Journal of the American College of Cardiology Vol. 49, No. 24, 2007

Published by Elsevier Inc.
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.02.055

A Meta-Analysis of the Effect of Exercise Training on Left Ventricular Remodeling in Heart Failure Patients

The Benefit Depends on the Type of Training Performed

Mark J. Haykowsky, PhD,* Yuanyuan Liang, PhD,† David Pechter, BA,* Lee W. Jones, PhD,§ Finlay A. McAlister, MD, MSc,‖ Alexander M. Clark, PhD‡

Edmonton, Alberta, Canada; and Durham, North Carolina

Objectives The aim of this study was to determine the effect of exercise training and type of exercise (aerobic vs. strength vs. combined training) on left ventricular (LV) remodeling in heart failure (HF).

Background A number of randomized controlled trials have examined the effect of exercise training on LV remodeling in individuals with HF. However, the results of these trials have been inconclusive.

Methods The authors searched MEDLINE (1966 to 2006), Cochrane Central Register of Controlled Trials (issue #3, 2006), CINAHL (1982 to 2006), EMBASE (1988 to 2006), PubMed (1966 to 2006), and reference lists of identified studies for randomized controlled trials examining the effects of exercise training on ejection fraction (EF), end-diastolic volume (EDV), and end-systolic volume (ESV) in clinically stable patients with HF. Primary study authors were also contacted if appropriate. Studies were selected and data were extracted independently by 2 reviewers. Weighted mean differences (WMD) were calculated using a random effects model.

Results Fourteen trials reported EF data (n = 812 patients). Seven trials reported both EDV and ESV data (n = 569). Aerobic training significantly improved EF (9 trials, 538 patients, WMD = 2.59%; 95% confidence interval [CI] 1.44% to 3.74%), EDV (371 patients; WMD = −11.49 ml; 95% CI −19.95 to −3.02 ml) and ESV (371 patients; WMD = −12.87 ml; 95% CI −17.80 to −7.93 ml). Combined aerobic and strength training was not associated with significant improvements in EF, EDV, or ESV.

Conclusions Aerobic training reverses LV remodeling in clinically stable individuals with HF. This benefit was not confirmed with combined aerobic and strength training. (J Am Coll Cardiol 2007;49:2329–36) © 2007 by the American College of Cardiology Foundation

Heart failure (HF) is an increasingly common syndrome associated with poor prognosis and high health care costs (1). A cardinal feature of HF is the progressive chamber dilation and deterioration in pump function resulting from increased hemodynamic load and neurohormonal stress. This process, termed left ventricular (LV) remodeling (2), is associated with increased morbidity and mortality; therefore, interventions that halt or reverse ventricular remodeling should improve these clinical outcomes. Indeed, the favorable benefits associated with pharmacologic, electrophysiologic, or device therapies are due, in part, to these therapies' ability to slow or reverse LV remodeling (3–8).

See page 2337

As part of the cadre of interventions to manage HF effectively, exercise training is now recommended by a number of international scientific organizations for patients with mild to moderate HF symptoms (9,10). This recognition stems from studies reporting that exercise training can improve peak oxygen consumption (VO_{2peak}) (9–11), muscle strength and mass (11), New York Heart Association functional class (12), and quality of life (9,13) in HF patients. Although exercise training can restore the abnormal autonomic, neurohormonal, and hemodynamic function associated with the HF syndrome (12,14–16), and, in some studies (17), has been shown to reverse LV remodel-

From the *Faculty of Rehabilitation Medicine, †Alberta Research Centre for Child Health Evidence, and ‡Faculty of Nursing, University of Alberta, Edmonton, Alberta, Canada; §Department of Surgery, Duke University Medical Center, Durham, North Carolina; and the ‖Division of General Internal Medicine, University of Alberta Hospital, Edmonton, Alberta, Canada. Dr. Haykowsky holds a Canadian Institutes of Health Research (CIHR) New Investigator award. Drs. Clark and McAlister hold salary awards from the Alberta Heritage Foundation for Medical Research. Dr. McAlister also holds a CIHR New Investigator Award and the Merck Frosst/Aventis Chair in Patient Health Management at the University of Alberta.

Manuscript received December 14, 2006; revised manuscript received Feburary 16, 2007, accepted February 20, 2007.

Abbreviations and Acronyms

CI = confidence interval
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
HF = heart failure
LV = left ventricle/ventricular
SMD = standardized mean difference
Vo_{2peak} = peak oxygen consumption
WMD = weighted mean difference

ing in clinically stable HF patients, several other investigators (18,19) reported no benefits with exercise training on LV end-diastolic volume (EDV), end-systolic volume (ESV), or ejection fraction (EF). Thus, uncertainty remains regarding the effects of exercise training on LV remodeling in patients with HF. In an attempt to resolve this issue, we performed a meta-analysis to examine the effects of exercise training on these outcomes and determine whether the type of exercise training influenced these effects.

Methods

Data sources. The authors searched MEDLINE (1966 to 2006); Cochrane Central Register of Controlled Trials (issue #3, 2006), CINAHL (1982 to 2006), EMBASE (1988 to 2006), PubMed (1966 to 2006) using the following MESH terms and text words: *heart failure, exercise, exercise therapy, exercise test, therapeutic exercise, cardiac rehabilitation,* and *kinesiotherapy*. We also hand-searched reference lists of all identified studies, previous systematic reviews (20), and the Cochrane Collaboration's review of exercise rehabilitation for HF. We excluded non-English articles.

Study selection. Two investigators (M.J.H. and A.M.C.) independently reviewed the titles and abstracts of all citations to identify studies reporting the effect of exercise training on EF and/or LV volumes in patients with HF. Both investigators obtained the full text of potentially relevant articles and independently reviewed them using prestandardized data abstraction forms and eligibility criteria defined a priori. We excluded studies that were not randomized or were crossover trials, did not have a usual care control group, had an intervention group that also received a pharmacologic intervention, or had HF patients who were not clinically stable for at least 1 month before the exercise intervention.

Data extraction and quality assessment. The 2 investigators extracted all outcome data independently. When necessary, original investigators were contacted to clarify data. Authors for 2 studies provided further data. Quality was assessed using the previously validated Jadad scale (21) (a 5-point scale based on adequacy of reporting for randomization, double-blinding, and disclosure of withdrawals and dropouts) and adequacy of allocation concealment.

Data synthesis and analysis. Data were analyzed using the change from baseline data for both exercise and control groups. Results were combined as weighted mean differences (WMD) with 95% confidence intervals (CI) using a random effects model. Heterogeneity was quantified using the I^2 statistic. As we anticipated heterogeneity on the basis of type of exercise, we planned to explore differences in effects for different types of exercise training (aerobic training, strength training, or combined aerobic and strength training). Sensitivity analyses were performed to examine the robustness of the effect by using standardized mean difference (SMD) for LV volume data. In addition, we conducted sensitivity analyses to determine whether blinding of the person assessing EF, EDV, and ESV to group allocation influenced the magnitude of any observed effects. Publication bias was tested visually using the funnel plot (22) and quantitatively using the Begg adjusted-rank correlation test (23) and Egger regression asymmetry test (24).

Results

Study selection and evaluation. We identified 1,647 citations from electronic databases. After initial screening, 19 full manuscripts were reviewed, but 5 of these manuscripts were excluded because they did not report EF (n = 2), did not include a control group (n = 2), or were an additional publication from an already included trial (n = 1) (Fig. 1).

Studies included in the systematic review. Fourteen unique randomized trials were identified (Table 1). (12,13,17–19,25–33). The trials included clinically stable patients with HF symptoms and impaired LV systolic function (weighted mean EF = 23%), who were relatively young (mean age 57 ± 5 years) and predominantly men (89%). Most trials incorporated aerobic training at an intensity between 60% and 80% of baseline Vo_{2peak} for 20 to 60 min per exercise session (12,13,17,19,26–28,31,33) (Table 1). Four trials examined the effects of combined aerobic and strength training (18,29,30,32), and one trial examined strength training alone (25). The length of the training program varied between 2 and 12 months.

No trial was double-blind (which is not surprising given the type of intervention), and very few trials described randomization procedures. Only 4 trials (12,17,18,25) stated that the persons assessing EF, EDV, and ESV were blinded to group allocation (i.e., blinded ascertainment of outcomes). Therefore, trials scored relatively poorly on the Jadad scale: 7 received a score of 1 of 5, 5 studies received a score of 2 of 5, and 2 studies scored 3 of 5.

Quantitative data synthesis. EXERCISE TRAINING AND LV EJECTION FRACTION. Although exercise training was associated with a significant improvement in EF when data from all trials were pooled (14 trials; 812 patients; WMD = 1.83%; 95% CI 0.45% to 3.21%), this analysis demonstrated substantial heterogeneity (I^2 = 49.2%). However, the results from the trials of aerobic training demonstrated relatively consistent benefits in EF (9 trials, 538 patients, WMD = 2.59%; 95% CI 1.44% to 3.74%, I^2 = 17.2%) (Fig. 2). The 1 trial testing strength training alone was inconclusive (WMD in EF = −4.5%, 95% CI −13.14% to +4.14%). Trials testing combined training (aerobic plus strength exercise) were also inconclusive (4 trials, 249 patients, WMD for EF = 0.37%; 95% CI −2.23% to +2.97%, I^2 = 25.7%).

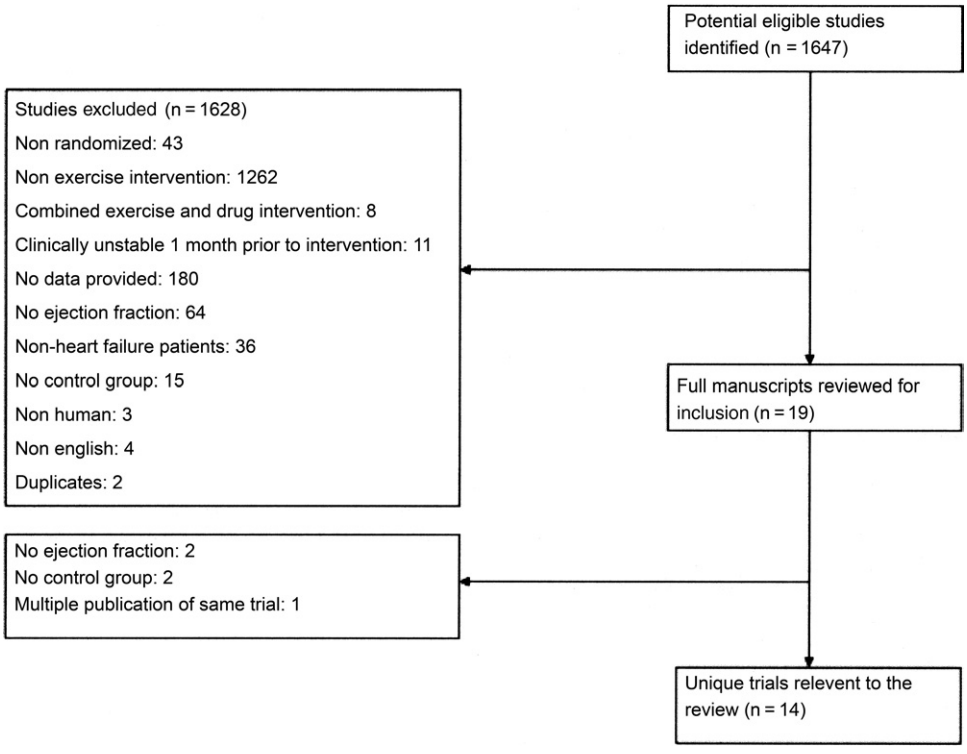

Figure 1 Flow of Trials Through the Selection Process

EXERCISE TRAINING AND LEFT VENTRICULAR VOLUMES. Seven of 14 trials examined the effect of exercise training on LV volumes (12,13,17–19,32,33). Aerobic training was performed in 5 of these trials (12,13,17,19,33); combined aerobic and strength training was performed in the remaining trials (18,32). Overall, exercise training was associated with a significant decline in EDV (569 patients; WMD = −9.75 ml; 95% CI −16.64 to −2.86 ml) and ESV (569 patients; WMD = −12.31 ml; 95% CI −17.12 to −7.49 ml). Although aerobic training led to significant improvements in EDV (371 patients; WMD = −11.49 ml; 95% CI −19.95 to −3.02 ml) and ESV (371 patients; WMD = −12.87 ml; 95% CI −17.80 to −7.93 ml) (Figs. 3 and 4), the effects of combined aerobic and strength training were inconclusive for both EDV (198 patients; WMD = +0.39 ml; 95% CI −25.84 to +26.62 ml, I^2 = 0%) (Fig. 3) and ESV (WMD = −0.73 ml; 95% CI −23.19 to +21.72 ml; I^2 = 0%) (Fig. 4).

Given that the investigators of 2 aerobic intervention trials (17,33) referenced their volume data to body surface area, and the remaining aerobic trials reported absolute volumes, we performed sensitivity analysis using the SMD. These results further confirmed that aerobic training was associated with a significant and favorable decline in EDV (SMD = −0.36; 95% CI −0.56 to −0.15; I^2 = 0%) and ESV (SMD = −0.50; 95% CI −0.72 to −0.28; I^2 = 8.6%).

Our analysis of the impact that blinding of the person assessing EF, EDV, and ESV had on the observed results revealed an inconsistent effect. For EF, the 4 trials that reported blinded ascertainment of outcomes reported a smaller and less consistent effect with exercise training (blinded trials: WMD = 0.80%, 95% CI −2.86% to 4.46% but with 83% heterogeneity; nonblinded trials: WMD = 2.17%, 95% CI 1.00% to 3.34% with 0% heterogeneity). However, the blinded outcome ascertainment trials reported nonsignificantly greater benefits than the nonblinded outcome trials on EDV (blinded trials: WMD = −15.5 ml, 95% CI −35.81 to 4.80 ml; nonblinded trials: WMD = −7.14 ml, 95% CI −13.80 to −0.48 ml) and ESV (blinded trials: WMD = −16.91 ml, 95% CI −30.78 to −3.04 ml; nonblinded trials: WMD −11.08 ml, 95% CI −16.44 to −5.71 ml).

ADDITIONAL END POINTS. Aerobic exercise training was associated with a statistically significant increase in Vo_{2peak} (9 trials; 538 patients; WMD = 2.98 ml·kg·min^{-1}; 95% CI 2.47 to 3.49 ml·kg·min; I^2=16.3%), whereas the effect of combined aerobic and strength training on this end point remains uncertain (88 patients; WMD = 1.83 ml·kg·min; 95% CI −1.87 to +5.53 ml·kg·min; p value for heterogeneity = 0.002; I^2 = 83.7%).

Publication bias. There was no evidence of publication bias (Begg adjusted-rank correlation test, p = 0.66; Egger regression asymmetry test, p = 0.92).

Discussion

This review indicates that aerobic exercise training reverses ventricular remodeling in clinically stable individuals with

Table 1 Description of Included Studies

Study, Year (Ref.)	Study Sample	Sample Size, n	Men, %	Mean Age, yrs	Key Components of Exercise Intervention	Duration of Intervention, months	Method Used to Measure EF	Drug Therapy (%)
Koch et al., 1992 (25)	NYHA functional class II–III HF (etiology: IC or IDC), LVEF <40%	EXT, 12	67	56	ST (KOCH bench) 90 min per session × 40 sessions over 90 days using small number of muscle groups	3	Echo	ACE: 92 BB: NR DIU: 50
		CNT, 13	85	54	—	3		ACE: 100 BB: NR DIU: 85
Belardinelli et al., 1995 (26)	NYHA functional class II–III HF (etiology: IC and IDC)	EXT, 36	86	55	AT (CE), 3 days/week at 60% Vo_{2peak} × 40 min	2	Echo	ACE: 92 BB: NR DIU: 83
		CNT, 19	84	54	—	2		ACE: 100 BB: NR DIU: 84
Belardinelli et al., 1996 (27)	Clinically stable HF (etiology: IC)	EXT, 29	93	55	AT (CE), 3 days/week at 60% Vo_{2peak} × 40 min	2	RV	ACE: 83 BB: NR DIU: 100
		CNT, 14	79	54	—	2		ACE: 79 BB: NR DIU: 100
Kiilavuori et al., 1996 (28)	NYHA functional class II–III HF (etiology: IC or IDC), LVEF <40%	EXT, 12	100	52	AT (CE, ROW, SW, WLK) 3 days/week at 50–60% Vo_{2peak} × 30 min	6	Echo	ACE: 92 BB: 33 DIU: 92
		CNT, 15	93	52	—	6		ACE: 93 BB: 13 DIU: 73
Belardinelli et al., 1999 (13)	NYHA functional class II–IV HF (etiology: IC or IDC), LVEF ≤40%	EXT, 50	90	56	AT (CE), 2–3 days/week at 60% Vo_{2peak} × 40 min	14	Echo	ACE: 90 BB: NR DIU: 92
		CNT, 49	88	53	—	14		ACE: 88 BB: NR DIU: 90
Hambrecht et al., 2000 (12)	NYHA functional class I–III HF (etiology: IC or IDC), LVEF <40%, peak power output >25 W	EXT, 36	100	54	AT (CE), 7 days/week at 70% Vo_{2peak} × 20–60 min	6	Echo	ACE: 94 BB: 8 DIU: 78
		CNT, 37	100	55	—	6		ACE: 95 BB: 16 DIU: 78
McKelvie et al., 2002 (18)	NYHA functional class I–III HF (etiology: IC, IDC, HYP, VALV), LVEF ≤40%, 6MWD <500 m	EXT, 90	82	65	AT (AE, CE, TM, WLK), 2–3 days/ week at 60%–70% HR_{max} × 30 min plus ST (AC, KE, LP) 2–3 days/week, 1–3 sets × 10–15 repetitions at 40%–60% 1RM	12	RV	ACE: 91 BB: 20 DIU: 81
		CNT, 91	80	66	—	12		ACE: 92 BB: 23 DIU: 86
Myers et al., 2002 (19)	NYHA functional class II–III HF (etiology: IDC)	EXT, 12	83	53	AT (CE), 5 days/week at 60%–80% Vo_{2max} and BORG RPE 13–15 × 45 min	2	CM	ACE: 100 BB: 75 DIU: 83

Continued on next page

Table 1 Continued

Study, Year (Ref.)	Study Sample	Sample Size, n	Men, %	Mean Age, yrs	Key Components of Exercise Intervention	Duration of Intervention, months	Method Used to Measure EF	Drug Therapy (%)
		CNT, 12	83	58	—	2		ACE: 92 BB: 75 DIU: 83
Giannuzzi et al., 2003 (17)	NYHA functional class II–III HF (etiology: IC, IDC, VALV), LVEF ≤35%, Vo_{2peak} <20 ml·kg·min^{-1}	EXT, 45	100	60	AT (CE, WLK), 3 to 5 days/week at 60% Vo_{2peak} × 30–60 min	6	Echo	ACE: 91 BB: 22 DIU: 91
		CNT, 45	100	61	—	6		ACE: 93 BB: 20 DIU: 91
Roveda et al., 2003 (29)	NYHA functional class II–III HF (IC, IDC, Chagas), LVEF ≤40%	EXT, 7	71	53	AT (CE), 3 days/week at HR at AnT × 25 to 40 min plus ST (sit-ups, push-ups, pull-ups) × 10 min	4	NR	ACE: 100 BB: 0 DIU: 100
		CNT, 9	67	53	—	4		ACE: 100 BB: 0 DIU: 78
Sabelis et al., 2004 (30)	NYHA functional class II–III HF (etiology: IC or IDC)	EXT, 16	100	60	AT (CE-INT training) 4 days/week at 50% Vo_{2peak} and 70% HR_{peak} for 11–50 min plus ST (5BX program strengthening the abdominal, gluteal, posterior leg and arm muscles) 4 days/week	6.5	Echo	Data reported for all subjects ACE: 79 BB: 45 DIU: 45
		CNT, 13	100	60	—	6.5		
Klocek et al., 2005 (31)	NYHA functional class II–III HF (etiology: IC), LVEF <40%	EXT, 28	100	56	AT (n = 14, CE), 3 days/week at 60% HR_{max} × 25 min (INT). AT (n = 14, CE), 3 days/week at 75% HR_{max} × 25 min (CONT)	6	Echo	ACE: 100 BB: 54 DIU: 100
		CNT, 14	100	55	—	6		ACE: 100 BB: 57 DIU: 100
Jonsdoittir et al., 2006 (32)	NYHA functional class II–III HF (etiology: IC, AF, VALV, HYP)	EXT, 21	76	68	AT (CE), 2 days/week at 50% PPO × 15 min plus ST (CWT) of arms and legs at 20%–40% 1RM × 20 min	5	Echo	ACE: 38 BB: 52 DIU: 81
		CNT, 22	82	69	—	5		ACE: 23 BB: 64 DIU: 86
Passino, et al., 2006 (33)	NYHA functional class I–III HF (etiology: IC, IDC), LVEF <45%, Vo_{2peak} <25 ml·kg·min^{-1}	EXT, 44	89	60	AT (CE, 3 days/week at 65% Vo_{2peak} × 30 min)	9	NR	ACE: 78 BB: 72 DIU: 100
		CNT, 41	85	61	—	9		ACE: 79 BB: 73 DIU: 100

AC = arm curl; ACE = angiotensin converting enzyme inhibitor; AE = arm ergometer; AF = atrial fibrillation; AnT = anaerobic threshold; AT = aerobic training; BB = beta-blocker; BORG RPE = Borg rate of perceived exertion; CE = cycle ergometer; CM = cardiac magnetic resonance imaging; CNT = control group; CONT = continuous aerobic training; CWT = circuit weight training; DIU = diuretic; ECHO = echocardiography; EXT = exercise training group; HF = heart failure; HR = heart rate; HR_{max} = maximal heart rate; HYP = hypertensive; IC = ischemic cardiomyopathy; IDC = idiopathic dilated cardiomyopathy; INT = interval training; KE = knee extension; LP = leg-press; LVEF = left ventricular ejection fraction; NR = not reported; NYHA = New York Heart Association; PPO = peak power output; RM = one-repetition maximum; ROW = rowing; RV = radionuclide ventriculography; ST = strength training; SW = swimming; TM = treadmill; VALV = valvular; Vo_{2peak} = peak aerobic power; Vo_{2max} = maximal aerobic power; WLK = walking; 6MWD = distance walked in 6 min.

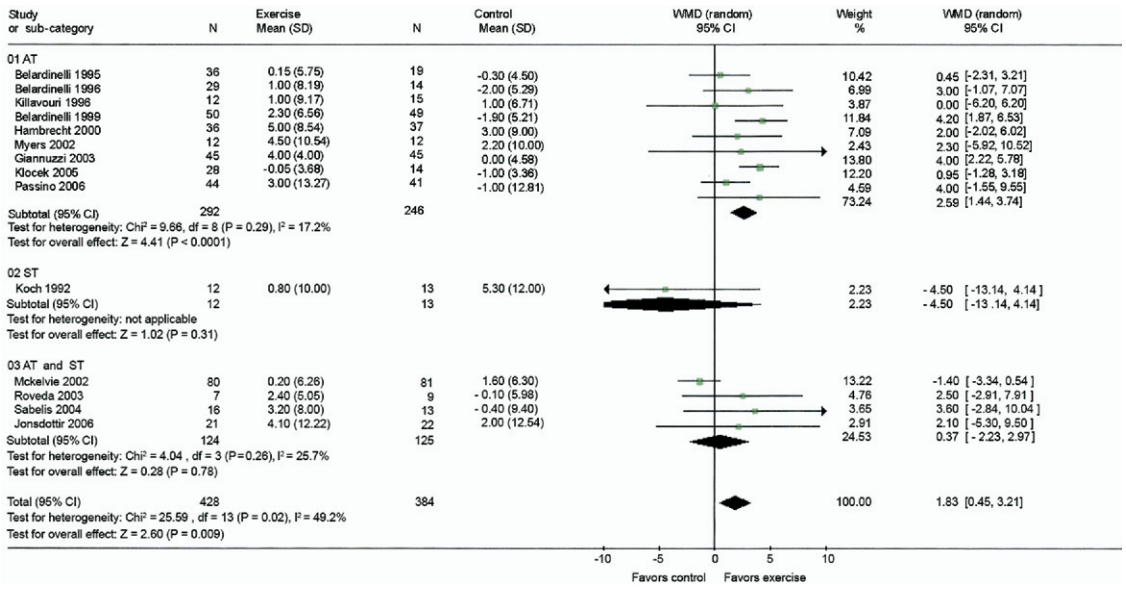

Figure 2 **Exercise Training and Ejection Fraction**

AT = aerobic training; CI = confidence interval; ST = strength training; WMD = weighted mean differences.

HF. The favorable changes in LV volumes and EF associated with aerobic training were supplementary to pharmacologic benefits; that is, they occurred despite the patients being prescribed medications with a proven antiremodeling effect (Table 1). Overall, the magnitude of the improvement in EF is consistent with the magnitude of benefits seen with angiotensin-converting enzyme inhibitors or cardiac resynchronization therapy (3,34).

The mechanism whereby aerobic training attenuates LV remodeling is not known; however, it may be due to the reduction in vasoconstrictive neurohormones or a decline in hemodynamic loading. Braith et al. (14) and others (12,15,33) have reported that aerobic training reduces resting plasma angiotensin II, aldosterone, vasopressin, atrial natriuretic peptide, brain natriuretic peptide, epinephrine, and norepinephrine levels. Coats et al. (16) also reported that short-term aerobic training is associated with a decrease in sympathetic tone and a concomitant increase in vagal activity in stable HF patients. The improved sympathovagal balance, coupled with the decline in vasoconstrictive neurohormones, is associated with a reduction in vascular load that may attenuate LV remodeling. Indeed, Hambrecht

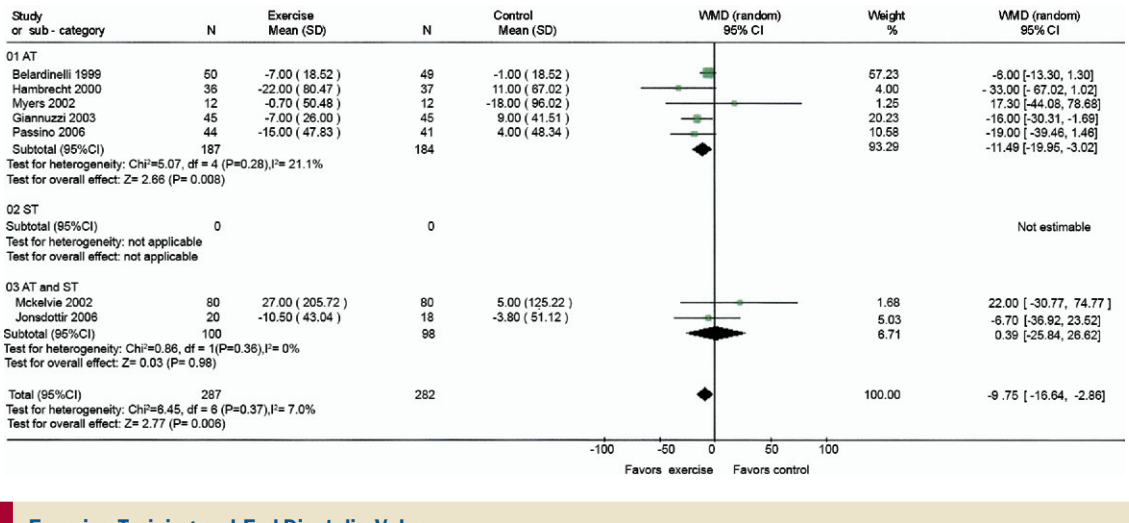

Figure 3 **Exercise Training and End-Diastolic Volume**

Abbreviations as in Figure 2.

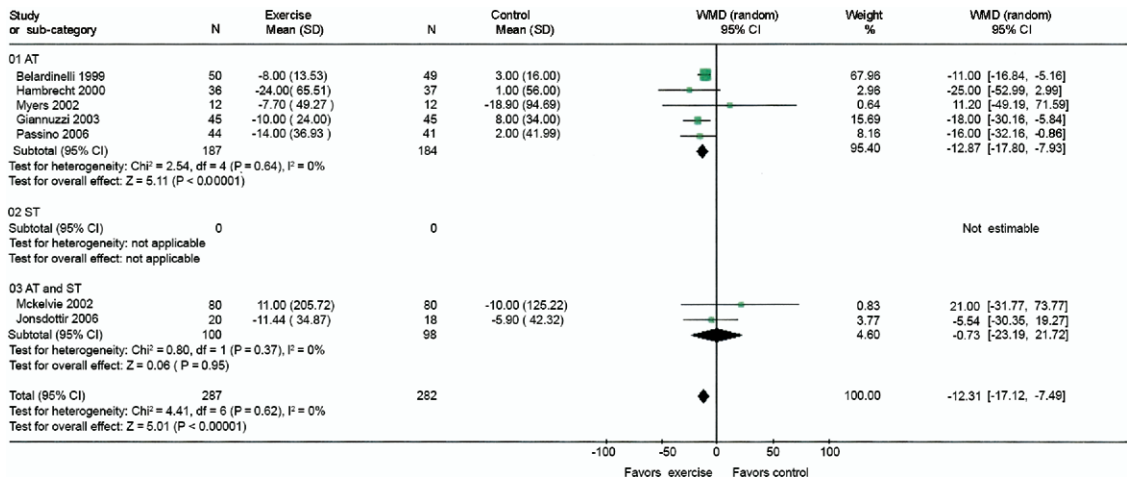

Figure 4 **Exercise Training and End-Systolic Volume**

Abbreviations as in Figure 2.

et al. (12,15) have shown that the reduction in resting LV end-diastolic volume and increase in peak exercise stroke volume that occurred with aerobic training were related to the decline in resting and peak exercise systemic vascular resistance, respectively (12). Belardinelli et al. (27,35) extended these findings by demonstrating that aerobic training also improves myocardial contractility and diastolic filling in individuals with ischemic cardiomyopathy and impaired LV systolic function. Our finding of increased EF after aerobic training is likely attributable to enhanced preload, myocardial contractility, and vascular reserve.

An unexpected finding was that strength training was not associated with demonstrable benefit in LV remodeling; indeed, the favorable antiremodeling role of aerobic exercise was not confirmed when this mode of exercise was combined with strength training. This may be because of the heightened systolic and diastolic pressure loading that occurs with strength training (36–38). Moreover, the strength-training-mediated increase in LV wall stress, coupled with the impaired contractile and preload reserve, could explain why LV stroke volume and EF do not increase when HF patients perform this type of exercise (36,37).

Our finding that aerobic training is associated with a significant increase in Vo_{2peak} is similar to previous systematic reviews that examined the effect of exercise rehabilitation on clinical outcomes in HF (39,40). Indeed, a recent meta-analysis by Piepoli et al. (41) found that exercise training was associated with a reduction in overall mortality in individuals with HF. Importantly, 8 of the 9 trials included in their analysis incorporated aerobic exercise training. A limitation of previous meta-analyses (39,40) is that they did not examine the effect of exercise or mode of exercise training on LV remodeling. Also, in contrast to previous reviews (20,39), we excluded studies that were not strictly randomized.

Study limitations. As with most meta-analyses, our conclusions are constrained by the restricted nature of trial participants: the vast majority of HF patients in these trials were clinically stable younger men with systolic dysfunction, which is not typical of the demographic profile in population-based studies of HF patients (42). A more representative population is currently being recruited to the HF-ACTION trial, the largest randomized controlled trial to date examining the effect of exercise training on clinical outcomes in HF (9). Another limitation of our analysis is low use of beta-blockers in the studies included. Indeed, beta-blockers have been shown to have a greater effect on LV size and ejection fraction compared to that found with exercise training in this meta-analysis (8). An additional limitation is the lack of trials examining the effect of strength training alone on LV remodeling. Finally, our conclusions were constrained by the quality of the trials reviewed, the majority of which did not incorporate blinding at any stage. In particular, only 4 of these trials included blinded outcomes ascertainment (i.e., the persons assessing EF, EDV, and ESV were not blinded to treatment group allocation in most of these trials). Although we did not find a consistent difference in the effects demonstrated in blinded and nonblinded trials, future trials of the impact of exercise training on LV remodeling should incorporate blinded outcomes ascertainment, given the known interobserver variability in assessments of EF, EDV, and ESV with current techniques.

Conclusions

Aerobic training is an inexpensive and effective nondrug, nondevice, nonsurgical intervention that reverses ventricular remodeling and improves Vo_{2peak} in clinically stable individuals with HF and LV systolic dysfunction. These benefits were not confirmed with combined aerobic and strength training.

Acknowledgment

The authors thank the investigators listed in reference 32 for providing further details about their study.

Reprint requests and correspondence: Dr. Mark J. Haykowsky, 2-50, Corbett Hall, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, Alberta T6G 2G4, Canada. E-mail: mark.haykowsky@ualberta.ca.

REFERENCES

1. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006;113:e85–151.
2. Pfeffer JM, Pfeffer MA, Braunwald E. Influence of chronic captopril therapy on the infarcted left ventricle of the rat. Circ Res 1985;57:84–95.
3. Konstam MA, Rousseau MF, Kronenberg MW, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. Circulation 1992;86:431–8.
4. St. John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 2003;107:1985–90.
5. Wong M, Staszewsky L, Latini R, et al. Valsartan benefits left ventricular structure and function in heart failure: Val-HeFT echocardiographic study. J Am Coll Cardiol 2002;40:970–5.
6. Tsutamoto T, Wada A, Maeda K, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. J Am Coll Cardiol 2001;37:1228–33.
7. Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med 2006;355:1873–84.
8. Groenning BA, Nilsson JC, Sondergaard L, Fritz-Hansen T, Larsson HB, Hildebrandt PR. Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure. J Am Coll Cardiol 2000;36:2072–80.
9. Pina IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: a statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation 2003;107:1210–25.
10. Recommendations for exercise training in chronic heart failure patients. Eur Heart J 2001;22:125–35.
11. Haykowsky MJ, Ezekowitz JA, Armstrong PW. Therapeutic exercise for individuals with heart failure: special attention to older women with heart failure. J Card Fail 2004;10:165–73.
12. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. JAMA 2000;283:3095–101.
13. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation 1999;99:1173–82.
14. Braith RW, Welsch MA, Feigenbaum MS, Kluess HA, Pepine CJ. Neuroendocrine activation in heart failure is modified by endurance exercise training. J Am Coll Cardiol 1999;34:1170–5.
15. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. J Am Coll Cardiol 1995;25:1239–49.
16. Coats AJ, Adamopoulos S, Radaelli A, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. Circulation 1992;85:2119–31.
17. Giannuzzi P, Temporelli PL, Corra U, Tavazzi L. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) Trial. Circulation 2003;108:554–9.
18. McKelvie RS, Teo KK, Roberts R, et al. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). Am Heart J 2002;144:23–30.
19. Myers J, Wagner D, Schertler T, et al. Effects of exercise training on left ventricular volumes and function in patients with nonischemic cardiomyopathy: application of magnetic resonance myocardial tagging. Am Heart J 2002;144:719–25.
20. van Tol BA, Huijsmans RJ, Kroon DW, Schothorst M, Kwakkel G. Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis. Eur J Heart Fail 2006;8:841–50.
21. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
22. Light RJ, Pillemer DB. Summing Up. The Science of Reviewing Research. Cambridge, MA: Harvard University Press, 1984.
23. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
25. Koch M, Douard H, Broustet JP. The benefit of graded physical exercise in chronic heart failure. Chest 1992;101:231S–5S.
26. Belardinelli R, Georgiou D, Cianci G, Berman N, Ginzton L, Purcaro A. Exercise training improves left ventricular diastolic filling in patients with dilated cardiomyopathy. Clinical and prognostic implications. Circulation 1995;91:2775–84.
27. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Effects of exercise training on left ventricular filling at rest and during exercise in patients with ischemic cardiomyopathy and severe left ventricular systolic dysfunction. Am Heart J 1996;132:61–70.
28. Kiilavuori K, Sovijarvi A, Naveri H, Ikonen T, Leinonen H. Effect of physical training on exercise capacity and gas exchange in patients with chronic heart failure. Chest 1996;110:985–91.
29. Roveda F, Middlekauff HR, Rondon MU, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. J Am Coll Cardiol 2003;42:854–60.
30. Sabelis LW, Senden PJ, Fijnheer R, et al. Endothelial markers in chronic heart failure: training normalizes exercise-induced vWF release. Eur J Clin Invest 2004;34:583–9.
31. Klocek M, Kubinyi A, Bacior B, Kawecka-Jaszcz K. Effect of physical training on quality of life and oxygen consumption in patients with congestive heart failure. Int J Cardiol 2005;103:323–9.
32. Jonsdottir S, Andersen KK, Sigurosson AF, Sigurosson SB. The effect of physical training in chronic heart failure. Eur J Heart Fail 2006;8:97–101.
33. Passino C, Severino S, Poletti R, et al. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. J Am Coll Cardiol 2006;47:1835–9.
34. McAlister FA, Ezekowitz JA, Wiebe N, et al. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. Ann Intern Med 2004;141:381–90.
35. Belardinelli R, Georgiou D, Ginzton L, Cianci G, Purcaro A. Effects of moderate exercise training on thallium uptake and contractile response to low-dose dobutamine of dysfunctional myocardium in patients with ischemic cardiomyopathy. Circulation 1998;97:553–61.
36. McKelvie RS, McCartney N, Tomlinson C, Bauer R, MacDougall JD. Comparison of hemodynamic responses to cycling and resistance exercise in congestive heart failure secondary to ischemic cardiomyopathy. Am J Cardiol 1995;76:977–9.
37. Cheetham C, Green D, Collis J, Dembo L, O'Driscoll G. Effect of aerobic and resistance exercise on central hemodynamic responses in severe chronic heart failure. J Appl Physiol 2002;93:175–80.
38. Keren G, Katz S, Gage J, Strom J, Sonnenblick EH, LeJemtel TH. Effect of isometric exercise on cardiac performance and mitral regurgitation in patients with severe congestive heart failure. Am Heart J 1989;118:973–9.
39. Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. Am J Med 2004;116:693–706.
40. Rees K, Taylor RS, Singh S, Coats AJ, Ebrahim S. Exercise based rehabilitation for heart failure. Cochrane Database Syst Rev 2004:CD003331.
41. Piepoli MF, Davos C, Francis DP, Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ 2004;328:189.
42. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation 2004;109:1004–9.