitivity) are important risk factors for cardiovascular disease [1,2]. A progressive relationship between plasma glucose and cardiovascular risk extends from normal glucose levels right into the diabetes range [3]. Regular physical activity has been found to decrease the incidence of type 2 diabetes mellitus [4] and to improve glucose tolerance in people with impaired glucose tolerance [5]; it is also associated with a reduced risk of a cardiovascular event [6,7]. Studies demonstrating that a single bout of exercise results in an acute decrease in insulin resistance [8] have suggested that exercise reduces the risk of type 2 diabetes mellitus by chronically increasing insulin sensitivity [9,10]. Randomized controlled trials, however, have not consistently ruled out the possibility that the beneficial effects of habitual exercise on glucose tolerance might be due to concomitant weight loss or changes in diet [11–14]. Furthermore, it is unclear whether improvements in glucose tolerance associated with habitual exercise are simply related to the transient effects of the last bout of exercise, or are the long-lasting results of habitual physical activity. Finally, none of these studies has enrolled individuals with documented coronary artery disease (CAD). Individuals with stable CAD have a higher prevalence of dysglycemia than

Correspondence to Dr Neville G. Suskin, University of Western Ontario, London Health Sciences Centre, 339 Windermere Rd, London, ON, Canada N6A 5A5
Tel: +1 519 6858300 x33488; fax: +1 519 6633506;
e-mail: neville.suskin@lhsc.on.ca

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healthy age-matched and weight-matched controls [15]. Glucometabolic abnormalities (impaired glucose tolerance or undiagnosed diabetes mellitus) have been reported in over 50% of individuals with acute myocardial infarction [16] and are associated with increased mortality in patients with and without diagnosed diabetes mellitus [16,17]. Therefore, individuals with CAD might stand to benefit more from the effects of regular exercise training on insulin resistance than individuals without CAD.

The purpose of this study was to determine the effects of exercise training on the degree of insulin resistance in patients with CAD independent of changes in weight, diet or the effect of an acute bout of exercise. We hypothesized that patients with CAD and high normal or impaired glucose tolerance performing 12 weeks of aerobic exercise training while on a non-weight-reducing diet would have a greater decrease in the degree of insulin resistance than controls measured at 72 h following their last bout of exercise.

Methods

The study was performed at the Hamilton Health Science Cardiac Rehabilitation Program following Institutional Review Board approval. All participants provided written and verbal informed consent.

Inclusion criteria

The study population included men and women over 18 years of age identified from the practices of local cardiologists. Fasting plasma glucose concentration of the participants was 5.4–7.7 mmol/l and they had confirmed CAD (diagnosed on the basis of a previous myocardial perfusion study, cardiac catheterization, history of myocardial infarction, coronary artery angioplasty or coronary artery bypass surgery).

Exclusion criteria

Individuals were excluded if they had known diabetes mellitus, heart failure, uncorrected significant valvular or congenital heart disease, significant obstructive pulmonary disease, uncontrolled hypertension, participated in a regular exercise program within the preceding three months, inability to perform exercise training, atrial fibrillation, a permanent pacemaker or regularly used corticosteroids. Individuals who had experienced their index cardiac event within 3 months before the start of the study were also excluded. Furthermore, individuals were excluded if their run-in-phase fasting blood glucose was < 5.4 or ≥ 11.1 mmol/l at 2 h following a 75-g oral glucose load.

Screening visit

Individuals who satisfied the above criteria underwent a screening visit consisting of a full explanation of the study, and appropriate history and physical evaluation by one of the study physicians (NGS or RSM). Height (m), weight (kg), waist and hip circumference (cm) and percentage body fat using bioelectrical impedance [18], were measured. A 75-g oral glucose tolerance test [19] using fasting and 2-h samples was then performed following an overnight (≥ 12 h) fast. Participants satisfying the study selection criteria subsequently entered the run-in phase.

Run-in phase (≤ 6 weeks)

The study dietician assessed all the participants using 24-h food recall and semiquantitative food frequency questionnaires [20]. An individualized isocaloric American Heart Association (AHA) Phase I diet [21] with written and verbal instructions was prescribed for each patient. The purpose of the run-in phase was to have the participants follow an AHA Phase I diet for at least 3 weeks, as determined by the study dietician. Baseline testing was carried out on completion of the run-in phase.

Baseline testing

Measurements included an oral glucose tolerance test, waist circumference, percentage body fat, a symptom-limited cycle ergometer test with measurement of oxygen consumption and the 3-h 29-sample frequently sampled intravenous glucose tolerance test (FSIGT) to determine the degree of insulin resistance. The cycle ergometer test was performed according to accepted guidelines [22]; oxygen uptake (VO_2) was continuously measured throughout the cycle ergometer test and the peak VO_2 served as the index of exercise capacity.

The FSIGT was performed in the usual fashion, 72 h following the baseline cycle ergometer test after an overnight fast. A glucose injection (300 mg/kg as a 50% solution) was given at time 0 min and a 0.04 U/kg of human insulin (Novolin R) was injected at time 20 min. The degree of insulin resistance was determined by one of the investigators (DF) blinded to the patient's group allocation using the validated minimal model technique [23]. The minimal model-derived insulin sensitivity (MINMOD-IS) measure (the lower the insulin sensitivity, the greater is the degree of insulin resistance) was defined as the fraction of glucose cleared/min by insulin-dependent glucose disposal relative to the concentration of insulin, and was expressed in 10^4/min/(μU/ml) [24].

After satisfactory completion of baseline testing, participants were randomized to either 12 weeks of exercise training or usual activity. Randomization was computer-generated following a nonblocked strategy and delivered using sealed envelopes. All individuals recording the outcome measurements were blinded to the group allocations of the participants. To maintain a stable weight throughout the study, in addition to the well-controlled AHA Phase I diet, exercise training participants underwent supervised weekly weigh-ins and were prescribed

supplemental food in proportion to the AHA Phase I diet by the study dietician if weight loss of ≥ 1 kg occurred on two consecutive weekly supervised weigh-ins. Participants in the usual activity group were instructed to continue their usual activity and to follow the AHA Phase I diet and to weigh themselves weekly on the same home scale, first thing in the morning with minimal attire. Participants contacted the study dietician if ≥ 1 kg weight change occurred over 2 weeks. Appropriate dietary adjustments were then made to ensure a stable weight.

The exercise training group was prescribed exercise four times/week for 12 weeks. This exercise consisted of walking, stationary cycling or treadmill exercise for 40 min/session at 75% of their baseline cycle ergometer test peak heart rate, with 5-min warm-up and cool-down periods. Participants were taught how to monitor their heart rate during exercise and to adjust their exercise intensity accordingly. Two of these sessions were conducted under supervision at the Hamilton Health Science Cardiac Rehabilitation Program, whereas the remaining sessions were carried out at home.

Ten to 12 weeks following randomization all participants underwent endpoint assessments, which consisted of the same testing as baseline. These assessments were oral glucose tolerance test and clinical evaluation (week 11), cycle ergometer test (week 12) and FSIGT (72 h after cycle ergometer test). All participants were instructed not to perform any exercise training between the final cycle ergometer test and FSIGT.

Statistical issues

Overall 50 patients were required to satisfy the study's sample size assumptions that at least a 15% decrease in the degree of insulin resistance with exercise training compared with usual activity could be demonstrated, with 80% power, a two-tailed α error of 5% and a potential 20% loss to follow-up rate [25]. The MINMOD-IS measure was log transformed to normalize its distribution, and then analyzed using appropriate parametric statistics (such as *t*-tests for continuous measures) to compare the changes in the degree of insulin resistance over the course of the study between the exercise training and usual activity groups. In addition, we evaluated changes of MINMOD-IS as an outcome using multiple regression for treatment (exercise training) effect after adjusting for the baseline MINMOD-IS, and a number of other variables of prognostic importance (e.g. weight, peak VO_2 and fasting glucose at baseline). The MINMOD-IS measure was then back-transformed for presentation in the text, tables and figures. The remaining variables had normal distributions. Remaining analyses comparing outcomes between the exercise training and usual activity groups used independent *t*-tests for continuous data. Spearman's correlation coefficient was used to assess the relationships between the change in the degree of insulin resistance during the study and other important study variables, such as changes in weight and peak VO_2. Analyses were deemed significant if a two-tailed *P*-value of < 0.05 was achieved. All values are reported as the mean ± standard deviation unless otherwise specified.

Results

Twenty-six participants were randomized to usual activity and 29 to exercise training (Table 1). No patients were lost to follow-up. The average age of the participants was similar in the usual activity (66.1 ± 5.7 years) and exercise training groups (65.5 ± 7.0 years). Following randomization, there were no important clinical differences between the usual activity and exercise training groups in terms of weight, percentage of body fat, waist circumference, total, low-density lipoprotein and high-density lipoprotein cholesterol, peak VO_2, fasting plasma glucose, triglycerides or insulin sensitivity. The exercise training group had moderately higher 2-h plasma glucose levels after a 75-g glucose load (7.65 ± 2.61 vs. 6.90 ± 1.85 mmol/l); however, neither group met the criteria for abnormal fasting or impaired glucose tolerance [26].

Following the 12-week intervention (Table 2), peak VO_2 and peak power output increased by 0.18 ± 0.10 l/min (11.5%) and 108.10 ± 115.5 kpm/min (15.1%), respectively, in the exercise training group, which were significantly higher ($P < 0.0001$ and $P < 0.0005$, respectively) than those in the usual activity group (0.02 ± 0.1 l/min and 11.30 ± 75.2 kpm/min). Participants' weight and waist circumferences did not change significantly during the study (exercise training, -0.20 ± 1.5 kg and 0.50 ± 3.1 cm; usual activity, 0.03 ± 1.7 kg and -1.40 ± 3.5 cm). The degree of insulin resistance (Figs 1 and 2)

Table 1 Baseline characteristics

Characteristic	Usual activity	Exercise training
Number of participants (women)	26 (2)	29 (3)
Age (years)[a]	66.1 ± 5.7	65.5 ± 7.0
Weight (kg)[a]	83.2 ± 11.5	84.7 ± 11.8
Waist circumference (cm)[a]	100.1 ± 8.0	100.3 ± 8.2
Percent body fat[a,b]	28.9 ± 6.0	30.5 ± 7.2
Cardiac background[c]		
Myocardial infarction, *N* (%)	14 (53.8)	12 (41.4)
Angina, *N* (%)	17 (65.4)	17 (58.6)
Coronary artery bypass, *N* (%)	17 (65.4)	15 (51.7)
Coronary angioplasty, *N* (%)	11 (42.3)	14 (48.3)
Total cholesterol (mmol/l)[a]	4.23 ± 0.66	4.39 ± 0.85
LDL cholesterol (mmol/l)[a]	2.45 ± 0.66	2.50 ± 0.57
HDL cholesterol (mmol/l)[a]	1.06 ± 0.23	1.07 ± 0.16
Triglycerides (mmol/l)[a]	1.41 ± 0.41	1.81 ± 0.89
Peak VO_2 (l/min)[a]	1.55 ± 0.28	1.57 ± 0.30
Peak power (kpm/min)[a]	713.1 ± 159.4	714.8 ± 164.5
Fasting blood glucose (mmol/l)[a]	5.88 ± 0.57	5.95 ± 0.63
2-h glucose (mmol/l)[a]	6.90 ± 1.85	7.65 ± 2.61
Insulin sensitivity [$\times 10^4$/min/(μU/ml)][a,d]	2.55 ± 1.24	2.47 ± 1.19

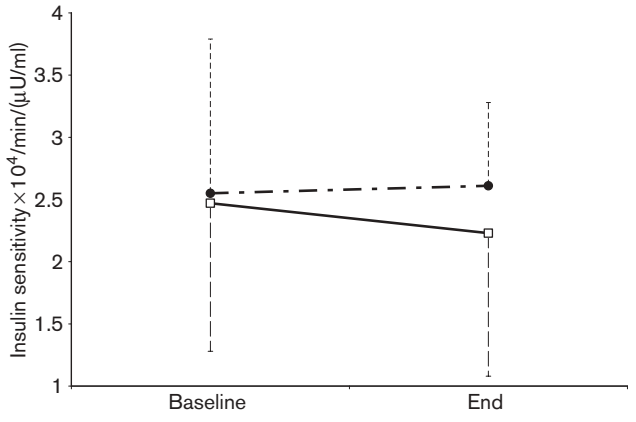
HDL, high-density lipoprotein; LDL, low-density lipoprotein. [a]Mean ± standard deviation. [b]Measured by impedance plethysmography [18]. [c]Not exclusive. [d]MINMOD-IS, minimal model-derived insulin sensitivity [23].

Table 2 Change (week 12 – baseline) over the 12-week study period

Characteristic	Usual activity (*n*)	Exercise training (*n*)	*P*-value
Weight (kg)[a]	0.03 ± 1.72 (26)	– 0.15 ± 1.46 (29)	ns
Waist circumference (cm)[a]	– 1.38 ± 3.51 (21)	0.48 ± 3.07 (23)	ns
Percent body fat[a,b]	0.16 ± 3.16 (23)	1.08 ± 4.59 (26)	ns
Total cholesterol (mmol/l)[a]	0.02 ± 0.39 (20)	– 0.04 ± 0.59 (21)	ns
LDL cholesterol (mmol/l)[a]	0.02 ± 0.40 (19)	– 0.08 ± 0.45 (20)	ns
HDL cholesterol (mmol/l)[a]	– 0.01 ± 0.10 (19)	0.03 ± 0.12 (21)	ns
Triglycerides (mmol/l)[a]	0.02 ± 0.41 (19)	0.02 ± 0.65 (20)	ns
Peak VO_2 (L/min)[a]	0.02 ± 0.14 (26)	0.18 ± 0.14[c](29)	0.0001
Peak power (kpm/min)[a]	11.34 ± 75.16 (26)	108.10 ± 115.50[c](29)	0.0005
Fasting blood glucose (mmol/l)[a]	– 0.12 ± 0.44 (22)	0.21 ± 0.62 (24)	0.04
2-h glucose (mmol/l)[a]	– 0.17 ± 1.03 (22)	– 0.05 ± 1.79 (24)	ns
Insulin sensitivity [$\times 10^4$/min/(μU/ml)][a,d]	0.06 ± 0.67 (22)	– 0.24 ± 1.15 (21)	ns

HDL, high-density lipoprotein; LDL, low-density lipoprotein. [a]Mean ± standard deviation. [b]Measured by impedance plethysmography [18]. [c]Within group pre–post difference $P < 0.05$. [d]MINMOD-IS, minimal model-derived insulin sensitivity [23].

Fig. 1



Overall changes in insulin sensitivity of usual activity versus excessive exercise training. *P*, not significant; ●, usual activity; □, exercise training; error bars, standard deviation.

did not change significantly within or between groups during the study [exercise training, -0.24 ± 1.15; usual activity, $0.06 \pm 0.67 \times 10^4$/min/(μU/ml)]. A modest increase was observed in the fasting plasma glucose level in the exercise training group compared with the usual activity group (0.21 ± 0.62 vs. -0.12 ± 0.44 mmol/l, $P = 0.04$), whereas there was no difference in plasma glucose 2 h after the 75-g glucose load or in lipid profile during the study. No significant correlations (Spearman) were seen between changes in the degree of insulin resistance during the study and changes in weight ($\rho = 0.01$, $P = 0.9$), peak VO_2 ($\rho = -0.06$, $P = 0.7$), waist circumference ($\rho = -0.1$, $P = 0.3$), hip circumference ($\rho = -0.1$, $P = 0.5$) or percentage body fat ($\rho = -0.1$, $P = 0.6$). In addition, after adjusting for baseline differences of MINMOD-IS, weight, peak VO_2 and fasting glucose using multiple regression, the change in the degree of insulin resistance within and between groups remained insignificant ($P = 0.2$).

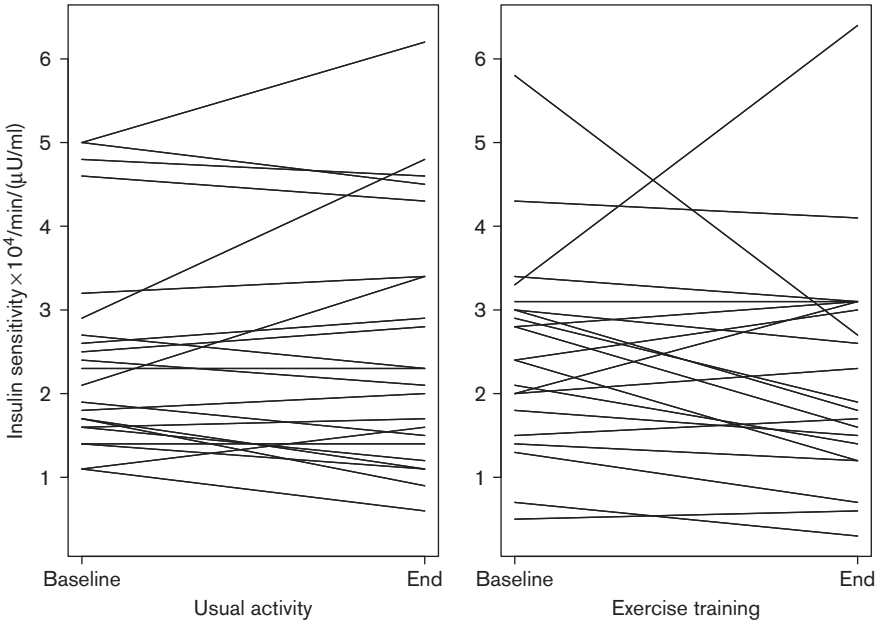
Discussion

In participants with CAD and stable body weight, we demonstrated that 12 weeks of moderate-intensity aerobic exercise training resulted in a modest but significantly greater improvement of peak VO_2 than no exercise training, but that it had no significant impact on the degree of insulin resistance or glucose tolerance.

Others have observed that either insulin resistance or the incidence of clinical conditions that result from increased insulin resistance (such as impaired glucose tolerance or diabetes mellitus) are decreased by physical activity [11–13,27]. None of these trials, however, examined the effects of habitual exercise on the degree of insulin resistance while keeping body weight constant. These trials also did not separate the effect of habitual exercise training on insulin resistance from the known beneficial effect of acute exercise on insulin resistance. Indeed, the inability to separate the effects of increased habitual exercise from that of weight loss on the incidence of diabetes mellitus, has been noted in two randomized trials [13,28]. A third study examined for, but did not demonstrate, a significant incremental benefit for exercise training over weight loss on the incidence of diabetes mellitus [29].

The unique feature of our study was that we attempted to control for any effect that diet might have on the degree of insulin resistance by placing all the participants on an AHA Phase I diet during the run-in phase, and subsequently maintained body weight within 1 kg of baseline by having the study dietician regularly adjust the study participants' caloric intake of their AHA Phase I diet if their weight changed by more than 1 kg overall from baseline for two consecutive weeks. Others have demonstrated a lack of effect of exercise training on insulin sensitivity when weight was held constant; however, this study was in a non-CAD population [30]. This strategy is impractical in the real world, where weight loss is advantageous but was the only effective

Fig. 2



Individual changes in insulin sensitivity of usual activity versus exercise training.

mechanism to demonstrate the independent effect of exercise training on the degree of insulin resistance.

We also controlled for the known acute beneficial effect of a single bout of exercise on the degree of insulin resistance. We did this by measuring insulin sensitivity 72 h following the cycle ergometer testing in all participants at baseline and at study termination, with an enforced rest period during those 72 h. The 72-h waiting time following the cycle ergometer test was selected in view of evidence that the beneficial effects of acute exercise on insulin sensitivity dissipated after 48–72 h [8], and that when weight was held constant, exercise training did not improve the degree of insulin resistance when measured 96 h after the last acute exercise session [31].

Despite the fact that our study participants were only minimally deconditioned at baseline (achieved 80% of predicted peak VO_2), it is possible that a greater exercise training intensity level might yield a different result. The exercise training intensity in our study was, nonetheless, consistent with those routinely used in clinical cardiac rehabilitation programs [32] and the training effect (significant 12% increase in VO_2) we observed was similar to that in previous studies examining the impact of exercise training on insulin sensitivity [30,33]. Moreover, two other studies (in patients without CAD) that evaluated the impact of exercise training on insulin sensitivity while controlling for the effects of acute exercise did not demonstrate any improvement in insulin sensitivity in men (16% improvement in VO_2) or women (23% improvement in VO_2), in the absence of weight loss [30]. It is also possible that people with more severe insulin resistance would have responded differently. Our participants, however, had a similar degree of insulin resistance as, and thus were representative of, individuals with CAD [15].

The fact that our study included only five women was unintentional; however, it effectively points to our results being reflective of the male experience only and any comment on whether women would behave in a similar manner requires further study. In addition, we did not measure adiponectin; an adipose tissue-derived hormone that plays an important role in reducing insulin resistance and is independently predictive of less adverse cardiovascular events [34]. Measurement of adiponectin might have allowed greater insight as to whether lack of change in body weight reflected the actual metabolically stable adipose tissue function during our study.

In conclusion, we have demonstrated that 12 weeks of moderate exercise training (compared with usual activity) in the absence of weight loss did not result in any significant change in the degree of insulin resistance in people with CAD without known diabetes mellitus. It might be that the best way to reduce the degree of insulin resistance is through a combination of diet, exercise and weight loss. Furthermore, the previously

documented improvement in the degree of insulin resistance immediately following a bout of exercise does not seem to persist between training sessions if those sessions are scheduled once every three days. Further studies are required to determine whether more vigorous training with greater improvement in exercise performance would result in a reduction in the degree of insulin resistance in the absence of weight loss in individuals with CAD.

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No conflict of interest exists for any author.

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