ORIGINAL ARTICLE

R. Steiner · K. Meyer · K. Lippuner · J.-P. Schmid
H. Saner · H. Hoppeler

Eccentric endurance training in subjects with coronary artery disease: a novel exercise paradigm in cardiac rehabilitation?

Abstract This study evaluated the effects of 8 weeks of eccentric endurance training (EET) in male subjects (age range 42–66 years) with coronary artery disease (CAD). EET was compared to concentric endurance training (CET) carried out at the same metabolic exercise intensity, three times per week for half an hour. CET ($n=6$) was done on a conventional cycle ergometer and EET ($n=6$) on a custom-built motor-driven ergometer. During the first 5 weeks of the training program the metabolic load was progressively increased to 60% of peak oxygen uptake in both groups. At this metabolic load, mechanical work rate achieved was 97 (8) W [mean (SE)] for CET and 338 (34) W for EET, respectively. Leg muscle mass was determined by dual-energy X-ray absorptiometry, quadriceps strength with an isokinetic dynamometer and muscle fibre composition of the vastus lateralis muscle with morphometry. The leg muscle mass increased significantly in both groups by some 3%. Strength parameters of knee extensors improved in EET only. Significant changes of $+11$ (4.9)%, $+15$ (3.2)% and $+9$ (2.5)% were reached for peak isometric torque and peak concentric torques at $60°\ s^{-1}$ and $120°\ s^{-1}$, respectively. Fibre size increased significantly by 19% in CET only. In conclusion, the present investigation showed that EET is feasible in middle-aged CAD patients and has functional advantages over CET by increasing muscle strength. Muscle mass increased similarly in both groups whereas muscle structural composition was differently affected by the respective training protocols. Potential limitations of this study are the cautiously chosen conditioning protocol and the restricted number of subjects.

Keywords Metabolic load · Work rate · Strength · Muscle mass · Muscle ultrastructure

R. Steiner · K. Meyer · J.-P. Schmid · H. Saner
Cardiovascular Prevention and Rehabilitation,
Department of Cardiology, University Hospital,
3010 Bern, Switzerland

K. Lippuner
Osteoporosis Unit, University Hospital,
3010 Bern, Switzerland

H. Hoppeler (✉)
Department of Anatomy, University of Bern,
Bühlstrasse 26, 3009 Bern, Switzerland
E-mail: hoppeler@ana.unibe.ch
Tel.: +41-31-6314637
Fax: +41-31-6313807

Introduction

There is abundant evidence that physical activity delays the progression of coronary artery disease (CAD) by multiple biological mechanisms and may even lead to its regression (Shephard and Balady 1999; Fletcher et al. 2001). Traditionally, moderately intense aerobic exercise is known to mediate these health benefits (Pate et al. 1995) and has thus become a cornerstone in cardiac rehabilitation programs (Shephard and Balady 1999; Fletcher et al. 2001). Additionally, the importance of muscle strength has received attention in order to maintain a functional autonomy in the elderly (Frontera et al. 1988; Shephard and Balady 1999; Fletcher et al. 2001). In healthy subjects, muscle strength is classically trained with resistance training programs. Until recently, patients with cardiac diseases were discouraged from strength training because of the increase in cardiac afterload that is thought to occur during weightlifting exercises, particularly when strength training is carried out with resistances close to individual maximal loads (MacDougall et al. 1992; Shephard and Balady 1999). But it has been shown that there are no adverse effects of strength training in CAD when resistance exercise is carried out with a high number of repetitions and only moderate loads (Kelemen et al. 1986). Furthermore, an additional benefit for aerobic performance capacity, estimated as time to exhaustion, has been shown for this type of activity under certain conditions (Kelemen et al. 1986; McCartney et al. 1991).

Eccentric muscle work is an essential part of our daily activities (Dickinson et al. 2000; Lindstedt et al. 2001). We use eccentric muscle work during normal walking, and in particular when walking downhill, to convert potential energy into heat. Eccentric muscle action is characterised by a low metabolic demand for a high power output. This was convincingly demonstrated in classical experiments involving concentric and simultaneous eccentric cycling on mechanically connected ergometers by Abbott et al. (1952). When carried out by unaccustomed subjects, eccentric muscle work can lead to substantial structural muscle damage followed by delayed onset muscle soreness (Fridén et al. 1983a). Repetitive bouts of eccentric work lead to adaptations making muscle more resistant to eccentric stress (Clarkson and Tremblay 1988). With chronic eccentric training muscle becomes essentially refractory to damage induced by eccentric contractions (Fridén et al. 1983b; LaStayo et al. 1999, 2000).

For development of muscle strength and to achieve muscle hypertrophy, combined concentric and eccentric muscle activation is recommended for resistance training programs at all fitness levels, from novice to advanced (Kraemer et al. 2002). Eccentric resistance training (Komi and Buskirk 1972; Colliander and Tesch 1990; Hortobágyi et al. 1996) and also eccentric endurance training (EET) on motor-driven ergometers (Fridén et al. 1983b; LaStayo et al. 2000) have been shown to improve muscle strength more than concentric training alone. Despite the high mechanical load on muscle tissue in eccentric exercise, the blood pressure response is similar to that of concentric exercise, provided that Valsalva manoeuvres are avoided (MacDougall et al. 1992). We reasoned that because of the high mechanical load that can be achieved during eccentric exercise this mode of training could be an option to achieve gains in muscular strength and eventually muscle mass at low cardiovascular demands.

We have previously shown that EET results in a similar haemodynamic response to concentric endurance training (CET) when carried out at the same metabolic workload. This, despite a several-fold higher mechanical work rate with EET than with CET. From this it was concluded that EET can be considered to be a safe training paradigm in this patient population (Meyer et al. 2003). The aim of the present study was to explore the structural and functional adaptation of EET in these CAD patients. Specifically, we hypothesised that EET provides a larger gain in muscle strength, muscle mass and muscle fibre size than CET when carried out at the same metabolic demand.

Methods

Subjects and conditioning program

Thirteen male patients with documented stable CAD who were participating in the outpatient cardiac rehabilitation program at University Hospital Bern were included in the study. The study protocol was approved by the local Ethics Committee on Human Research. Patients were informed about the study at the entry of the rehabilitation program and were clinically examined. After having given written informed consent they were randomly assigned to the CET or EET group. The randomisation procedure on the small number of subjects led to a considerable variability of some of the baseline characteristics. One patient in the EET group did not complete the entire study period. As a consequence there are some minor differences for the population means reported in a previous study on the same patient groups (Meyer et al. 2003). The anthropometrical characteristics of the remaining 12 subjects, as well as the medication they received, are presented in Table 1. Medication was not changed over the study period.

All tests reported below were performed before and repeated after the 8-week training period. EET or CET was integrated into a standard comprehensive rehabilitation program such that light callisthenics, stretching and relaxation procedures were identical for all subjects. Aerobic training was carried out by the CET group on an Ergometrics standard cycle ergometer (Ergoline, Bitz, Germany) whereas the EET group trained on a custom-built motor-driven eccentric ergometer (Meyer et al. 2003). The entire training period lasted 8 weeks; CET and EET were carried out three times per week for half an hour. Training intensity was increased gradually over the first 5 weeks of the rehabilitation program to a level corresponding to 60% of the peak oxygen uptake ($\dot{V}O_{2peak}$) achieved in the ramp test performed at the entry into the rehabilitation program. At this time invasive determination of central haemodynamic variables was carried out (Meyer et al. 2003). Because of ethical considerations we were not allowed to increase work rate after the catheter measurements. Therefore, exercise intensity was kept constant for the last 3 weeks of the program. At all times during the entire rehabilitation program we strived to have the CET and EET groups work at the same relative metabolic work intensity, as judged from their individual heart rates.

Rating of perceived exertion

Subjects were asked to report a rating of perceived exertion (RPE) every 5 min during each training session by using the Borg RPE-scale (6–20 rating) (Borg 1982). Separate ratings of the

Table 1 Baseline characteristics of patients by training groups. Values are means (SE), except disease categories* and medications, where the values are frequency counts. *BMI* Body mass index, $\dot{V}O_{2peak}$ peak oxygen uptake, *MI* myocardial infarction, *CABG* coronary artery bypass grafting, *PTCA* percutaneous coronary angioplasty, *LVEF* left ventricular ejection fraction, *ASA* acetylsalicylic acid, *ACE* angiotensin-converting enzyme, AT_1 angiotensin II type 1 receptor

	Concentric (n = 6)	Eccentric (n = 6)
Age (years)	56 (3.5)	55 (2.6)
Body height (cm)	169 (0.8)	173 (3.9)
Body mass (kg)	77 (5.7)	83 (5.1)
BMI (kg m^{-2})	27.1 (1.9)	27.6 (1.3)
Body fat (%)	25.4 (2.9)	21.1 (2.1)
$\dot{V}O_{2peak}$ (ml kg^{-1} min^{-1})	28.0 (2.6)	28.7 (2.1)
MI*	5	5
CABG*	2	1
PTCA*	3	5
LVEF (%)	65 (3)	56 (3)
Medications		
ASA	6	6
Beta blockers	4	4
ACE inhibitors	3	3
AT$_1$ antagonists	1	0
Ca channel blockers	1	1
Statins	5	5
Nitrates	1	0
Diuretics	1	0

cardiorespiratory effort (dyspnoea) and of the specific leg exertion were requested.

Anthropometry and body composition

Body mass and height were obtained during the clinical examination. Body mass index (BMI) was calculated by dividing mass by height squared. Body composition was determined by fan-beam dual X-ray absorptiometry (DXA) on a QDR-4500A (Hologic Inc., Bedford, USA) before and after the training period. The DXA device measured lean mass, fat mass and bone mineral content of the whole body. Additionally, lower limbs were separated from trunk analysis by the means of the integrated software. Lower limb muscle mass was calculated from the measured fat-free mass according to an equation given by Shih et al. (2000). Values of the left and right limb were averaged for analysis.

Muscle strength

Muscle strength of the knee extensors was measured as peak torque on an isokinetic Cybex Norm dynamometer (Lumex, Ronkonkoma, USA). Before each test, subjects were familiarised with the testing device and the test procedures. Isometric peak torque was measured at a knee angle of 60°. Dynamic measurements were performed over a range of motion from 15° to 100° knee flexion (Kraemer and Fry 1995). Isokinetic concentric peak torque was measured at angular velocities of $+60°$ s^{-1} and $+120°$ s^{-1}, isokinetic eccentric peak torque was measured at negative angular velocities of $-20°$ s^{-1} and $-60°$ s^{-1}. Values of the left and right limb were averaged for analysis.

Muscle biopsies and morphometric analysis

Biopsies were to be taken before and after the training period, so heavy exercise was avoided 48 h prior to the biopsies. A sample of the right vastus lateralis muscle at mid-thigh level was obtained under local anaesthesia using the Bergström needle (Bergström 1962). Each sample was divided into two parts; one half was immediately frozen in isopentane-cooled liquid nitrogen and stored for later analysis. The other half was fixed in buffered glutaraldehyde for electron microscopy (Hoppeler et al. 1985). The ultra-structural analysis of the muscle fibres was performed using standard stereological methods (Weibel 1979). Ultra-thin transverse or slightly oblique sections were analysed by electron microscopy for capillary number and fibre cross-sectional area at a final magnification of approximately x1,400. The volume density of mitochondria, myofibrils and lipid droplets were estimated at a final magnification of approximately x24,000.

Choice of subjects and statistics

Because eccentric exercise training is not an established rehabilitation procedure in CAD patients we had to comply with requirements of the Ethical Committee which resulted in a difficulty of recruiting subjects for this study. Despite the restricted number of subjects, simple statistical analysis was performed. Two-tailed paired and unpaired Student's t-tests were applied to analyse intragroup changes from pre- to post-training and intergroup differences, respectively. The level of statistical significance was set at $P < 0.05$.

Results

Over the entire training period we did not observe any complications in the cardiovascular or musculoskeletal systems. The final mechanical work rate achieved was close to 60% of $\dot{V}O_{2peak}$, corresponding to 76% of the individual maximal heart rate, and was 97 (8) W for CET and 338 (34) W for EET, respectively ($P < 0.001$).

Perceived exertion

In none of the 8 weeks of training did the average RPE score during the sessions exceed 11 ('fairly light') in either the CET or the EET group. There was a tendency in CET to perceive cardiorespiratory effort slightly higher than leg effort whereas in the EET group the leg rating was generally higher, particularly during the first 5 weeks when exercise intensity was ramped up.

Body composition and leg muscle mass

BMI did not change over the training period in either of the groups. DXA showed an unchanged body fat content for EET [21.1 (2.1)% before versus 21.6 (1.7)% after training], while a small but statistically significant decrease was noted in CET [25.4 (2.9)% to 24.4 (2.9)%; $P < 0.001$]. Leg muscle mass increased significantly in both groups, with a similar magnitude. The gains were 191 (37) g per leg ($+2.7\%$; $P < 0.01$) for CET and 259 (93) g per leg ($+3.6\%$; $P < 0.05$) for EET, respectively. The increase between the groups was not statistically different.

Muscle strength

Changes in muscle strength for different testing modes are compiled in Fig. 1a for CET and Fig. 1b for EET.

For the CET group, peak isometric and peak isokinetic torques at all measured velocities did not change between pre- and post-training tests. In the EET group, isometric peak torque [$+11$ (4.9)%; $P < 0.05$] and isokinetic concentric peak torque at slower [$+15$ (3.2)%; $P < 0.01$] and faster velocity [$+9$ (2.5)%; $P < 0.05$] was increased, whereas the average increase of isokinetic eccentric peak torque for both velocities ($+6\%$) was not statistically significant.

Muscle morphometry

Muscle morphological characteristics are reported in Table 2. Qualitatively, normal muscle ultrastructure was preserved after training in both groups and no morphological abnormalities were observed during morphometric analysis of the tissue.

Muscle fibre cross-sectional area increased only in CET ($+19\%$; $P < 0.05$). Capillary supply, expressed as capillaries per muscle fibre, remained unchanged in both groups. The volume density of total mitochondria was
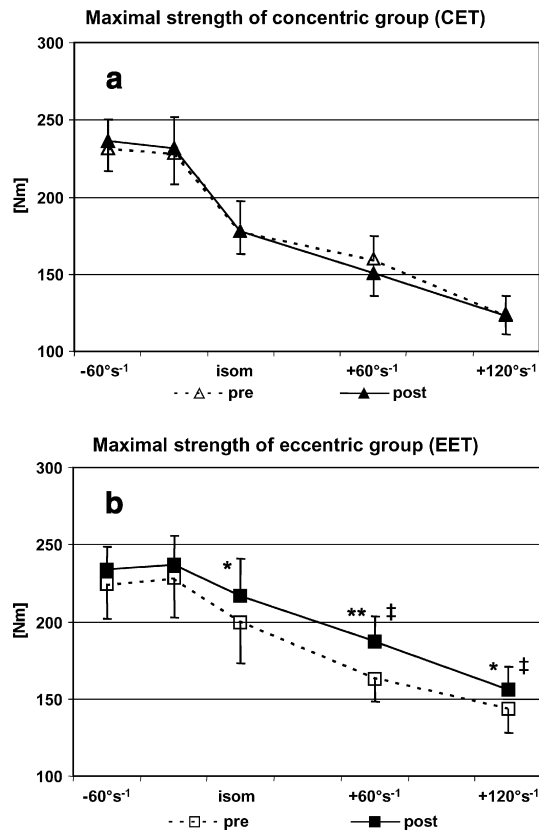
Fig. 1 a Maximal voluntary isokinetic peak torque of knee extensor muscles at different angular velocities before (*pre*) and after (*post*) 8 weeks of training on a concentric cycle ergometer. Values are means (SE). No statistically significant differences from pre- to post-test ($P=$ns). **b** Maximal voluntary isokinetic peak torque of knee extensor muscles at different angular velocities before (pre) and after (post) 8 weeks of training on an eccentric cycle ergometer. Values are means (SE). Significant (*$P<0.05$, **$P<0.01$) difference from pre-test; [‡]significantly ($P<0.05$) more change than in the concentric group

sarcoplasmic components (sarcoplasm, sarcoplasmic reticulum, lipid droplets and nuclei) make up the reference space, the muscle fibre volume. The volume density of lipids (approximately 0.5% of muscle fibre volume; not reported separately) was not significantly affected by either of the training interventions.

Discussion

The main finding of this study is a functional gain, i.e. improved muscular strength with EET compared to CET. However, this functional gain is not the consequence of the expected structural modifications. Leg muscle mass increased similarly in both groups, while muscle fibre size remained unchanged in EET. We therefore have to assume that this functional improvement is likely due to neuronal coordinative factors. As a limitation of this study we see the short period of 5 weeks available for ramping up the training intensity and thus the relatively low and constant workload that the subjects experienced over the last 3 weeks of training intervention. These constraints were required by ethical considerations of using a novel training paradigm for the first time in a CAD patient population.

Most studies on eccentric muscle work used few contractions at sub-maximal to maximal loads on isokinetic dynamometers (Colliander and Tesch 1990; Higbie et al. 1996; Hortobágyi et al. 1996). These studies therefore belong to the literature dealing with classical strength-type training paradigms. There are only a few studies with conditioning protocols comparable to the present study whereby eccentric load is applied continuously over the cranks of a cycle ergometer for time periods of 30 min per training session (Fridén et al. 1983b; LaStayo et al. 1999, 2000). However, these studies were realised with young healthy subjects and not with patients. To our knowledge EET has not previously been used as a part of a cardiac rehabilitation program. An important purpose of the present investigation, therefore, was to examine the feasibility of EET in middle-aged patients with CAD and to compare its effects on muscle mass, strength and muscle fibre

also unchanged in both groups, despite an increased volume density of subsarcolemmal mitochondria in CET and a decrease of subsarcolemmal as well as interfibrillar mitochondria in the EET group. These mitochondrial changes are reflected in opposite changes of the myofibrils, which together with the remaining

Table 2 Muscle structure before and after 8 weeks of concentric (CET, $n=6$) and eccentric (EET, $n=6$) cycle ergometer training, respectively. Values are means (SE). Mitochondria (central, subsarcolemmal, total), myofibrils and remaining components (incl. lipid droplets) are measured and expressed as percentage of volume

	Fibre area (μm^2)	Capillaries per fibre (n)	Mitochondria (%)			Myofibrils (%)	Remaining components (%)
			Central (%)	Subsarcolemmal (%)	Total (%)		
CET							
Pre	3524 (216)	1.87 (0.2)	4.41 (0.5)	0.82 (0.2)	5.23 (0.7)	81.3 (1.0)	13.5 (0.7)
Post	4209 (417)*	2.04 (0.2)	4.64 (0.4)	1.16 (0.2)*	5.97 (0.5)	77.5 (0.9)*	16.5 (0.7)*
EET							
Pre	4523 (460)	2.14 (0.2)	4.39 (0.5)	0.89 (0.2)	5.27 (0.6)	79.6 (1.1)	15.1 (0.9)
Post	4402 (282)	2.07 (0.2)	3.67 (0.2)	0.53 (0.1)	4.20 (0.3)	81.8 (0.7)*	14.1 (0.7)*

*Intragroup difference $P<0.05$

ultrastructure to those obtained with concentric exercise carried out for the same time and at the same metabolic load. We could demonstrate that EET is feasible and well tolerated, as previously shown in younger healthy subjects (Fridén et al. 1983b; LaStayo et al. 1999, 2000). Despite a work rate almost 3.5-times higher in EET than in CET the RPEs were similarly low in both populations. The tendency for a slightly greater perceived effort of the legs with EET, observed in particular during ramping up the intensity (LaStayo et al. 1999), has previously been observed (Fridén et al. 1983b; LaStayo et al. 2000). The perception of muscle soreness was queried qualitatively. Some patients reported discreet muscle soreness for a maximum of 24 h after ramping. However, none of the trainings had to be cancelled due to muscle soreness.

We found no measurable effect of our training programs on BMI. With regard to the moderate exercise intensity in both groups, the short conditioning period and the absence of a nutritional intervention, this result is not surprising and similar to other exercise interventions of similar duration (Kelemen et al. 1986; Colliander and Tesch 1990). We consider the small change in body composition revealed by DXA in CET to be of negligible clinical relevance.

There is currently no data available for the influence of EET on leg muscle mass. We found a similar increase of leg muscle mass in both groups. It has been shown that concentric exercise training, even when carried out at higher workloads, does not lead to an increase in muscle cross-sectional area in previously untrained male subjects (Hoppeler et al. 1985). The fact that leg muscle mass is increased in both populations may be related to the relative state of deconditioning as a consequence of the primary pathology of our subjects. When eccentric exercise is used in a resistance training setting, muscle mass increases similarly (Jones and Rutherford 1987; Colliander and Tesch 1990) or more (Higbie et al. 1996) than when concentric resistance training is carried out. An additional consideration with regard to muscle hypertrophy is related to the medication taking by our patients. In animal experiments ß-adrenergic receptor, i.e. the ß2-receptor, plays an important role for skeletal muscle hypertrophy (Hinkle et al. 2002). The importance of angiotensin II in acting on the type 1 (AT_1) receptor for muscle growth is judged ambiguously. In animal experiments angiotensin-converting enzyme inhibitors and AT_1 antagonists both inhibit training-induced muscle hypertrophy (Gordon et al. 2001). On the other hand, in animal experiments angiotensin II can induce skeletal muscle wasting by enhancing protein degradation (Brink et al. 2001). Whether the medical treatment of our patients has influenced muscle hypertrophy negatively cannot be assessed from this study. In any case the patients in the EET and the CET group received nearly the same medication and must thus have been affected similarly.

By evaluating muscle strength with an isokinetic dynamometer, we found an average increase of 12% in peak isometric and peak isokinetic concentric torque with EET. This is similar to isokinetic values reported for resistance conditioning programs (Jones and Rutherford 1987; Frontera et al. 1988). Surprisingly, peak isokinetic eccentric torques increased only by 6%. Due to training specificity we would have expected eccentric torques to improve more than concentric torques after an eccentric training regime (Higbie et al. 1996; Hortobágyi et al. 1996). However, it proved difficult to implement isokinetic eccentric torque measurements in this population. Clearly, the difficulties in coordinating eccentric movement lead to a greater variability of this testing procedure. Similar problems with estimating eccentric torques have previously been reported (Westing et al. 1988). Comparing the results in strength gain to those of studies with comparable conditioning protocols, we found them to be of similar magnitude to those reported by Fridén et al. (1983b), but only a third of those reported by LaStayo et al. (2000). We consider the main reason for this discrepancy to be the absolute work rate achieved at the end of the intervention period. Whereas the final work rate in the protocol used by LaStayo et al. (2000) was 489 W, Fridén et al. (1983b) finished at 300 W and our study ended at 338 W. It could be hypothesised that the observed difference in muscle response might be related to a mechanical threshold. No increase of maximal muscle strength was seen in CET between the pre- and post-training isokinetic tests. In view of the relatively low mechanical load of 97 W during the concentric training this is not surprising (McCartney et al. 1991; LaStayo et al. 1999, 2000). The structural findings indicate that the functional strength gains after EET can most likely be attributed to central factors (see also Colliander and Tesch 1990; Hortobágyi et al. 1996). This aspect deserves to be studied specifically in the future.

Muscle fibre size was found to be increased significantly by 19% in CET and to be unchanged in EET. This was contrary to our hypothesis as we would have expected EET to increase fibre size more than CET. It has previously been shown by LaStayo et al. (2000) that eccentric exercise training of similar duration (but higher intensity) led to an increase of fibre size of no less than 52%. In contrast, Fridén et al. (1983b) using eccentric exercise at similar intensities as in our study did not report significant gains in muscle fibre size. In this context we have to consider that fibre size determined by morphometry is a biased estimate and its estimation in biopsy material is fraught with difficulties. Small differences, such as those suggested by the significant gains in muscle mass in EET and CET may therefore be difficult to resolve in biopsies (Zumstein et al. 1983). Moreover, we do not know whether the training regime used in the present study would influence the total fibre number; this would impact on fibre size. Capillarity assessed by the capillary to fibre ratio (uninfluenced by shifts in fibre size) remained constant in both populations. Total mitochondrial volume did not change significantly in

either of the populations; however, we found an increase in mitochondrial volume density of 14% in CET. This increase was mainly due to a significant (42%) increase in the population of subsarcolemmal mitochondria. These findings taken together can be seen as an adaptation to the low intensity endurance type exercise carried out by CET (Hoppeler 1986). With regard to EET there is very little information available in the literature. LaStayo et al. (2000) found mitochondrial volume density to be unchanged in eccentric exercise training, albeit carried out at much higher workloads and more often per week, while Fridén et al. (1983b) found mitochondrial volume densities (obtained from longitudinal sections) to be increased. His data show surprisingly low initial mitochondrial densities, which may partly be responsible for the observed significant increases after EET. As it stands now it is too early to decide on the effect of EET on the mitochondrial populations in muscle fibres.

In conclusion, we have shown that eccentric exercise training is feasible in middle-aged men with CAD and without musculoskeletal complication. It provides functional improvements by increasing muscular strength, presumably as a result of the 3.5-times higher eccentric mechanical work rate achieved at a given metabolic load. The increase in muscle mass was found to be similar in concentric and eccentric exercise while muscle fibre size and ultrastructure were not significantly altered after EET. It will be necessary to reach higher workloads in eccentric training in future studies to further explore the potential of this novel training paradigm.

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