Meta-Analysis of Aerobic Interval Training on Exercise Capacity and Systolic Function in Patients With Heart Failure and Reduced Ejection Fractions

Mark J. Haykowsky, PhD[a,*], Meagan P. Timmons[a], Calvin Kruger[a], Margaret McNeely, PhD[a], Dylan A. Taylor, MD[b], and Alexander M. Clark, PhD[c]

It is unknown if vigorous to maximal aerobic interval training (INT) is more effective than traditionally prescribed moderate-intensity continuous aerobic training (MCT) for improving peak oxygen uptake (Vo_2) and the left ventricular ejection fraction (LVEF) in patients with heart failure with reduced ejection fraction. MEDLINE, PubMed, Scopus, and the Web of Science were searched using the following keywords: "heart failure," high-intensity interval exercise," "high-intensity interval training," "aerobic interval training," and "high-intensity aerobic interval training." Seven randomized trials were identified comparing the effects of INT and MCT on peak Vo_2, 5 of which measured the LVEF at rest. The trials included clinically stable patients with heart failure with reduced ejection fraction with impaired left ventricular systolic function (mean LVEF 32%) who were relatively young (mean age 61 years) and predominantly men (82%). Weighted mean differences were calculated using a random-effects model. INT led to significantly higher increases in peak Vo_2 compared with MCT (INT vs MCT, weighted mean difference 2.14 ml O_2/kg/min, 95% confidence interval 0.66 to 3.63). Comparison of the effects of INT and MCT on the LVEF at rest was inconclusive (INT vs MCT, weighted mean difference 3.29%, 95% confidence interval −0.7% to 7.28%). In conclusion, in clinically stable patients with heart failure with reduced ejection fraction, INT is more effective than MCT for improving peak Vo_2 but not the LVEF at rest. **(Am J Cardiol 2013;111:1466−1469)**

Randomized controlled exercise intervention trials for clinically stable patients with heart failure with reduced ejection fraction (HFREF) have primarily incorporated moderate-intensity continuous aerobic exercise training (MCT).[1,2] Despite beneficial antiremodeling benefits,[1] MCT is associated with a small (0.6 ml/kg/min) to moderate (3 ml/kg/min) increase in peak exercise oxygen uptake (Vo_2).[1,2] We recently reported that a single bout of near maximal (96% of peak heart rate) aerobic interval exercise increased postexercise regional and global left ventricular (LV) systolic function in clinically stable patients with HFREF.[3] However, it is unclear if vigorous to maximal aerobic interval training (INT), based on American College of Sports Medicine guidelines for the classification of exercise intensity,[4] is more effective than traditional MCT at improving peak Vo_2 and the LV ejection fraction (LVEF) in patients with HFREF (mean LVEF ≤50%). Accordingly, we performed a systematic review and meta-analysis to examine the effects of INT compared with those of MCT on these outcomes.

[a]Faculty of Rehabilitation Medicine, [b]Division of Cardiology, Faculty of Medicine & Dentistry, and [c]Faculty of Nursing, University of Alberta, Edmonton, Alberta, Canada. Manuscript received November 30, 2012; revised manuscript received and accepted January 15, 2013.

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*Corresponding author: Tel: 780-492-5970; fax: 780-492-4429.

E-mail address: mark.haykowsky@ualberta.ca (M.J. Haykowsky).

Methods

We searched MEDLINE (1948 to 2012), PubMed, Scopus (1960 to 2012), and the Web of Science (no limit to years published) using the following keywords: "heart failure," high-intensity interval exercise," "high-intensity interval training," "aerobic interval training," and "high-intensity aerobic interval training." We also hand-searched the reference lists of all identified studies and previous reviews. The primary and secondary end points were peak Vo_2 and the LVEF at rest, respectively. Two investigators independently reviewed the titles and abstracts of all citations. Data were extracted by 2 reviewers (M.J.H., M.M.) and analyzed using the change from baseline data, and results were combined as weighted mean differences with 95% confidence intervals using RevMan software (Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was assessed using chi-square tests. Quality assessment of randomized controlled trials and concealment of treatment allocation were determined as previously described.[1]

Results

After initial review of 88 citations and 5 additional citations identified from manual searches (Figure 1), 7 unique randomized trials were identified comparing the effects of INT with those of MCT on peak Vo_2 in patients with HFREF,[5−11] 5 of which measured the LVEF at

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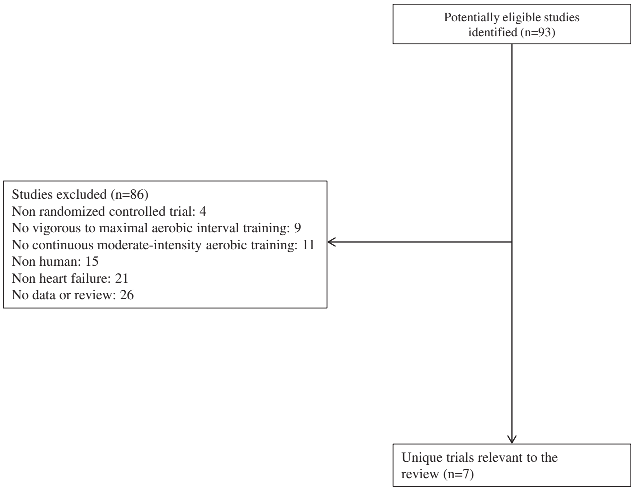

Figure 1. Flow of trials through the selection process.

rest[5,6,8,9,11] (Table 1). Reasons for exclusion are reported in Figure 1. The trials included clinically stable patients with HFREF with impaired LV systolic function (mean LVEF 32%) who were relatively young (mean age 61 ± 9 years) and predominantly men (82%). No trial was double-blind (as expected with this type of intervention), very few trials described randomization procedures, no trial reported blinding of assessors across all objective outcomes, and concealment of treatment allocation was unclear for all trials. Thus, trials scored relatively poorly on the Jaded scale (Table 1).

INT led to significantly larger increases in peak VO_2 compared with MCT (INT vs MCT, weighted mean difference 2.14 ml O_2/kg/min, 95% confidence interval 0.66 to 3.63; Figure 2). However, the effects of INT compared with those of MCT on the LVEF at rest were inconclusive (INT vs MCT, weighted mean difference 3.29%, 95% confidence interval −0.7% to 7.28%; Figure 3). Because of

Table 1
Description of included studies

Study	Group (n)	Cause of HF (DCM/ICM) (%)	Age (yrs)	Men	LVEF (%)	Training Program					Jaded Score (1−5)
						Mode	Frequency (Days/Week)	Intensity	Duration (Minutes)	Program Length (Weeks)	
Dimopoulos et al[7]	MCT (14)	57/36	62	100%	31	CE	3	50%−60% PPO	40	12	2
	INT (10)	60/40	59	90%	35	CE	3	100%−120% PPO × 30 seconds followed by 30 seconds of rest	40	12	
Freyssin et al[10]	MCT (14)	NR/86	55	50%	31	CE, TM	5	HR at VT_1 + gym	360 min/week	8	2
	INT (12)	NR/83	54	50%	28	CE	5	80%−120% PPO × 30 seconds followed by 1 minute of rest × 12 times + gym	168 min/week	8	
Fu et al[9]	MCT (13)	27/60	66	62%	39	CE	3	60% peak VO_2	30	12	1
	INT (14)	20/67	68	64%	38	CE	3	80% peak VO_2 × 3 minutes followed by 3 minutes at 40% peak VO_2 × 5	30	12	
Iellamo et al[6]	MCT (8)	0/100	63	100%	32	TM	2−5	45%−60% HRR	30−45	12	2
	INT (8)	0/100	62	100%	34	TM	2−5	75%−80% HRR × 4 minutes followed by 4 minutes at 45%−50% HRR × 4	—	12	
Nechwatal et al[8]	MCT (18)	70/30	47	95%	27	CE	6	75% maximal HR (maximal PO 55 W)	15	3	2
	INT (17)	70/30	45	90%	29	CE	6	30 seconds at 35%−50% PO from SRT followed by 1 minute recovery (maximal interval and recovery PO 74 and 34 W, respectively)	15	3	
Smart and Steele[5]	MCT (13)	NR/70	63	100%	30	CE	3	70% peak VO_2	30	16	1
	INT (10)	NR/50	59	80%	27	CE	3	70% peak VO_2 (1 minute exercise and rest)	60	16	
Wisloff et al[11]	MCT (8)	0/100	74	88%	33	TM	3	70%−75% peak HR	47	12	3
	INT (9)	0/100	77	78%	28	TM	3	90%−95% peak HR × 4 minutes followed by 50%−70% peak HR × 4	38	12	

CE = cycle ergometer; DCM = dilated cardiomyopathy; gym = gymnastics; HR = heart rate; HRR = heart rate reserve; ICM = ischemic cardiomyopathy; NR = not reported; PPO = peak power output; SRT = steep ramp test (power output increases by 25 W every 10 seconds); TM = treadmill; VT_1 = first ventilation threshold.

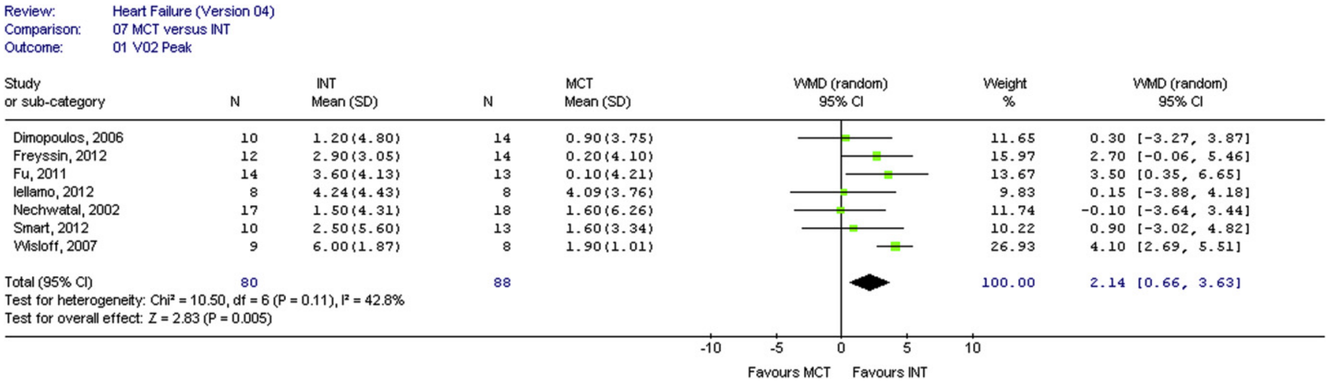

Figure 2. Effects of INT versus MCT on peak V_{O_2}. CI = confidence interval; WMD = weighted mean difference.

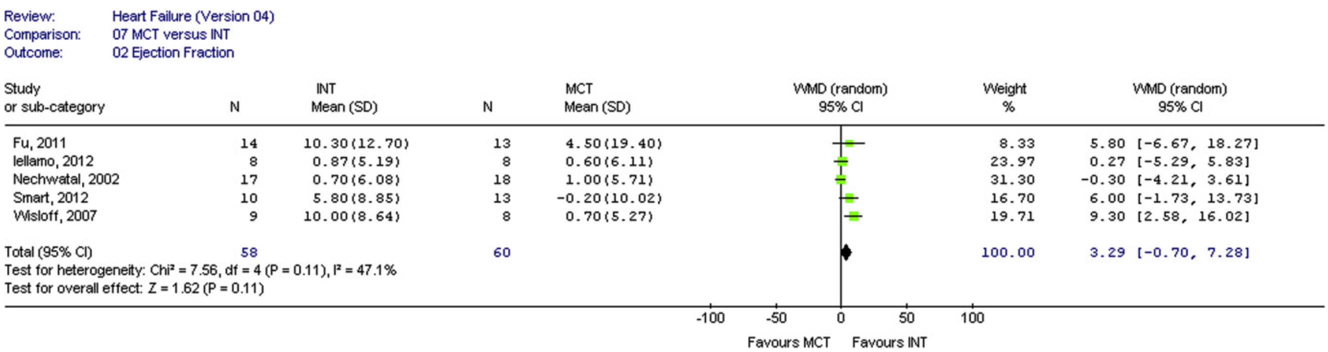

Figure 3. Effects of INT versus MCT on the LVEF at rest. CI = confidence interval; WMD = weighted mean difference.

population differences, moderate levels of clinical heterogeneity existed across studies (Figures 2 and 3). However, in terms of methodologic heterogeneity, the intensity of exercise for the INT and MCT groups was similar across studies.

Discussion

Our findings indicate that in clinically stable patients with HFREF, INT is more effective than MCT for improving peak V_{O_2}. The biologic mechanisms through which INT results in higher changes in peak V_{O_2} may be due to intensity-dependent improvements in exercise cardiovascular and skeletal muscle function.[3,8,9,11,12] Tomczak et al,[3] using cardiac magnetic resonance imaging, recently found that an acute bout of INT was associated with a significant increase in the LVEF and a concomitant decrease in systemic vascular resistance 30 minutes after the cessation of exercise in clinically stable patients with HFREF. Meyer et al[12] performed the first study of INT in clinically stable patients with HFREF and found that 3 weeks of training resulted in a significant increase in the ventilation threshold, peak exercise oxygen pulse, and peak V_{O_2}. In a later study, Nechwatal et al[8] reported that 3 weeks of INT significantly increased submaximal exercise cardiac index (9%) and decreased systemic vascular resistance (7%), with no change after MCT in patients with HFREF. Fu et al[9] extended these findings by showing that 12 weeks of INT significantly increased peak exercise stroke volume (30%) and cardiac output (31%) and decreased systemic vascular resistance (23%), with no change after MCT in patients with HFREF. Finally, improved skeletal muscle oxidative capacity may play an important role in the INT-mediated increase in peak V_{O_2}, as Wisloff et al[11] demonstrated that the change in peroxisome proliferator−activated receptor γ coactivator 1α, a regulator of mitochondrial biogenesis, was significantly higher after INT compared with MCT in older patients with HFREF. A consequence of the INT-mediated improvement in cardiovascular and skeletal muscle function is that convective oxygen delivery and oxygen utilization would increase to a greater extent than with MCT during peak exercise in clinically stable patients with HFREF. Despite benefits for peak V_{O_2}, INT was not more effective than MCT at attenuating LV remodeling, as the LVEF at rest was not significantly different between groups.

Despite the benefits of INT, this form of training is not without risk. Specifically, vigorous physical exercise is associated with an acute and transient increase myocardial infarction or sudden death in patients with structural heart disease.[13] In this review, 6 of 7 studies reported on the safety of INT, and there was no evidence of serious adverse cardiac events associated with this form of training, and the percentage of subjects completing INT (90%) was similar to that completing MCT (91%). Nevertheless, before performing INT, all patients with HFREF should undergo cardiopulmonary exercise testing,[13] and all training sessions should be performed in a supervised setting after careful assessment and with monitoring.

Our conclusions are constrained by the quality of the trials reviewed. Specifically, few trials included provided clear descriptions of the randomization and allocation of participants to treatments. In addition, no trials reported on blinding of assessors for all outcome measures. Accordingly, higher quality large-scale randomized controlled trials are required to determine the safety, mechanisms of improvement of peak Vo_2, and survival benefits of INT compared with MCT in clinically stable patients with heart failure.

Disclosures

The authors have no conflicts of interest to disclose.

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