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ORIGINAL REPORT

CLINICAL BENEFITS OF THE ADDITION OF LOWER EXTREMITY LOW-INTENSITY RESISTANCE MUSCLE TRAINING TO EARLY AEROBIC ENDURANCE TRAINING INTERVENTION IN PATIENTS WITH CORONARY ARTERY DISEASE: A RANDOMIZED CONTROLLED TRIAL*

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Objective: **Muscle resistance training is often combined with aerobic endurance training during rehabilitation of patients with coronary artery disease. However, the clinical effects of additional lower-extremity low-intensity muscle resistance training during early rehabilitation (within the first month after coronary revascularization) in patients with coronary artery disease remain unclear.**

Design: **Prospective randomized controlled trial.**

Subjects: **Sixty patients with coronary artery disease.**

Methods: **Subjects were randomly assigned to early aerobic endurance training ($n=30$) or combined aerobic endurance and resistance muscle training ($n=30$). Subjects performed 18 (standard deviation 2) exercise sessions (at 65% VO_{2peak}, for 40 mins/session). In resistance muscle training, additional low-intensity (12–20 repetition maximum) resistance muscle exercises were performed. The following parameters were evaluated: exercise capacity, body composition, blood lipid profile, glycaemic control, blood endothelial progenitor cell and cytokine content, and muscle performance.**

Results: **A total of 47 patients with coronary artery disease completed the intervention. Total body lean tissue mass tended to increase with greater magnitude ($p=0.07$), and blood high-density lipid cholesterol content increased with significantly greater magnitude in resistance muscle training ($p<0.05$), compared with aerobic endurance training. Maximal exercise capacity, ventilatory threshold, and muscle performance increased, and steady-state exercise respiratory exchange ratio, and adipose tissue mass reduced significantly ($p<0.05$), without differences between groups ($p<0.05$).**

Conclusion: **In early aerobic endurance training intervention in patients with coronary artery disease, additional low-intensity resistance muscle training contributes to a greater increase in blood high-density lipid cholesterol content, and tends to affect lean tissue mass.**

Key words: cardiac rehabilitation; muscle resistance training; coronary artery disease; strength training.

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INTRODUCTION

Aerobic endurance training is an important treatment modality in the rehabilitation of revascularized coronary artery disease (CAD) patients, and has been shown to result in significant increases in peak oxygen uptake (VO_{2peak}) (1). A reduced mortality risk in patients with CAD is, at least in part, related to an improvement in VO_{2peak} (2). Thus, rehabilitation programmes significantly reduce cardiovascular mortality in these patients (3). International guidelines have therefore been published, in which aerobic endurance training is the basic component of exercise intervention, while resistance muscle training should be added (4, 5).

The addition of resistance muscle training to cardiac rehabilitation increases lean tissue mass with greater magnitude (6–8). This may be important, because lean tissue mass is a significant independent predictor of mortality in older individuals (9). However, whether a greater increase in lean tissue mass also contributes to other clinical benefits in patients with CAD remains a topic of intense debate (6–8, 10–16).

For example, some studies report a greater improvement in maximal exercise performance capacity when adding resistance muscle training to aerobic endurance training intervention (11, 13), while others fail to confirm this (7, 12, 15). Muscle strength, as assessed by dynamometry testing, has been evaluated in a few reports, with inconsistent findings (7, 11, 14). Moreover, the impact of additional resistance muscle training during an aerobic endurance training intervention in patients with CAD on submaximal exercise performance capacity,

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blood lipid profile, glycaemic control, endothelial progenitor cell and cytokine content, is not known. These parameters could affect long-term prognosis in patients with CAD and should be improved as effectively as possible.

The effect of the addition of resistance muscle training during early aerobic endurance training intervention (within the first month after coronary revascularization) in patients with CAD has been explored in only a few studies (10, 11, 13), even though many rehabilitation centres initiate exercise intervention within this time-frame. As a result, the clinical benefits and medical safety of the addition of resistance muscle training in the rehabilitation of patients with CAD shortly after coronary revascularization are not well understood.

Therefore, in this study, we examined the effects of additional resistance muscle training during early aerobic endurance training intervention in patients with CAD on: maximal and submaximal exercise performance capacity, body composition, blood lipid profile, glycaemic control, endothelial progenitor cell and cytokine content, and muscle performance. We hypothesized that, by the addition of resistance muscle training during early aerobic endurance training intervention, significantly greater improvements in muscle strength and mass, exercise capacity, and blood parameters would be achieved.

METHODS

Subjects

Sixty patients with CAD participated in this study, of whom 47 completed the entire exercise intervention (see Fig. 1). Exercise intervention was considered to be completed when at least 90% of training sessions were attended. Data from these 47 subjects are presented in this paper (see Table I). Sixty percent of the subjects had an acute myocardial infarction, while 40% were being treated for stable angina pectoris. Subjects were revascularized by percutaneous coronary intervention (66%) or coronary artery bypass graft surgery (34%). None of the subjects developed congestive heart failure within the study follow-up (based on echocardiography). Exclusion criteria on admission were: complicated hospitalization (renal failure, sepsis), delayed/complicated sternum healing, presence of pulmonary or renal co-morbidity, peripheral artery disease, orthopaedic limitations, myocardial ischaemia and/or severe ventricular arrhythmias during baseline exercise testing. Subjects were informed about the nature and risks of the experimental procedures before their written informed consent was obtained. This study was approved by the medical ethics committee of the hospital.

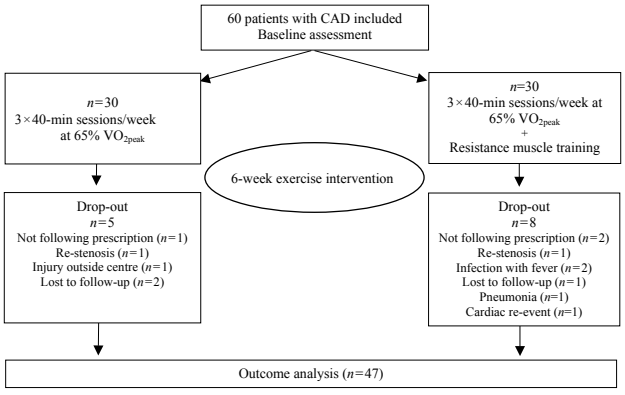

Fig. 1. Study flowchart. CAD: coronary artery disease.

Table I. *Baseline subject characteristics*

	AET	RMT	*p*-value
General features			
Patients, *n*	25	22	
Age, years, mean (SD)	58.9 (7.2)	60.4 (8.9)	0.54
Gender, females, *n*	2	1	
Body mass index, kg/m^2, mean (SD)	27.0 (3.2)	26.6 (3.1)	0.72
Cardiac pathology/intervention			
Referred to hospital with			
Acute myocardial infarction, *n*	15	13	0.59
Angina pectoris, *n*	10	9	
Coronary arteries revascularized with			
CABG, *n*	6	10	0.12
PCI, *n*	19	12	
Medication prescription			
Ca-antagonists, *n*	4	5	0.71
Beta-blockers, *n*	16	18	0.21
Nitrates, *n*	15	13	0.95
ACE inhibitors, *n*	16	14	0.98
Anti-platelets, *n*	25	22	1
Statins, *n*	22	18	0.69
Oral blood glucose lowering, *n*	1	3	0.33
Exercise intervention features			
Supervised training sessions, *n*, mean (SD)	18.0 (2.1)	18.8 (2.3)	0.21
Exercise intervention period, days, mean (SD)	48 (9)	50 (5)	0.47
Interval cardiac event-study entry, days, mean (SD)	18 (8)	18 (5)	0.95

No significant differences were observed between groups ($p > 0.05$). AET: aerobic endurance training; RMT: aerobic endurance and resistance muscle training; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; SD: standard deviation; ACE: angiotensin-converting enzyme; Ca: calcium.

Study design

This was a prospective randomized controlled trial with parallel interventions. *The trial was registered at* www.clinicaltrials.gov *(identifier:* ISRCTN81212339). All subjects participated in an exercise intervention programme, starting within 18 (standard deviation 7) days after coronary revascularization. Subjects were randomly assigned to aerobic endurance training (AET, $n = 30$), or aerobic endurance plus additional resistance muscle training (RMT, $n = 30$), by toss of a coin. The subjects and physical therapists who supervised the subjects were not blinded for treatment allocation. The investigators who performed the measurements were blinded for treatment allocation. The results were not disclosed to the subjects until programme termination. Prior to and after exercise intervention, plasma lipid profile and glycaemic control, blood endothelial progenitor cell and cytokine content, maximal and submaximal exercise performance capacity, body composition, muscle performance, and habitual activity were assessed. Subjects were requested not to perform heavy exercise/work, or execute hospital-based exercise sessions the day before testing. All measurements were taken at the same time of day prior to and after exercise intervention.

Diet and habitual activity during intervention

Subjects were advised by the cardiologist to increase their habitual activity, as suggested by international guidelines (4). No caloric intake restriction intervention was implemented in the studied population.

Primary and secondary outcome parameters

The primary outcome parameter in this study was the peak oxygen uptake. The secondary outcome parameters were lean tissue mass and muscle strength. The exploratory endpoints of interest were blood parameters and submaximal exercise capacity.

Measurements

Habitual activity level. The International Physical Activity Questionnaire (17) was used to assess the time, in minutes, that subjects were engaged in moderate-to-vigorous intensity sports physical activity during the last 2 weeks, unrelated to the intervention.

Blood analysis. Subjects reported at the laboratory at 09.00 h following an overnight fast. After 10 min of rest a venous blood sample was collected. Blood samples were immediately centrifuged at 1000 g and 4ºC for 5 min, after which the plasma was frozen in liquid nitrogen and stored at –80ºC until analysis.

Clinical parameters. Blood samples were analysed for glucose and insulin, total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), plasma triglycerides, C-reactive protein (CRP) (Beckman Synchron LX 20 Analyzer®, Beckman Coulter Inc., Diamond Diagnostics, USA), and glycosylated haemoglobin (HbA1c) (Hi-Auto A1c Analyzer®, Menarini Diagnostics Inc., Florence, Italy). The homeostasis model assessment (HOMA) index was calculated to estimate whole-body insulin sensitivity: [insulin$_{(mU/l)}$ × glucose$_{(mmol/l)}$]/22.5. Plasma interleukin-6 (IL-6) and interleukin-8 (IL-8) was determined BD™ Cytometric Bead Array Human Inflammation Kit® (BD Biosciences, New Jersey, USA).

Endothelial progenitor cells. A 6-colour multi-parameter flow cytometric panel was used to characterize mono nuclear cells (MNCs). Five million MNCs in 50 µl Dulbecco`s Phosphate Buffered Saline (DPBS) (Lonza, Basel, Switserland) were incubated for 30 min at room temperature in the dark with the following antibodies: CD3-FITC, CD15-FITC, CD133-PE (Miltenyi Biotec, Bergisch Gladbach, Germany), CD14-PerCP-Cy5.5, CD34-PE-Cy7, VEGFR-2-APC (R&D Systems, Minneapolis, USA) and CD45-APC-Cy7. Cells were washed in cellWASH™ and resuspended in cellFIX™ (BD Biosciences, New Jersey, Franklin Lakes, USA). The cell suspensions were transferred into TruCount tubes™ (BD Biosciences, New Jersey, Franklin Lakes, USA) to enable absolute cell count enumerations. Tubes were vortexed vigorously before analysis on a FACSCanto™ II with FACSDiva 6.1.2 software (BD Biosciences, New Jersey, Franklin Lakes, USA). At least 1000 CD34+ cells were acquired. Gating strategy was as follows: beads were gated in the CD133-PE/SSC-A dot plot. Within the non-beads population, the total cell population was gated in the FSC-A/SSC-A dot plot excluding dead cells and noise. The FITC channel was used as dump channel to exclude remaining granulocytes in the MNC fraction and lymphocytes based on CD3+CD15+ expression. Within the not-CD3+CD15+ population, CD34+ cells were gated. CD14 antibodies were used to avoid monocyte contamination. The CD34+CD14- cells were back gated using a FSC-A/SSC-A dot plot to further exclude positive cells as result of aspecific binding. Within this back gated CD34+CD14- population, several subpopulations were considered: CD34+CD133+VEGFR2+, CD34+VEGFR2+. The CFU-Hill Liquid Medium Kit (Stemcell Technologies, Vancouver, Canada) was used to culture and quantify colony forming unit – Hill (CFU-Hill) colonies. Five million MNCs/well were plated on a fibronectin-coated 6-well plate (BD Biosciences, New Jersey, Franklin Lakes, USA) in CFU-Hill Liquid Medium. After 2 days, non-adherent cells were collected and re-plated at 1×10^6 and 10^6 cells/well on a fibronectin-coated 24-well plate (BD Biosciences, New Jersey, Franklin Lakes, USA) in CFU-Hill Liquid Medium. Three days later, CFU-Hill colonies were counted.

Peak oxygen uptake and workload capacity. During the exercise test to volitional fatigue an electronically braked cycle (Ergofit GmbH & Co., Pirmasens, Germany) was used (cycling frequency: 70 rpm, starting and incremental load: between 10 and 40 W. These loads were based on subjects' age, gender, body height and weight) (18), with pulmonary gas exchange analysis (Schiller CS200®, Schiller AG, Baar, Switzerland). On the morning of each test day, a gas and volume calibration was performed. During the tests, environmental temperature was kept stable (19–21ºC). Oxygen uptake (VO_2), expiratory volume (VE), and respiratory exchange ratio (RER) were collected breath-by-breath and averaged every 10 s. Using a 12-lead electrocardiogram (ECG) device, heart rate (HR) was monitored. In addition, maximal cycling resistance (W_{peak}) was reported. Ventilatory threshold (VT) was calculated using the V-slope method (19).

Submaximal exercise performance. Subjects performed a cardiopulmonary exercise test on an electronically braked cycle (Ergofit GmbH & Co, Pirmasens, Germany) (cycling frequency: 70 rpm). Subjects were seated on the bike for 3 min to obtain resting data. Subjects were then instructed to cycle against a resistance corresponding to 40% of baseline W_{peak}, for 6 min. Finally, after 6 min of cycling subjects remained seated on the bike for an additional 3 min. During subsequent testing, the resistance load remained at 40% of baseline W_{peak}. VO_2, VE, and RER were collected breath-by-breath and averaged every 10 s (Schiller CS200®, Schiller AG, Baar, Switzerland). Exercise-onset and -offset VO_2 kinetics was calculated algebraically and expressed as a mean response time (MRT) in s (20). Resting VO_2 was the averaged data between the second and third min prior to exercise. Steady-state VO_2, VE, and RER was defined as the averaged value between the fifth and sixth min of cycling.

Calculation of exercise-onset VO_2 kinetics. The difference between rest and steady-state VO_2, multiplied by exercise time (6 mins), is the expected amount of VO_2 for the exercise session. The summed VO_2 is the actual amount of VO_2 during the exercise session. The difference between expected and summed VO_2 is the oxygen deficit. Dividing of the oxygen deficit by the difference between rest and steady-state VO_2 gives MRT. The resultant MRT, multiplied by 60, produced a value expressed in seconds.

Calculation of exercise-offset VO_2 kinetics: the difference between rest and steady-state VO_2, multiplied by exercise time (3 mins), is the expected amount of VO_2 for the recovery session. The summed VO_2 during recovery is the actual amount of VO_2 during the recovery session. The difference between expected and summed VO_2 is the oxygen deficit. Division of the oxygen deficit by the difference between recovery and steady-state VO_2 equals MRT. The resultant MRT, multiplied by 60, gives a value in seconds.

Body composition. Body mass was measured using a calibrated analogue weight scale. Segmental and whole-body adipose tissue mass and lean mass were determined using whole body dual X-ray absorptiometry (Lunar DPXL®, GE Medical Systems Benelux NV, Diegem, Belgium) (21). To determine body composition in different segments, the following areas were selected: from *malleolus medialis tibiae to tibia plateau* (lower leg), from *tibia plateau* to upper border of *crista illiaca* (upper leg), from upper border of *crista illiaca* to upper border of *acromion* (trunk). Arms and head were not included in this analysis.

Muscle performance. Maximal voluntary unilateral knee-extensor strength of the right leg was evaluated using an isokinetic dynamometer (Biodex Medical Systems®, Shirley, New York, USA). After a 5-min standardized warm-up on a cycle ergometer, strength tests were performed in a seated standardized position on a backward-inclined (5º) chair (22).

Maximal isometric torque. Three maximal isometric knee-extensions (5 s) were performed at a knee angle of 45º. The highest isometric extension torque (Nm) of the manually smoothed curves at this knee angle was selected as the maximal isometric torque.

Maximal dynamic torque. Subjects performed 4 maximal consecutive isokinetic knee-extensions at a velocity of 60º/s, 180º/s and 240º/s. Maximal contractions were interspersed by 120-s rest intervals. Knee-extensions were initiated at a joint angle of 90º to an angle of 160º. The highest of 4 isokinetic extension torques (Nm) was selected as maximal dynamic torque.

Maximal strength endurance. Subjects performed 30 maximal dynamic knee-extensions at a velocity of 180º/s. Knee-extensions were initiated at a joint angle of 90º to an angle of 160º. The mean work (J) of

the first 3 contractions was compared with the last 3 contractions and expressed as a percentage decrease (work fatigue).

Intervention

Exercise intervention. Subjects were randomly assigned to aerobic endurance training (AET), or combined aerobic endurance and resistance muscle training (RMT). The aerobic endurance exercises were identical between groups. In RMT, resistance muscle training was added to aerobic endurance training.

Under close supervision all subjects performed 18 (SD 2) exercise sessions within 49 (SD 8) days (on average 3 exercise sessions/week) in the cardiac rehabilitation centre of the hospital at 65% of baseline VO_{2peak}, for 40 mins for each exercise training session (17 mins cycling, 13 mins walking, 10 mins arm cranking) (23). The training intensity was guided by heart rate monitoring (Polar®, Oy, Finland). The target heart rate was kept constant during intervention.

Resistance muscle training for the lower extremities was performed through sitting leg extension and leg press (Technogym UK Ltd, Bracknell, UK). The starting load was determined at the first training session by the Wathen et al. (24) formulae and methodology for 1RM (repetition maximum) estimation. At entry to the exercise intervention, weight during RMT was determined at 65% of 1RM, and performed for 12 repetitions. During intervention subjects performed 2 sets, with 30 s of recovery between sets (25). Repetition number was gradually increased during intervention (from 12 repetitions during weeks 1 and 2, up to 15 repetitions during weeks 3 and 4, and 20 repetitions during weeks 5 and 6). The load of RMT was adapted throughout the intervention according to the perceived effort of the subject. When the load of RMT was too high (i.e. the subject was unable to execute all repetitions, and indicated by Borg scale >16/20), this load was lowered. We selected this patient-directed approach, and high-volume lower-intensity RMT, because we felt that this would maximize the safety of the RMT intervention (through early intervention), and minimize loss of motivation. Subjects noted the resistance used (kg) in their training diary.

Statistical analysis

All calculations were performed using the Statistical Package for the Social Sciences 15.0 (SPSS®). Data are expressed as means and SDs. For non-time-dependent variables (baseline comparison), one-way analysis of variance (ANOVA) or χ^2 analysis was applied. To assess whether differences existed between the application of the AET and RMT training regimen, we used a two-way ANOVA repeated measures with treatment (AET and RMT) and time as the two factors. Data on endothelial progenitor cells (EPCs) were not normally distributed. To compare groups at baseline, and the change in EPCs between groups, a Mann–Whitney U test was used. To analyse the impact of intervention within the total population, a Wilcoxon signed-rank test was used. Bonferroni corrections were applied for repeated comparisons. The relationships of changes between parameters were examined with Pearson correlation coefficients. Statistical significance was set at $p < 0.05$ (two-way).

RESULTS

Subjects

A total of 47 subjects (age 60 years (SD 8), 94% male subjects, body mass index 26.8 kg/m² (SD 3.0)) completed the exercise intervention after random assignment to either AET or RMT within 18 days (SD 7) after coronary revascularization (see Table I). Five subjects dropped out of AET, and 8 out of RMT ($p = 0.35$ between groups, see Fig. 1). No orthopaedic injuries occurred within the rehabilitation facility. In AET and RMT, 18.0 (SD 2.1) and 18.8 (SD 2.3) exercise sessions, respectively, were attended ($p = 0.49$ between groups). In RMT, training load did not change during leg press (from 91.1 kg (SD 24.8) at entry to 92.6 kg (SD25.6) at 6 weeks, $p = 0.34$), but decreased significantly during sitting leg extension (from 12.5 kg (SD 3.7) at entry to 10.7 kg (SD 3.4) at 6 weeks, $p < 0.01$).

Habitual activity

Baseline habitual activity was not different between groups ($p = 0.68$). Habitual activity, unrelated to exercise intervention, increased during follow-up (from 131 mins (SD 181) at entry to 195 mins (SD 187) at 6 weeks, $p < 0.05$), without differences between groups (with 64 mins (SD 145) in AET, and 116 mins (SD 250) in RMT; $p = 0.50$).

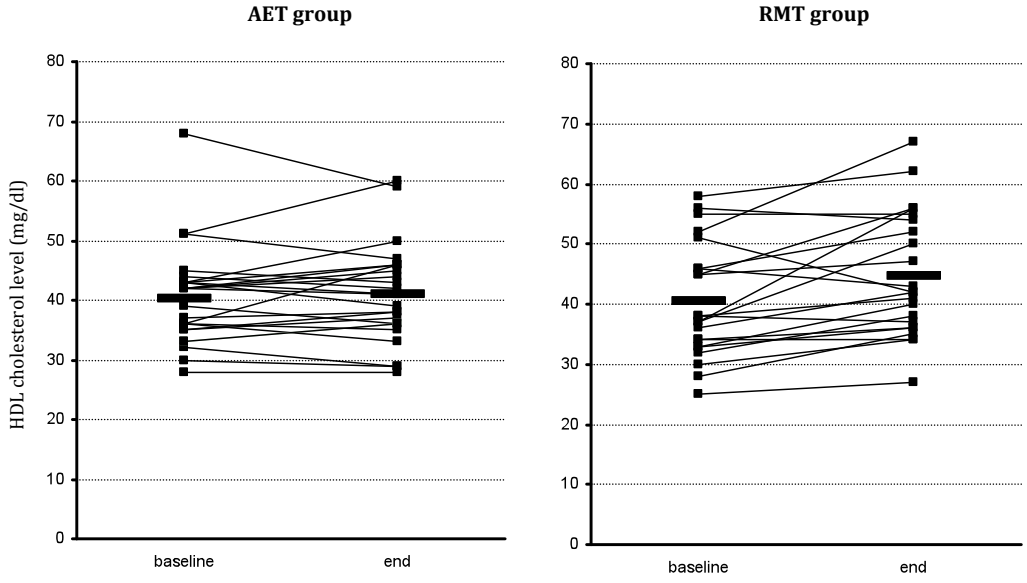

Fig. 2. Change in blood high-density lipoprotein cholesterol (HDL-c) level. AET: aerobic endurance training; RMT: aerobic endurance and resistance muscle training.

Body composition

As result of exercise intervention, adipose tissue mass decreased significantly ($p < 0.05$), without differences between groups ($p = 0.68$) (see Table II). Total body lean tissue mass tended to increase with greater magnitude as result of RMT (with 0.8 kg (SD 1.1)) vs AET (with 0.0 kg (SD 1.4)) ($p = 0.07$).

Blood analyses

Baseline blood insulin level and HOMA index were significantly different between groups ($p < 0.05$) (see Table II). As result of exercise intervention, blood $HbA1_c$ level tended to decrease ($p = 0.06$), but without differences between groups ($p = 0.20$). Plasma HDL-c content increased with significantly greater magnitude as result of RMT (with 4.5 mg/dl (SD 6.4)) vs AET (with 0.6 mg/dl (SD4.3)) ($p < 0.05$, see Fig. 2). Changes in plasma HDL-c content correlated significantly with changes in VO_{2peak} ($r = 0.32$, $p < 0.05$), and plasma CRP level ($r = –0.46$, $p < 0.05$).

Maximal workload and oxygen uptake capacity

As result of exercise intervention, VO_{2peak}, W_{peak}, HR_{peak}, and ventilatory threshold increased significantly ($p < 0.05$) (see Table II), while RER_{peak} decreased significantly ($p < 0.05$), without differences between groups ($p < 0.05$).

Table II. *Impact of exercise intervention (*n = *47)*

	Aerobic endurance training		Aerobic endurance and resistance muscle training		*p-value*	
	Baseline Mean (SD)	End Mean (SD)	Baseline Mean (SD)	End Mean (SD)	Total group	Group time*
Blood parameters						
Glucose, mg/dl	102 (7)	102 (7)	105 (21)	101 (12)	0.32	0.34
Glycosylated haemoglobin, %	5.6 (0.3)	5.6 (0.2)	5.6 (0.7)	5.5 (0.5)	0.06	0.20
Insulin, mU/l	9.6 (4.0)*	10.0 (3.6)	6.7 (2.1)*	7.5 (3.3)	0.30	0.76
HOMA index	2.5 (1.1)*	2.6 (0.9)	1.8 (0.8)*	1.9 (0.9)	0.54	0.95
Total cholesterol, mg/dl	136 (24)	143 (35)	136 (34)	139 (27)	0.13	0.64
HDL cholesterol, mg/dl	40 (8)	41 (8)	40 (10)	45 (10)	<0.01	<0.05
LDL cholesterol, mg/dl	88 (19)	93 (27)	86 (24)	89 (23)	0.12	0.64
Triglycerides, mg/dl	119 (39)	117 (46)	104 (35)	101 (39)	0.67	0.89
C-reactive protein, mg/dl	0.5 (0.4)	0.4 (0.3)	0.5 (0.6)	0.6 (0.6)	0.98	0.75
Interleukin-6, pg/ml	3.2 (1.6)	3.2 (2.3)	3.2 (1.4)	2.5 (0.9)	0.33	0.33
Interleukin-8, pg/ml	4.0 (1.8)	4.1 (1.6)	4.1 (1.6)	4.8 (1.8)	0.12	0.27
Endothelial progenitor cell colonies, $\times 10^6$ cells	8.1 (5.3)	8.9 (8.8)	5.7 (5.9)	7.8 (7.1)	0.28	0.63
CD34+VEGFR2+, number cells/ml	94 (169)	129 (302)	37 (78)	33 (65)	0.61	0.80
CD34+CD133+VEGFR2+, number cells/ml	19 (44)	19 (46)	5 (7)	5 (7)	0.85	0.89
Body composition						
Adipose tissue mass – trunk, kg	9.5 (3.4)	8.8 (3.1)	8.4 (3.2)	7.6 (3.0)	<0.01	0.86
Adipose tissue mass – upper legs, kg	8.8 (2.8)	8.5 (2.7)	7.5 (2.3)	7.4 (2.5)	<0.05	0.43
Adipose tissue mass – lower legs, kg	1.1 (0.4)	1.1 (0.4)	1.0 (0.4)	0.9 (0.4)	0.43	0.43
Adipose tissue mass – total body, kg	19.4 (6.3)	18.4 (6.0)	16.8 (5.3)	16.0 (5.3)	<0.01	0.68
Lean tissue mass – trunk, kg	17.5 (2.0)	17.5 (2.0)	18.2 (2.6)	18.6 (2.5)	0.20	0.12
Lean tissue mass – upper legs, kg	20.6 (3.0)	20.6 (3.1)	20.7 (3.2)	21.1 (3.4)	0.07	0.25
Lean tissue mass – lower legs, kg	4.6 (0.8)	4.6 (0.8)	4.7 (0.9)	4.7 (1.0)	0.88	0.23
Lean tissue mass – total body, kg	42.7 (5.6)	42.7 (5.6)	43.6 (6.5)	44.4 (6.5)	0.07	0.07
Maximal exercise capacity						
VO_{2peak}, ml/min	1,836 (480)	2,089 (504)	1,719 (378)	2,036 (502)	<0.01	0.56
W_{peak}	157 (41)	184 (42)	144 (27)	176 (41)	<0.01	0.45
HR_{peak}, beats/min	130 (15)	140 (16)	123 (20)	127 (16)	<0.05	0.27
RER_{peak}	1.12 (0.09)	1.10 (0.07)	1.10 (0.06)	1.07 (0.05)	<0.01	0.53
Ventilatory threshold, ml/min	1,116 (348)	1,375 (382)	1,002 (267)	1,241 (364)	<0.01	0.84
Muscle performance						
Isometric 45 degrees: peak torque, Nm	157 (38)	167 (35)	164 (25)	173 (41)	<0.05	0.95
Isokinetic 60 degrees/s: peak torque, Nm	156 (47)	166 (47)	163 (37)	175 (37)	<0.01	0.85
Isokinetic 180 degrees/s: peak torque, Nm	110 (29)	119 (29)	116 (21)	126 (22)	<0.01	0.75
Isokinetic 240 degrees/s: peak torque, Nm	101 (22)	112 (22)	106 (21)	115 (21)	<0.01	0.57
Strength endurance: fatigue index	41.5 (7.8)	40.4 (6.7)	43.1 (7.6)	41.3 (7.3)	0.23	0.74
Submaximal exercise capacity						
Steady-state VO_2, l/min	1.04 (0.21)	1.09 (0.26)	1.00 (0.19)	1.05 (0.22)	0.07	0.82
Steady-state RER	0.94 (0.06)	0.91 (0.08)	0.92 (0.05)	0.87 (0.04)	<0.01	0.36
Steady-state VE, l/min	27 (4)	28 (6)	26 (5)	26 (5)	0.91	0.37
Exercise-onset VO_2 kinetics, s	58 (13)	55 (13)	66 (10)	58 (16)	0.08	0.41
Exercise-offset VO_2 kinetics, s	57 (17)	53 (17)	65 (9)	62 (8)	0.25	0.87

*Significantly different between groups at baseline ($p < 0.05$).

HOMA: homeostasis model assessment; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VO_2: peak oxygen uptake; W: cycling power output; HR: heart rate; RER: respiratory exchange ratio; VE: expiratory volume; SD: standard deviation.

Muscle performance

As result of exercise intervention, maximal dynamic knee extension torques increased significantly ($p < 0.05$), as well as maximal isometric knee extension torque ($p < 0.05$), without differences between groups ($p < 0.05$) (see Table II).

Submaximal exercise capacity

As result of exercise intervention, steady-state VO_2 tended to increase ($p = 0.07$) and steady-state RER decreased significantly ($p < 0.01$), while exercise-onset VO_2 kinetics tended to accelerate ($p = 0.08$), without differences between groups ($p = 0.41$) (see Table II).

DISCUSSION

This study examined the effects of additional resistance muscle training during early aerobic endurance training intervention in patients with CAD on a broad range of important health parameters. The findings were as follows: (*i*) a significantly greater increase in plasma HDL-c was found when following combined aerobic endurance and RMT, compared with AET; (*ii*) despite the addition of resistance muscle training during an aerobic endurance training intervention, and a tendency to a greater increase in lean tissue mass, no further clinical benefits were observed.

Aerobic endurance training intervention is expected to increase plasma HDL-c content (26). However, the impact of additional resistance muscle training on the change in plasma HDL-c content during aerobic endurance training intervention remains speculative (27). In patients with CAD, to our knowledge no single study examined the impact of AET vs RMT on plasma HDL-c level. It might be hypothesized that a prolonged exercise session in the RMT group contributes to a greater increase in plasma HDL-c (26). However, the resistance muscle exercises prolonged the exercise session by only approximately 5–8 mins, including the recovery periods. It seems difficult to attribute a 4 mg/dl greater increase in plasma HDL-c level to an exercise session prolongation of 5–8 mins (26). Further study is thus warranted to confirm our findings. Some studies suggest that changes in skeletal muscle fibre type composition during exercise intervention are instrumental to, at least in part, changes in plasma HDL-c content as result of exercise intervention (28). Significant positive correlations have been described between the percentage of type 1 skeletal muscle fibre and plasma HDL-c content (28). Nonetheless, changes in skeletal muscle fibre type composition are not measurable in exercise intervention for up to 2 months in cardiovascular disease risk patients (29). Moreover, even though we did not obtain skeletal muscle biopsies, our results did not indicate greater changes in oxidative capacity as result of RMT (based on ventilatory threshold, and submaximal exercise test), as expected from a greater increase in percentage of type 1 skeletal muscle fibre. Thus, the origin of the greater increase in plasma HDL-c as result of RMT, compared with AET, is unknown. A greater increase in plasma HDL-c is important for patients with CAD, because this prevents angiographic progression of coronary stenosis (30).

In contrast to our expectations, the addition of resistance muscle training during an aerobic endurance training intervention did not contribute to greater clinical benefits, despite a tendency to a greater increase in lean tissue mass. There are several possible reasons for the lack of a greater clinical effect: presence of many clinical benefits that resulted from AET, short intervention programme duration, too few different types of resistance muscle exercises, and/or too low exercise intensity during resistance muscle training. As result of AET, many clinical benefits were obtained, including an improvement in maximal and submaximal exercise performance, muscle strength, and decrease in adipose tissue mass. Such changes are instrumental to improve long-term patient prognosis. However, because of the great clinical effectiveness of AET, the clinical benefits from the addition of resistance muscle training might have been camouflaged. It might be argued that our exercise intervention duration was too short. However, in clinical practice patients with CAD most often exercise for such short duration because of financial restrictions and/or lack of motivation/drop-out (1, 31). Although the odds of finding significantly greater clinical benefits as result of RMT vs AET during long-term exercise intervention (> 12 weeks) might be greater as opposed to shorter exercise interventions, our study assessed the impact of RMT vs AET as often performed in current clinical practice. We hypothesize that in order to increase the clinical benefits of resistance muscle training in patients with CAD, a greater number of sets and/or types of resistance muscle exercises should be applied. Marzolini et al. (7) have shown that, with increasing number of resistance muscle exercise sets, lean tissue mass increased by a greater magnitude as result of an exercise regimen. However, the choice of proper resistance muscle training intensity and volume to achieve maximal muscle strength gain remains a topic of intense debate (32). It follows that optimization of resistance muscle exercise modalities remains warranted in current cardiac rehabilitation. Finally, it might be argued that the intensity of resistance muscle training was low, even though clinical guidelines propose resistance muscle training with lower intensity (5). Our results do, however, indicate that the application of resistance muscle training, as well as dynamometry testing, in early rehabilitation of low-risk patients with CAD is medically safe: drop-out for medical reasons was equal between groups, and no orthopaedic injuries occurred in the RMT group. Previous studies examining the impact of the addition of resistance muscle training in early cardiac rehabilitation reported similar findings (10, 11, 13).

The results of the present study both agree and disagree with previous literature examining the impact of the addition of resistance muscle training during early aerobic endurance training intervention in patients with CAD (10, 11, 13). Hung et al. (10) found a similar increase in VO_{2peak} and muscle strength when applying RMT vs AET. Stewart et al. (13) found a greater increase in VO_{2peak} and muscle strength when applying RMT vs AET. Finally, Gayda et al. (11) found no change in body composition and muscle strength as result of RMT or AET, but a greater increase in VO_{2peak} as result of RMT vs AET. The applied resistance muscle training modalities (repetition number,

type of exercise, number of sets) were heterogeneous between studies (10, 11, 13). It therefore remains difficult to formulate a proper conclusion about the impact of RMT vs AET in the early rehabilitation of patients with CAD. In congestive heart failure patients, the addition of resistance muscle training to an aerobic endurance training intervention does not seem to augment the increase in VO_{2peak} and muscle strength in some studies (33, 34), while it does in others (35).

The subjects' higher baseline cardiopulmonary exercise capacity compared with other studies (36) could be considered a limitation of the study. Moreover, this study lacked an *a priori* statistical power calculation, even though study sample sizes were considerably smaller in previous studies (10, 11, 13).

In conclusion, in early aerobic endurance training intervention in patients with CAD, the addition of low-intensity resistance muscle training is medically safe and contributes to a greater improvement in blood HDL-c content, and a tendency to a greater increase in lean tissue mass. Further study is required to confirm our findings on changes in blood lipid profile.

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