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REVIEW ARTICLE

Interval training for patients with coronary artery disease: a systematic review

Aimee K. Cornish · Suzanne Broadbent · Birinder S. Cheema

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Abstract Interval training (IT) may induce physiological adaptations superior to those achieved with conventional moderate-intensity continuous training (MCT) in patients with coronary artery disease (CAD). Our objectives were (1) to systematically review studies which have prescribed IT in CAD, (2) to summarize the findings of this research including the safety and physiological benefits of IT, and (3) to identify areas for further investigation. A systematic review of the literature using computerized databases was performed. The search yielded two controlled trials and five randomized controlled trials (RCTs) enrolling 213 participants. IT prescribed in isolation or in combination with resistance training was shown to induce significant and clinically important physiological adaptations in cardiac patients. IT was also shown to improve cardiorespiratory fitness (e.g. VO_{2max}, VO_{2AT}), endothelial function, left ventricle morphology and function (e.g. ejection fraction) to a significantly greater extent when compared with conventional MCT. No adverse cardiac or other life-threatening events occurred secondary to exercise participation in these studies. However, these findings must be interpreted with caution, as methodological limitations were present in all trials reviewed. In conclusion, robustly designed RCTs with thorough and standardized reporting are required to determine the risk and benefits of IT in the broader cardiac patient population. Further research is required to determine optimal IT protocols for the use in cardiac rehabilitation programmes, potentially contributing to novel exercise prescription guidelines for this patient population.

Keywords Coronary artery disease · Interval training · High intensity

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A. K. Cornish
Institute of Food, Nutrition and Human Health, Massey University, Wellington, New Zealand

S. Broadbent (✉)
School of Sport and Exercise Science, Institute of Sport, Exercise and Active Living, Victoria University, PO Box 14428, Melbourne, VIC 8001, Australia
e-mail: suzanne.broadbent@vu.edu.au

B. S. Cheema
School of Biomedical and Health Sciences, Family and Community Health Research Group (FaCH), University of Western Sydney, Campbelltown, NSW, Australia

Introduction

Cardiovascular diseases, such as coronary artery disease (CAD), account for over 17 million deaths worldwide each year, representing nearly one-third of the annual death toll (WHO 2008). It is well established that physical activity reduces the cardiovascular disease risk. Data collected over the past 40 years have shown that exercise training is safe, and can induce many health-related adaptations in individuals medically treated for cardiac disease (Jolliffe et al. 2001). The effectiveness of cardiac rehabilitation programs for the secondary prevention of CAD has also been well documented (Jolliffe et al. 2001). However, such rehabilitation programs remain drastically underutilized (Leon et al. 2005), and must continue to be improved to enhance patient uptake, optimize recovery, and more effectively reduce mortality risk profile.

The most recent position statement on exercise prescription for patients with CAD was published by the American College of Sports Medicine in the 2010 Guidelines for Exercise Testing and Prescription (ACSM 2010).

The evidence-based recommendation for aerobic training within the guidelines specifies supervised, large-muscle group continuous exercise (e.g. walking, jogging, cycling, swimming, group aerobics and rowing) performed at an intensity of generally 40-85% of heart rate reserve. The guidelines also indicate that rating of perceived exertion (RPE) may be used to monitor exercise intensity, with the goal of keeping the intensity at a moderate level (ACSM, 2010).

The efficacy of moderate-intensity continuous training (MCT) for patients with CAD has been systematically reviewed by Jolliffe et al. (2000) in a meta-analysis involving 8,440 patients in 32 randomized controlled trials (RCTs). The authors concluded that MCT is safe and physiologically beneficial, and reduces all-cause mortality in cardiac patients by approximately 27%.

Interval training (IT), which involves alternating brief (2–5 min) higher intensity (≥75% $VO_{2max/peak}$ or RPE >15) and moderate-intensity workloads throughout an exercise session, has traditionally been used to train athletes requiring high levels of both aerobic and anaerobic fitness (e.g. track and team sport athletes). Recently, several RCTs have demonstrated the safety and effectiveness of IT in cardiac patients (Nilsson et al. 2008; Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007). Interestingly, some of the data suggest that IT can induce significantly greater improvements in VO_{2max}, and other physiological parameters, versus MCT (Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007). Such findings are important for many reasons. For example, VO_{2max} has recently been noted as the single best predictor of death among cardiac patients (Kavanagh et al. 2002), and the enhancement of this outcome measure may therefore be associated with risk reduction.

There is currently a need to more thoroughly investigate and elucidate the modalities and dosages of exercise that can be prescribed to elicit safe, expeditious and peak recovery in patients with CAD (Fletcher et al. 2001; Guiraud et al. 2009). To our knowledge, the evidence-base for IT in cardiac patients has not been systematically reviewed to date. A greater understanding of these data, as well as the caveats of this research, is required to formulate novel research questions and advance exercise prescription guidelines in this patient population, which may contribute to enhanced evidence-based practice involving the prescription of IT.

Therefore, our objectives are threefold:

1. To systematically review studies which have prescribed IT in patients with CAD,
2. To summarize the findings of this research including the safety and physiological benefits of IT, and
3. To identify areas for further investigation.

Methods

A systematic review of all published literature, regardless of study design was conducted. Given the paucity of RCTs, and the heterogeneity of interventions and outcome measures across investigations, the pooling of effect sizes across studies in a meta-analysis was not considered appropriate at this stage.

Criteria for considering studies

Study designs

RCTs, non-RCTs and uncontrolled trials published in peer-reviewed journals were included. Abstracts, case reports and unpublished trials were excluded.

Participants

Trials involving adults (>18 years) diagnosed with and/or surgically treated for CAD were included.

Interventions

Trials prescribing IT in isolation, or in combination with other exercise modalities (e.g. resistance training), were included. Studies investigating the effect of single bouts of IT or interventions that were <8 weeks in duration were not included. IT was defined as an exercise program alternating higher intensity (≥75% $VO_{2max/peak}$ or RPE of >15) (Borg 1998) and lower intensity workloads.

Outcome measures

Trials evaluating physiological outcome measures potentially responsive to chronic exercise exposure, based on the empirical evidence of exercise in CAD and other clinical and healthy cohorts, were included.

Search method

We conducted a literature review in January 2010, from the earliest date available to December 31, 2009, limited to the English language, using computerized databases including PubMed, Medline, CINAHL, Google Scholar, SportDiscus, Embase, and Web of Science. The search combined key words related to CAD (i.e. heart disease, cardiac disease, myocardial infarction), cardiac rehabilitation (i.e. exercise rehabilitation, training, sports, physical activity) and IT (i.e. interval training, aerobic interval training, anaerobic interval training, high-intensity interval training). Articles retrieved were examined for further relevant references.

Data extraction and analyses

Outcome measures significantly adapted by the intervention were extracted for the assessment of study and intervention quality. Relative ES (mean $\text{change}_{\text{Treatment}}$ − mean $\text{change}_{\text{Control}}$) ÷ $\text{SD}_{\text{Pooled baseline}}$ and 95% confidence intervals ($\text{SD}_{\text{Pooled baseline}}$ × bias correction factor (Hedges) ± z value × standard error of ES estimate) were calculated for controlled trials and RCTs (Becker 2000).

Results

Studies retrieved and quality assessment

The search resulted in seven peer-reviewed articles, including two non-RCTs (Ehsani et al. 1981, 1982) and five RCTs (Munk et al. 2009; Nilsson et al. 2008; Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007). All non-RCTs involved an IT group and a non-exercising control group, both consisting of CAD patients but without randomization of participants to these two groups (Ehsani et al. 1981, 1982). The control group in these trials consisted of participants who could not make the time commitment to the IT group or lived too far away from the exercise venue (Ehsani et al. 1981, 1982). Statistical analyses performed in the controlled trials involved repeated measures comparisons within groups over time only, and did not involve statistical comparisons between groups over time (i.e. group × time effect).

Four of the five RCTs involved randomization of subjects to an IT group and a MCT group (Nilsson et al. 2008; Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007). Two RCTs included a non-exercising control group (Munk et al. 2009; Nilsson et al. 2008). All RCTs performed statistical comparisons between groups. Only one RCT specifically stated when the randomization of participants occurred (i.e. after baseline testing) (Nilsson et al. 2008). No RCT reported that collection of outcome measures were performed by blinded assessors, nor did any RCT involve an intention-to-treat strategy of analysis.

Overview of the participants

Sample size, gender and age

Two hundred and thirteen ($n = 213$) participants were enrolled in the seven trials reviewed (Table 1). Four trials enrolled fewer than 21 participants (Ehsani et al. 1981, 1982; Rognmo et al. 2004; Warburton et al. 2005), while the other trials enrolled 27 (Wisløff et al. 2007), 40 (Munk et al. 2009) and 80 participants (Nilsson et al. 2008).

All trials provided a gender breakdown. A total of 33 women and 180 men were enrolled. Three trials limited enrolment to men only (Ehsani et al. 1981, 1982; Warburton et al. 2005) with no explanations as to why women were excluded.

Mean age according to group assignment is presented in Table 1. In the two trials that provided an age range the youngest and eldest patient enrolled were 31 and 69 years (Ehsani et al. 1981, 1982).

Diagnosis of CAD, cardiac surgery, and comorbidities

Diagnosis of CAD was described in all trials but only three trials described the number of diseased vessels (Munk et al. 2009; Rognmo et al. 2004; Warburton et al. 2005). The percentage of participants who experienced a myocardial infarction was provided in five trials: 100% (Wisløff et al. 2007), 90% (Ehsani et al. 1981), 75% (Ehsani et al. 1982), 38% (Rognmo et al. 2004), and 35% (Warburton et al. 2005) while the participants in the RCT by Nilsson et al. (2008) had angiographically confirmed CAD or chronic heart failure (CHF).

Three trials described the surgical procedure received by participants prior to enrolment (Munk et al. 2009; Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007), with 16 coronary artery bypass surgeries and 50 percutaneous coronary interventions reported. The remaining participants received medications as their medical intervention. The remaining trials did not provide data on surgery received prior to enrolment.

Medication

All trials provided a description of the medications received by the participants. The most common medications were beta-blockers (55%), statins (45%), anticoagulant and antiplatelet agents (35%), ACE inhibitors (38%), and nitrates (28%). In two of the trials, the use of propranolol in four exercising participants was reduced or ceased during the intervention period (Ehsani et al. 1981, 1982).

Comorbidities of the enrolled participants were not presented in six of the trials, while Munk et al. (2009) presented the prevalence of diabetes (23%), hypertension (53%) and hyperlipidemia (73%) in their cohort.

Overview of the exercise interventions

Details of the exercise interventions prescribed have been provided in Table 1. Overall, the interventions were heterogeneous with respect to duration of intervention, session duration, specific training modalities, and intensity ranges.

Table 1 Overview of participants and exercise interventions

References, country	*N*	Study groups (*n*) Age (years)	Exercise intervention			
			Timing of exercise	Modality	Exercise prescription	Duration (weeks)
Non-randomized controlled trials						
Ehsani et al. (1981), USA	18	Exercise ($n = 10$) 54.8 ± 6 Control ($n = 8$) 49.6 ± 7	>4 months post-MI	AER/AN	*Exercise group* • Walking/jogging, bicycle ergometer training 0–3 months (continuous training) • 50–70% of VO_{2peak} • 30 min (plus 10 min warm up) per session • 3 sessions per week 3–12 months (interval training): • 70–80% of VO_{2peak} with 2–3 intervals of 2–5 min at 80–90% of VO_{2peak} • 30 min increasing to 50–60 min (plus 10 min warm up) per session at 6 months • 4–5 sessions per week *Control group* No exercise intervention	52
Ehsani et al. (1982), USA	13	Exercise ($n = 8$) 52 ± 3 Control ($n = 5$) 45 ± 2	>4 months post-MI	AER/AN	*Exercise group* • Walking/jogging, bicycle ergometer training 0–3 months (continuous training) • 50–70% of VO_{2peak} • 30 min (plus 10–15 min warm up) per session • 3 sessions per week 3–12 months (interval training) • 70–80% of VO_{2peak} with 2–3 intervals of 2–5 min at 80–95% of VO_{2peak} • 30 min per session increasing to 50–60 min (plus 10–15 min warm up) per session at 6 months • 5 sessions per week *Control group* No exercise intervention	52
Randomized controlled trials						
Rognmo et al. (2004), Norway	21	IT ($n = 8$) 62.9 ± 11.2 MCT ($n = 9$) 61.2 ± 7.3	>12 months post-cardiac treatment	AER/AN	*Interval training group* • Uphill treadmill walking • 50–60% VO_{2peak} (3 min) with four intervals at 80–90% VO_{2peak} (4 min) 33 min per session (including 5 min warm up) • 3 sessions per week *MCT group* • Uphill treadmill walking • 50–60% VO_{2peak} • 41 min per session • 3 sessions per week	10

Table 1 continued

References, country	*N*	Study groups (*n*) Age (years)	Exercise intervention			
			Timing of exercise	Modality	Exercise prescription	Duration (weeks)
Warburton et al. (2005), Canada	14	IT ($n = 7$) 55 ± 7 MCT ($n = 7$) 57 ± 8	≥6 months post-cardiac treatment	Mixed	*Interval training group* • Walking, stair climbing, cycling, arm ergometer training • 40% $VO_{2reserve}$ (2 min) with intervals at 90% $VO_{2reserve}$ (2 min) • 30 min (plus 10 min warm up and cool down) per session • 2 supervised sessions per week • 3 additional unsupervised sessions at 65% $VO_{2reserve}$ for 30 min • Standardized resistance training *MCT group* • Walking, stair climbing, cycling, arm ergometer • Training • 65% $VO_{2reserve}$ • 30 min (plus 10 min warm up and cool down) per session • 2 sessions per week • 3 identical unsupervised sessions per week *Resistance training* • Standardized resistance training	16
Wisløff et al. (2007), Norway	27	IT ($n = 9$) 76.5 ± 9 MCT ($n = 9$) 76.5 ± 9 Control ($n = 9$) 75.5 ± 13	>12 months after MI	AER/AN	*Interval training group* • Uphill treadmill walking • 50–60% peak heart rate (3 min) with intervals at 90–95% peak heart rate (4 min) • 38 min per session (including 10 warm up) *MCT group* • Aerobic training: • Uphill treadmill walking • 70% peak heart rate • 47 min per session • 3 session per week *Control group* • Aerobic training (supervised walking session and health advice) • 70% peak heart rate • 47 min per session • Every 3 weeks	12
Nilsson et al. (2008), Norway	80	IT ($n = 40$) 68.8 ± 7.9 Control ($n = 40$) 71.5 ± 7.8	>4 weeks after MI; stable CHF and LVEF <40% or ≥40% LVEF and symptoms of diastolic HF	AER/AN	*Interval training group* • Aerobic dance movements • Included upper and lower body exercises • 3 intervals of 5–10 min at RPE = 15–18 • 50 min per session • 2 days per week *Control group* • Usual care, no exercise intervention	16

Table 1 continued

References, country	*N*	Study groups (*n*) Age (years)	Exercise intervention			
			Timing of exercise	Modality	Exercise prescription	Duration (weeks)
Munk et al. (2009), Norway	40	IT ($n = 20$) 57 ± 14 Control ($n = 20$) 61 ± 10	>11 ± 4 days post-PCI	AER/AN	*Interval training group* • Cycle ergometer or treadmill walking/ running • Moderate intervals at 60–70% peak heart rate (3 min) with higher intervals at 90–95% peak heart rate (4 min) • 60 min per session (including 10 min warm up at 60–70% peak heart rate plus 5 min cool down and 15 min of stretching/ back exercises) • 3 days per week *Control group* • Usual care, no exercise intervention	26

MI myocardial infarction, *CHF* chronic heart failure, *HF* heart failure, *LVEF* left ventricular ejection fraction, *AER/AN* aerobic and anaerobic, *Mixed* aerobic/anaerobic plus resistance training, *IT* interval training, *MCT* moderate-intensity continuous training, VO_{2peak} peak oxygen consumption, $VO_{2reserve}$ oxygen consumption reserve

Length of exercise intervention

Four trials (Nilsson et al. 2008; Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007) prescribed 10–16 weeks of training. Munk et al. (2009) prescribed 26 weeks of training and Ehsani et al. (1981, 1982) prescribed 52 weeks. Follow-up assessments beyond the completion of the prescribed exercise training were completed in two trials (Nilsson et al. 2008; Munk et al. 2009). IT was prescribed throughout the intervention period in five trials (Munk et al. 2009; Nilsson et al. 2008; Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007), whereas Ehsani et al. (1981, 1982) prescribed continuous training for the initial 12 weeks, and IT for the remaining 40 weeks, of their 52-week intervention.

Phase of rehabilitation/exercise history

None of the seven trials outlined the phase of the cardiac rehabilitation or detailed the exercise training history of the participants (i.e. completed phases of cardiac rehabilitation). Only one trial detailed the exercise training history of the participants (Ehsani et al. 1982).

Timing of intervention

Time of enrolment relative to myocardial infarction and/or cardiac intervention was reported as an entry criterion in all trials (Table 1).

Modalities

All trials prescribed aerobic and anaerobic exercise training modalities and one trial also included resistance training (Rognmo et al. 2004). Of the five RCTs, three compared IT to MCT (Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007) and one of these studies also included a non-exercising control group (Wisløff et al. 2007). Both Nilsson et al. (2008) and Munk et al. (2009) compared IT to a non-exercise control group, and did not involve a MCT group. The trials by Ehsani et al. (1981, 1982) included an exercise group (prescribed a combination of MCT and IT) and a non-exercising control group.

All trials reviewed described the exercise training equipment used. Six trials involved the use of treadmills and/or bicycle ergometers (Ehsani et al. 1981, 1982; Munk et al. 2009; Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007), while one study also utilized arm ergometers and stair climbers (Warburton et al. 2005). Further, Ehsani et al. (1982) also provided patients with the option of exercising without equipment, by walking or jogging on an indoor track. Nilsson et al. (2008) prescribed aerobic dance exercise and movements but no exercise equipment.

Training intensity

All trials provided details regarding training intensity (Table 1).

IT Low intensity intervals were prescribed at 40% of reserve oxygen consumption ($VO_{2reserve}$) (Warburton et al. 2005), 50–60% of peak oxygen consumption (VO_{2peak}) (Rognmo et al. 2004), 50–60% of peak heart rate (Wisløff et al. 2007), 60–70% of peak heart rate (Munk et al. 2009), and 70–80% of VO_{2max} (Ehsani et al. 1981, 1982). High intensity intervals were prescribed at 90% of $VO_{2reserve}$ (Warburton et al. 2005), 80–90% of peak heart rate (Munk

et al. 2009), 80–95% of $VO_{2max/peak}$ (Ehsani et al. 1981, 1982; Rognmo et al. 2004) and 90–95% of peak heart rate (Wisløff et al. 2007). The RCT by Nilsson et al. (2008) prescribed high intensity intervals at RPE = 15–18 but did not describe the intensity of the lower intensity intervals.

MCT In three trials that included MCT, the prescribed intensities were 50–60% of VO_{2peak} (Rognmo et al. 2004), 65% of $VO_{2reserve}$ (Warburton et al. 2005), and 70% of peak heart rate (Wisløff et al. 2007).

Session duration

All trials outlined the length of each session (Table 1). Two trials matched the total work performed by the IT and MCT groups by adjusting session length to equal the same training load (Rognmo et al. 2004; Wisløff et al. 2007). Aerobic training was prescribed two to five times per week in all trials (Table 1).

Compliance, attrition and adverse events

Attendance to exercise sessions was reported to be >90% by Munk et al. (2009), and 92% (IT group) and 95% (MCT group) by Wisløff et al. (2007). In trials by Ehsani et al. (1981, 1982) compliance was reported to range from 4.2 to 4.7 sessions per week. Three trials did not provide any information about compliance (Nilsson et al. 2008; Rognmo et al. 2004; Warburton et al. 2005). None of the reviewed trials presented a priori definition of "compliance" within their methodology.

Participant attrition of approximately 4% occurred in three trials (Rognmo et al. 2004; Warburton et al. 2005; Nilsson et al. 2008). Reasons for attrition included: discontinuing training because of knee/ankle injuries; stroke; poor motivation; unwillingness to attend follow-up testing; orthostatic intolerance; one death due to cardiovascular disease. These participants were removed from the statistical analysis. None of the adverse events contributing to participant attrition were attributed to the exercise training. Only one trial reported an adverse event during training (orthostatic collapse), which was not considered serious and did not require hospitalization (Munk et al. 2009). No trial reported adverse cardiac symptoms (angina, syncope, fibrillation) or complications due to exercise training. Notably, none of the reviewed trials presented an a priori definition of adverse event within their methodology.

Physiological adaptations to IT

Significant physiological adaptations to exercise training are presented in Table 2 for non-randomized trials and Table 3 for RCTs. Non-randomized trials by Ehsani et al. (1981, 1982) have shown that participants who engaged in 12 weeks of MCT followed by 40 weeks of IT significantly improved health-related outcome measures including VO_{2peak}, exercise capacity, hemodynamic measures during maximal exercise, left ventricular (LV) morphology and function, body mass, and high-density lipoprotein cholesterol (Table 2). No improvements were noted in the control groups (Ehsani et al. 1981, 1982).

The RCTs showed that IT induced significantly greater increases in $VO_{2max/peak}$ (Munk et al. 2009; Nilsson et al. 2008; Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007), VO_2 at ventilatory threshold (Munk et al. 2009), time to fatigue (Nilsson et al. 2008; Wisløff et al. 2007), anaerobic threshold (Munk et al. 2009; Warburton et al. 2005; Wisløff et al. 2007), exercise/work economy (Wisløff et al. 2007), workload (Munk et al. 2009), improved 6-min walk distance (Nilsson et al. 2008), and improved LV size and function (Wisløff et al. 2007) as compared to the MCT group and the control groups (Table 3). Nilsson et al. (2008) showed that IT significantly improved 6-min walk test distance compared to the control group only.

LV function and hemodynamics were improved in three controlled trials (Ehsani et al. 1981, 1982; Wisløff et al. 2007), with significant increases during exercise in LV diastolic diameter diastolic volume, posterior wall thickness, surface area, fractional shortening, ejection fraction and rate pressure product (RPP). Ehsani et al. (1981, 1982) and Wisløff et al. (2007) conducted resting echocardiograms to assess LV function, but not exercise echocardiograms. Wisløff et al. (2007) reported that resting LV diastolic diameter and volume, both indicators of a reversal in post-infarct remodeling, significantly decreased in both the MCT and IT groups, while resting stroke volume, cardiac output and ejection fraction, indicators of improved myocardial contractile function, increased in the IT group only.

There were some differences in reported LV remodeling between authors. Ehsani et al. (1981, 1982) ascribed increased LV wall thickness to exercise-induced cardiac hypertrophy, whereas Wisløff et al. (2007) suggested that decreased LV wall thickness and end-diastolic/end-systolic volumes were due to an exercise-induced halt in post-myocardial infarction cardiac remodeling. Wisløff et al. (2007) also suggested that IT plus medications improved ejection fraction and myocardial contractile function.

Discussion

To our knowledge, this is the first systematic review of IT for CAD patients. Overall, this review suggests that IT prescribed in isolation or in combination with resistance

Table 2 Significant outcomes of non-randomized controlled trials

References, country	Outcomes	Pre-IT	Post-IT	Pre-control	Post-control	Relative effect size (95% CI)	*P* value[a]
Ehsani et al. (1981), USA	VO_{2peak} (ml kg^{-1} min^{-1})	26 ± 4	35 ± 4	Not reported	Not reported	Not applicable	<0.001
	Treadmill exercise time[b] (s)	458 ± 81	613 ± 77	415 ± 72	437 ± 99	1.64 (0.57–2.71)	<0.001
	Rate pressure product peak (HR × SBP × 10^{-3})	24.9 ± 5.1	29.8 ± 5.4	24.6 ± 4.8	23.7 ± 7.2	1.11 (0.11–2.11)	<0.01
	Ischemic ST-segment depression threshold						
	Heart rate peak (bpm)	119 ± 18	138 ± 17	125 ± 19	119 ± 16	1.29 (0.27–2.31)	<0.01
	Rate pressure product (HR × SBP × 10^{-3})	19.5 ± 5.2	24.0 ± 4.5	20.7 ± 5.2	18.6 ± 5.5	1.21 (0.20–2.22)	<0.001
	Left ventricular size						
	LV end-diastolic diameter (mm)	51 ± 7	56 ± 9	Not reported	Not reported	Not applicable	<0.01
	LV posterior wall thickness (mm)	9 ± 1	10 ± 1	Not reported	Not reported	Not applicable	<0.01
	Body surface area (m_2)	1.93 ± 0.2	1.89 ± 0.2	Not reported	Not reported	Not applicable	<0.01
Ehsani et al. (1982), USA	VO_{2peak} (ml kg^{-1} min^{-1})	26 ± 1	37 ± 2	25 ± 1	27 ± 2	1.61 (0.33–2.89)	<0.001
	Treadmill exercise time[b] (s)	469 ± 30	610 ± 15	461 ± 27	480 ± 28	3.92 (2.04–5.80)	<0.01
	Hemodynamic data during maximal treadmill exercise						
	Heart rate peak (bpm)	153 ± 6	168 ± 4	144 ± 6	150 ± 4	1.40 (0.16–2.63)	<0.02
	Systolic blood pressure peak (mmHg)	145 ± 9	166 ± 8	162 ± 9	169 ± 9	1.45 (0.20–2.69)	<0.01
	Rate pressure product peak (HR × SBP × 10^{-3})	22.10 ± 1.87	27.73 ± 2.11	23.31 ± 1.82	25.33 ± 1.66	1.81 (0.50–3.13)	<0.01
	Oxygen pulse peak	12 ± 1	16 ± 1	14 ± 1	16 ± 1	1.86 (0.53–3.19)	<0.001
	Echocardiographic and hemodynamic data during isometric exercise						
	LV end-diastolic diameter rest (mm)	47 ± 1	50 ± 1	51 ± 1	51 ± 2	2.79 (1.24–4.34)	<0.01
	LV end-diastolic diameter 60% MVC (mm)	52 ± 1	53 ± 1	55 ± 2	54 ± 2	1.29 (0.06–2.51)	<0.05
	LV end-systolic diameter rest (mm)	32 ± 1	35 ± 1	36 ± 1	36 ± 0.4	2.79 (1.24–4.34)	<0.01
	Fractional shortening 60% MVC (%)	23 ± 1	28 ± 2	19 ± 1	21 ± 1	2.79 (1.24–4.34)	<0.05

IT interval training, VO_{2max} maximal oxygen consumption, *LV* left ventricular, *MVC* maximal voluntary contraction

[a] Significant versus baseline values within IT group

[b] Exercise time to exhaustion in the Bruce test

training can induce significant and clinically important physiological adaptations in cardiac patients (Table 3). Further, IT has been noted to improve cardiorespiratory fitness (e.g. VO_{2max}, VO_{2AT}), endothelial function, left ventricle morphology and function (e.g. ejection fraction) to a significantly greater extent than conventional MCT (Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007; Table 3). Notably, these physiological adaptations were achieved without significant cardiovascular or other life-threatening events. Training compliance was high according to four trials presenting these data (Ehsani et al. 1981, 1982; Munk et al. 2009; Wisløff et al. 2007).

Although this review provides support for the prescription of IT in cardiac patients, the findings must be interpreted with caution. All trials reviewed suffered from methodological limitations according to the current standards of reporting (Moher et al. 2001). These limitations were evident with respect to: statistical analyses where no studies to date have mentioned the use of intention-to-treat strategy; lack of involvement of blinded outcomes assessors; inadequate reporting of pertinent participant characteristics such as comorbidities and previous participation in cardiac rehabilitation; considerable variation in the intensities of exercise intervals used, and in the duration of study lengths; and insufficient reporting about safety and compliance including a priori definitions of terms and statistical comparison of adverse events between groups.

Table 3 Significant outcomes of randomized controlled trials comparing IT to MCT

References, country	Outcomes	Pre-IT	Post-IT	Pre-MCT	Post-MCT	Relative effect size (95% CI)	*P* value
Rognmo et al. (2004), Norway	Peak oxygen uptake (ml kg^{-1} min^{-1})	31.8 ± 9.3	37.8 ± 12.4	32.1 ± 5.3	34.8 ± 5.7	0.41 (−0.45 to 1.28)	0.011[a]
	Peak ventilation (l min^{-1})	74.3 ± 22.7	88.4 ± 24.9	80.2 ± 15.6	86.6 ± 18.8	0.38 (−0.49 to 1.24)	<0.02[b]
	Treadmill test speed (km/h)	5.3 ± 1.7	6.8 ± 1.8	5.7 ± 0.4	6.4 ± 0.7	0.61 (−0.27 to 1.48)	<0.02[b]
Warburton et al. (2005), Canada	Oxygen pulse (ml beat)	16.2 ± 3.5	19.0 ± 4.3	16.7 ± 3.2	17.7 ± 2.6	0.50 (−0.56 to 1.56)	<0.05[b]
	Peak ventilation	89 ± 19	99 ± 19	92 ± 26	102 ± 20	0.00 (−1.05 to 1.05)	<0.05[b]
	VO_2 at AT (ml kg^{-1} min^{-1})	22 ± 4	29 ± 8	23 ± 3	23 ± 4	1.84 (0.59–3.09)	<0.05[a,b]
	Treadmill time to exhaustion (s)	800 ± 200	890 ± 190	720 ± 105	850 ± 90		<0.05[a,b]
Wisløff et al. (2007), Norway	VO_{2peak} (ml kg^{-1} min^{-1})	13.0 ± 1.6	19.0 ± 2.1	13.0 ± 1.1	14.9 ± 0.9	2.84 (1.53–4.15)	<0.05[a]
	VO_2 at AT (ml kg^{-1} min^{-1})	8.2 ± 0.8	11.6 ± 1.0	8.0 ± 0.7	10.1 ± 0.9	1.65 (0.58–2.72)	<0.05[a]
	Work economy						
	VO_2 (ml kg^{-1} min^{-1})	8.2 ± 0.8	7.0 ± 0.6	8.0 ± 0.7	7.6 ± 0.8	−1.01 (−2.00 to 0.03)	<0.05[a]
	Heart rate (bpm)	84 ± 9	76 ± 5	82 ± 6	81 ± 9	−0.87 (−1.84 to 0.10)	<0.05[a]
	Blood lactate (mmol l^{-1})	2.7 ± 0.3	1.6 ± 0.4	2.9 ± 0.3	2.5 ± 0.4	−2.22 (−3.40 to 1.05)	<0.05[a]
	Skeletal muscle molecular mechanisms of exercise capacity						
	PGC-1α (arbitrary units)	3.6 ± 0.5	5.3 ± 0.01	3.4 ± 0.1	4.1 ± 0.2	3.3 (1.5–4.5)	<0.01[a,c]
	Ca^{2+} uptake[d] (V_{max}, pmole/s/mg)	4.2 ± 0.8	8.3 ± 0.9	4.2 ± 0.8	5.1 ± 0.5	2.0 (1.01–3.62)	<0.01[a,c]
	Endothelial function						
	Flow mediated dilation (%)	3.5 ± 2	12 ± 1.0	3.5 ± 2.5	8.5 ± 2	1.63 (0.60–2.74)	<0.01[a,c]
	Total antioxidant status (mmol)	1.3 ± 0.06	1.5 ± 0.1	1.3 ± 0.08	1.4 ± 0.0	1.82 (0.57–3.04)	0.02[a,b]
	Oxidized LDL (U/L)	90 ± 12	84 ± 12	92 ± 16	92 ± 12	−0.44 (−1.40 to 0.48)	0.03[b]
	Left ventricle remodeling						
	ProBNP (pg/ml)	850 ± 300	350 ± 130	1,200 ± 500	1,000 ± 600	−0.67 (−1.60 to 0.80)	<0.02[a,c]
	LV diastolic diameter (mm)	66.7 ± 6.8	59.0 ± 6.8	69.1 ± 8.6	68.2 ± 6.5	−0.84 (−1.80 to 0.13)	<0.02[a]
	LV systolic diameter (mm)	53.9 ± 6.7	46.1 ± 8.2	56.6 ± 8.8	53.9 ± 7.4	−0.62 (−1.57 to 0.32)	<0.02[a]
	LV end-diastolic volume (ml)	248.1 ± 79.6	202.9 ± 72	245.5 ± 53.1	230.3 ± 41.0	−0.42 (−1.36 to 0.51)	<0.02[a]
	LV end-systolic diameter (ml)	177.4 ± 72.1	133.9 ± 57.8	172.9 ± 48.7	160.6 ± 34.3	−0.48 (−1.42 to 0.45)	<0.02[a]
	Resting hemodynamics						
	Stroke volume (ml)	57.1 ± 14.3	67.0 ± 19.9	63.5 ± 12.7	63.1 ± 15.7	0.73 (−0.23 to 1.68)	<0.01[b]
	Cardiac output (l min^{-1})	3.5 ± 0.5	3.9 ± 0.6	3.5 ± 0.9	3.4 ± 1.1	0.65 (−0.29 to 1.60)	<0.01[b]
	Ejection fraction (%)	28.0 ± 7.3	38.0 ± 9.8	32.2 ± 4.8	33.5 ± 5.7	1.34 (0.32–2.36)	<0.02[a]
Nilsson et al. (2008), Norway	6-min walking distance (m)	457 ± 77	515 ± 93	Not applicable	Not applicable	0.73 (−0.30 to 1.74)	<0.001[a]
	Cycle test time (s)	349 ± 113	406 ± 156	Not applicable	Not applicable	0.62 (−0.24 to 1.40)	0.003[a]
	Workload (W)	72 ± 18	85 ± 26	Not applicable	Not applicable	0.33 (−0.15 to 0.55)	0.001[a]

Table 3 continued

References, country	Outcomes	Pre-IT	Post-IT	Pre-MCT	Post-MCT	Relative effect size (95% CI)	*P* value
Munk et al. (2009), Norway	VO_{2peak} (ml kg^{-1} min^{-1})	23.2 ± 5.7	27.1 ± 8.0	Not applicable	Not applicable	0.20 (−0.17 to 0.54)	<0.01[a,b]
	Ventilator *y* threshold (ml kg^{-1} min^{-1})	15.6 ± 5.0	20.4 ± 7.1	Not applicable	Not applicable	0.44 (−0.50 to 1.40)	<0.01[a,b]
	Maximal workload (W)	180 ± 49	202 ± 46	Not applicable	Not applicable	0.17 (−0.98 to 1.20)	<0.01[a]
	Resting heart rate (bpm)	71 ± 10	68 ± 16	Not applicable	Not applicable	−0.04 (−1.08 to 1.02)	0.03[a,b]
	Peak heart rate (bpm)	153 ± 26	154 ± 34	Not applicable	Not applicable	−0.02 (−1.06 to 1.04)	0.75
	Systolic blood pressure (mmHg)	126 ± 16	129 ± 22	Not applicable	Not applicable	0.0 (−1.01 to 1.01)	0.61
	Diastolic blood pressure (mmHg)	80 ± 9	76 ± 13	Not applicable	Not applicable	−0.3 (−1.33 to 1.28)	0.08

IT interval training, *MCT* moderate-intensity continuous training, VO_{2peak} peak oxygen consumption, *LV* left ventricular, VO_2 *at AT* oxygen consumption at anaerobic threshold

[a] Significant change over time versus comparison group(s)

[b] Significant versus baseline values within IT group

[c] IT significantly different to control and MCT group (post-intervention values)

[d] Rate of maximal Ca^{2+} uptake in the sarcoplasmic reticulum in permeabilized samples of vastus lateralis muscle

Moreover, exercise intervention studies conducted in chronically diseases cohorts commonly involve a self-selected (relatively fit and motivated) sample of participants, and none of the trials reviewed has described a standardized recruitment and screening process to enrol a more heterogeneous, representative sample of CAD patients according to current guidelines (Moher et al. 2001). Thus, the combined sample size of our review ($n = 213$) may be a limitation as it reflects only a minority of patients referred for cardiac rehabilitation who are motivated to exercise, perhaps indicating limited generalizability of these data to the larger cardiac patient population. Future RCTs must address these limitations.

The phases of rehabilitation and details regarding exercise history were also not adequately presented in the trials to date. These data may be important for establishing the timeline to initiate IT, which may contribute to more systematic and effective rehabilitation. For example, IT may be particularly beneficial for CAD patients who have completed 12 weeks of MCT during phase II cardiac rehabilitation and have reached a physiological plateau (Ehsani et al. 1982). Furthermore, the optimal duration of IT programmes for CAD patients has yet to be defined, as short-term (<8 weeks) IT exercise regimes in healthy individuals have produced significant physiological improvements (e.g. peripheral and skeletal muscle adaptations) which may be applicable for older CAD patients (Gibala et al. 2006; McKay et al. 2009). At present, however, more research is required to determine the optimal modalities and doses of exercise and timecourse to adaptations to provide the greatest health benefits in patients with CAD (Fletcher et al. 2001; Guiraud et al. 2009).

The reviewed trials also did not detail if participants were receiving additional components of cardiac rehabilitation, such as dietary modification, smoking cessation, or physical activity recommendations beyond the structured exercise program, and compliance to medications were not specifically detailed. These are clearly confounding variables, and, accordingly, must be reported in future investigations.

Only three RCTs performed randomization of participants to IT and MCT groups (Rognmo et al. 2004; Warburton et al. 2005; Wisløff et al. 2007), and these trials each enrolled fewer than 30 participants. Accordingly, it may be premature to draw conclusions regarding the effectiveness of IT as compared to MCT. It is likely that both modalities of exercise can be implemented as important components of cardiac rehabilitation, and more robust RCTs involving standardized exercise interventions are required to elucidate the relative importance and contribution of each across a number of physiologically important variables, medication usage, and long-term morbidity and mortality (Haskell 1994; Hedback and Perk 1990; Kavanagh et al. 2002).

There is a need to more adequately determine the risks and benefits of IT in this cohort, the outcomes of which can potentially lead to the development of appropriate exercise prescription guidelines (Fletcher et al. 2001; Giannuzzi et al. 2003; Guiraud et al. 2009; Leon et al. 2005). The safety and efficacy of supervised (in-center) as well as unsupervised (home-based) training are important to investigate. Home-based MCT, for example, has been found to be safe (Ades et al. 2000), but the risks of home-based IT have yet to be determined. Home-based exercise programs have important cost and feasibility implications for enhancing long-term compliance and behavior change. Future investigations should also define and describe target subpopulations of cardiac patients, including women and ethnic minorities who are perhaps less likely to access or enrol in an in-center rehabilitation program.

In summary, the effectiveness of cardiac rehabilitation for patients with CAD has been well established but the optimal intensity and type of exercise protocol to yield the greatest health benefits has yet to be defined (Kavanagh et al. 2002). This review highlights significant physiological improvements from IT compared to conventional MCT or usual care control, but we also highlight variations in, and limitations of, the IT studies conducted to date. Further investigation through larger, more robust studies is required to develop effective training prescription guidelines for cardiac rehabilitation programmes.

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