# Exercise Training for Patients with Heart Failure: A Systematic Review of Factors that Improve Mortality and Morbidity

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**PURPOSE:** To determine the efficacy of exercise training and its effects on outcomes in patients with heart failure.

**METHODS:** MEDLINE, Medscape, and the Cochrane Controlled Trials Registry were searched for trials of exercise training in heart failure patients. Data relating to training protocol, exercise capacity, and outcome measures were extracted and reviewed.

**RESULTS:** A total of 81 studies were identified: 30 randomized controlled trials, five nonrandomized controlled trials, nine randomized crossover trials, and 37 longitudinal cohort studies. Exercise training was performed in 2387 patients. The average increment in peak oxygen consumption was 17% in 57 studies that measured oxygen consumption directly, 17% in 40 studies of aerobic training, 9% in three studies that only used strength training, 15% in 13 studies of combined aerobic and strength training, and 16% in the one study on inspiratory training. There were no reports of deaths that were directly related to exercise during more than 60,000 patient-hours of exercise training. During the training and follow-up periods of the randomized controlled trials, there were 56 combined (deaths or adverse events) events in the exercise groups and 75 combined events in the control groups (odds ratio [OR] = 0.98; 95% confidence interval [CI]: 0.61 to 1.32; $P = 0.60$). During this same period, 26 exercising and 41 nonexercising subjects died (OR = 0.71; 95% CI: 0.37 to 1.02; $P = 0.06$).

**CONCLUSION:** Exercise training is safe and effective in patients with heart failure. The risk of adverse events may be reduced, but further studies are required to determine whether there is any mortality benefit. **Am J Med. 2004;116:693–706.** ©2004 by Excerpta Medica Inc.

Numerous studies have documented that exercise training is associated with improvements in functional capacity and quality of life in patients with heart failure. Indeed, exercise training is recommended in a number of guidelines as a useful intervention for patients with stable disease (1,2).

Nonetheless, acceptance of exercise training by the medical community has been less enthusiastic, and many physicians remain concerned about methodology and safety regarding implementing exercise programs in this high-risk group. In part, these concerns reflect the failure of studies to address issues such as the optimal exercise type and program, and the effects of exercise training on mortality. Safety is an important concern, particularly since an ongoing exercise-training program is required to maintain improved quality of life, and a home-based program is necessary if it is to be feasible in the long-term. Because almost all of the published studies of exercise training in heart failure patients are small, we sought to address these questions in a systematic review of clinical trial data.

## METHODS

### Search Strategy and Study Selection

We searched MEDLINE (1966 to August 2003), Medscape (1979 to August 2003), and the Cochrane Controlled Trials Registry (1979 to August 2003), using combinations of the terms *exercise training*, *heart failure*, *left ventricular dysfunction*, *physical training*, *resistance training*, and *aerobic exercise*, for clinical trials of exercise training in patients with heart failure. There were no restrictions on the year of publication. We examined the latest editions of relevant journals that were not yet available on electronic databases. The reference lists of identified articles were subsequently scrutinized and relevant articles were included if they met the inclusion criteria.

Clinical trials were included if the baseline ejection fraction was <40%. Studies with two or more groups with different ejection fractions were included if data could be identified from subgroups with an ejection fraction <40% (3,4). Studies that included patients taking

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concurrent drug therapy were included (5–7). Editorials, review papers, and studies examining the effects of a single exercise session were excluded.

The majority of data were obtained from the manuscripts, but authors were contacted if it was unclear whether multiple publications were based on the same cohort or if no information on mortality or adverse events was reported. When two or more studies clearly resulted in multiple publications, the paper with the largest sample that focused on exercise training in patients with heart failure was included in the analysis, although all reviewed publications based on the selection criteria are listed in the references of this review (3–108). When a patient group underwent two periods of exercise training, studies were considered separate only when the training programs were separated by a detraining period that was at least equivalent to the initial training program (29,30).

### *Clinical Descriptors*

Information on clinical variables, such as age, sex, the nature of the underlying disease, ejection fraction, clinical status, and, if reported, peak oxygen consumption before and after training, was archived in a database.

### *Outcome Measures*

We defined adverse events as an incident causing temporary or permanent withdrawal from the exercise program, including but not restricted to hospitalization. We examined the relation between exercise training and changes in functional capacity. We only recorded directly measured peak oxygen consumption (mL/kg/min). Studies estimating other parameters in metabolic equivalents or 6-minute walk or step tests were not used in this part of the analysis. We recorded mortality rates and adverse events (including hospitalization or events causing temporary or permanent withdrawal from the exercise program) during exercise testing, training, and follow-up periods in exercising patients and nonexercising controls. We also conducted a composite analysis of total adverse events.

### *Statistical Analysis*

Relative risks were calculated using a Mantel-Haenszel stratified analysis. The predictors of an improvement in peak oxygen consumption were assessed in a general linear model. Results were considered significant when the $P$ value was $<0.05$. Analyses were performed using SPSS, version 10.0 (SPSS Inc., Chicago, Illinois).

## RESULTS

Of the 109 papers searched, 81 studies met the inclusion criteria. Of these, 30 (37%) were randomized parallel group trials, five (6%) were nonrandomized controlled trials, nine (11%) were randomized crossover trials, and 37 (46%) were longitudinal cohort studies (Table 1)—contributing a total of 2387 exercising subjects. Of 1197 patients enrolled in controlled studies, 622 were in the exercise-training group and 575 were in the nonexercising control group. Patients were on stable medical therapy, but details of therapy were not provided in all studies. Forty-seven studies were from specialist cardiology units, seven were from cardiac rehabilitation programs, and 27 were from university medical centers.

**Table 1.** Baseline Characteristics of Studies of Exercise Training in Patients with Left Ventricular Dysfunction

| Characteristic | Mean ± SD (Range) |
|---|---|
| Number of subjects | 30 ± 25 (5–181) |
| Age (years) | 59 ± 7* |
| Ejection fraction (%) | 27 ± 7 (<40) |
| Proportion of men (%) | 79 ± 25 (0–100) |
| Proportion with ischemia (%) | 61 ± 26 (0–100) |
| Increment in peak oxygen uptake† | 16.5 ± 6.9 (0–39) |

* Range unknown.
† In 57 studies.

Details of exercise program parameters, age, proportion of patients with ischemia, ejection fraction, and baseline and change in maximal oxygen consumption were obtained from 30 randomized controlled trials (Table 2) and the remaining studies (Table 3). Over 60,000 patient-hours of exercise training were reported, and the mean study duration was over 800 patient-hours of exercise.

### *Effects of Exercise Training on Functional Capacity*

In all 57 studies that measured maximal oxygen uptake directly, the mean (± SD) increment was 16.8% ± 8.0% (95% confidence interval [CI]: 13.7% to 17.9%). However, the greatest mean increase in peak oxygen consumption (16.5% ± 6.9%; 95% CI: 14.3% to 18.7%) was identified in the 40 studies that involved either continuous or intermittent aerobic exercise.

### *Exercise Mode*

Training programs varied in frequency (one to seven sessions per week), session duration (15 to 120 minutes), intensity (40% to 95%), and program duration (2 to 104 weeks) (Tables 1 to 3). No correlation was found among session frequency, session duration, exercise intensity, program duration, and functional improvement.

Intermittent and continuous aerobic exercise and strength training appeared to produce changes in peak oxygen consumption. However, studies of aerobic exercise training ($n = 40$) demonstrated a greater increment in peak oxygen consumption (16.5% ± 6.9%; 95% CI: 14.3% to 18.7%), compared with three studies that employed strength training alone (9.3% ± 9.2%; $P = 0.31$). The mean increment in aerobic programs also slightly

**Table 2.** Characteristics of Randomized Controlled Trials Meeting Selection Criteria

| First Author (Reference) | Controls (n) | Exercise Training Subjects (n) | Training Time, Frequency, Duration | Intensity and Nature of Training | Change in Oxygen Consumption | Follow-up | Drug Therapy |
|---|---|---|---|---|---|---|---|
| Belardinelli* (11) | 9 | 18 | 30 min, 3 sessions/wk, 8 wk | 40% max oxygen consumption; aerobic | 17% | 92 wk | 0% BB<br>67% ACE |
| Belardinelli (31) | 49 | 50 | 40 min, 3 sessions/wk, 52 wk | 60% max oxygen consumption; aerobic | 18% | 192 wk | 0% BB<br>90% ACE |
| Braith (62) | 9 | 10 | 28 min, 3 sessions/wk, 16 wk | 40%–80% max oxygen consumption; aerobic | 25% | 16 wk | 20% BB<br>70% ACE |
| Brosseau (63) | 16 | 16 | 28 min, 7 sessions/wk, 8 wk | 65%–75% maximum heart rate; aerobic | No oxygen data; 6-minute walk | 8 wk | 38% BB |
| Cider (38) | 12 | 12 | 60 min, 2 sessions/wk, 21 wk | 60% of one repetition maximum; aerobic + strength | <1%; indirect measures | 21 wk | 50% BB<br>46% ACE |
| Cider (64) | 10 | 15 | 45 min, 3 sessions/wk, 8 wk | 40%–70% heart rate reserve; aerobic | 7% | 8 wk | 87% BB<br>87% ACE |
| Dubach (65) | 13 | 12 | 100 min, 7 sessions/wk, 8 wk | 70%–80% heart rate reserve; aerobic | 29% | 8 wk | 0% BB<br>100% ACE |
| Giannuzzi (66) | 38 | 39 | 120 min, 3 sessions/wk, 26 wk | 80% maximum heart rate; aerobic | No oxygen data; cycle workload | 26 wk | 49% BB<br>77% ACE |
| Giannuzzi (67) | 45 | 45 | 30 min, 3–5 sessions/wk, 26 wk | 60% maximum heart rate; aerobic | 17% | 26 wk | 91% BB<br>22% ACE |
| Gielen (68) | 10 | 10 | 40–60 min, 4–6 sessions/wk, 26 wk | 70% max oxygen consumption; aerobic | 29% | 26 wk | 40% BB<br>100% ACE |
| Gordon (40) | 7 | 14 | 15 min, 3 sessions/wk, 8 wk | 35%–75% of 1 repetition maximum; strength | 4% | 8 wk | 29% BB<br>90% ACE |
| Hambrecht (69) | 37 | 36 | 40 min, 5 sessions/wk, 26 wk | 70% max oxygen consumption; aerobic | 26% | 26 wk | 10% BB<br>94% ACE |
| Hambrecht (18) | 10 | 10 | 40 min, 5 sessions/wk, 26 wk | 70% maximum heart rate; aerobic | 26% | 26 wk | 0% BB<br>100% ACE |
| Jette (70) | 8 | 18 | 60 min, 7 sessions/wk, 4 wk | 70%–80% maximum heart rate; aerobic | 0% | 4 wk | 61% BB<br>11% ACE |
| Johnson (35) | 9 | 9 | 30 min, 7 sessions/wk, 8 wk | 30% max inspiratory effort; inspiratory | No oxygen data; exercise time | 8 wk | No data |
| Keteyian (71) | 22 | 21 | 43 min, 3 sessions/wk, 24 wk | 60%–80% maximum heart rate; aerobic | 14% | 24 wk | 5% BB<br>95% ACE |
| Kiilavuori (33) | 15 | 12 | 30 min, 3 sessions/wk, 12 wk | 50%–60% max oxygen consumption; aerobic | 12% | 12 wk | 33% BB<br>92% ACE |

**Table 2.** continued

| First Author (Reference) | Controls (n) | Exercise Training Subjects (n) | Training Time, Frequency, Duration | Intensity and Nature of Training | Change in Oxygen Consumption | Follow-up | Drug Therapy |
|---|---|---|---|---|---|---|---|
| Kobayashi (72) | 14 | 14 | 30 min, 3 sessions/wk, 12 wk | 60%–70% anerobic threshold; aerobic | No oxygen data; exercise time | 12 wk | 71% BB 93% ACE |
| Koch (42) | 13 | 12 | 90 min, 3 sessions/wk, 12 wk | Unclear; strength | No oxygen data; exercise time | 12 wk | 33% BB 90% ACE |
| McKelvie (53) | 91 | 90 | 30 min, 3 sessions/wk, 52 wk | 60%–70% maximum heart rate; aerobic + strength | 14% | 52 wk | 23% BB 92% ACE |
| Myers (73) | 12 | 12 | 45 min, 5 sessions/wk, 8 wk | 60%–80% max oxygen consumption; aerobic | 17% | 8 wk | 75% BB 100% ACE |
| Oka (45) | 20 | 20 | 50 min, 3 sessions/wk, 12 wk | 70% maximum heart rate; aerobic + strength | 3% | 12 wk | 5% BB 70% ACE |
| Parnell (34) | 10 | 11 | 45 min, 6 sessions/wk, 8 wk | 50%–60% maximum heart rate; aerobic | No oxygen data; 6-minute walk test | 8 wk | 72% BB 100% ACE |
| Quittan (74) | 13 | 12 | 60 min, 3 sessions/wk, 12 wk | 50% max oxygen consumption; aerobic | 16% | 12 wk | 25% BB 100% ACE |
| Roveda (75) | 9 | 7 | 60 min, 3 sessions/wk, 16 wk | Anaerobic threshold; aerobic + strength | 39% | 16 wk | 0% BB 100% ACE |
| Tokmakova (76) | 7 | 15 | 40 min, 5 sessions/wk, 8 wk | 50% max oxygen consumption; aerobic | 16% | 8 wk | 0% BB 100% ACE |
| Tyni-Lenne (77) | 7 | 14 | 15 min, 3 sessions/wk, 8 wk | 70% work rate; strength | 4% | 8 wk | 48% BB 91% ACE |
| Tyni-Lenne (30) | 8 | 16 | 38 min, 3 sessions/wk, 8 wk | 60%–70% max work rate; aerobic + strength | 19% strength; 3% aerobic | 8 wk | 42% BB 4% ACE |
| Wielenga (78) | 32 | 35 | 30 min, 3 sessions/wk, 12 wk | Unclear; aerobic | 9% | 12 wk | No data |
| Willenheimer (29) | 20 | 17 | 15 min, 3 sessions/wk, 17 wk | 80% max oxygen consumption; aerobic | 7% | 40 wk | 0% BB 100% ACE |

* Randomization unclear.
ACE = angiotensin-converting enzyme [inhibitor]; BB = beta-blocker.

Table 3. Characteristics of Crossover and Longitudinal Cohort Studies Meeting Selection Criteria

| First Author (Reference) | Design | Controls (n) | Exercise Training Subjects (n) | Training Time, Frequency, Duration | Intensity and Nature of Training | Change in Oxygen Consumption | Follow-up | Drug Therapy |
|---|---|---|---|---|---|---|---|---|
| Adamopoulos (79) | Crossover | 20 | 24 | 30 min, 5 sessions/wk, 12 wk | 60%–80% maximum heart rate; aerobic | 15% | 12 wk | 17% BB<br>100% ACE |
| Barlow (80) | Longitudinal | 10 healthy subjects | 10 | 20 min, 5 sessions/wk, 8 wk | 70%–80% maximum heart rate, aerobic | Indirect | 8 wk | 0% BB<br>90% ACE |
| Beneke (12) | Longitudinal | | 16 | 15–25 min, 5 sessions/wk, 3 wk | 70% max oxygen consumption; aerobic | 16% | 3 wk | 50% BB<br>94% ACE |
| Coats (60) | Crossover | | 17 | 20 min, 5 sessions/wk, 8 wk | 70%–80% maximum heart rate; aerobic | 18% | 8 wk | 0% BB<br>88% ACE |
| Conraads (81) | Longitudinal | | 23 | 60 min, 3 sessions/wk, 16 wk | 50% of 1 repetition max; 90% anerobic threshold; aerobic + strength | 3% | 16 wk | 61% BB<br>96% ACE |
| Davey (82) | Crossover | | 22 | 20 min, 5 sessions/wk, 8 wk | 70%–80% maximum heart rate; aerobic | 9% | 8 wk | 0% BB<br>41% ACE |
| Delagardelle (83) | Longitudinal | | 20 | 40 min, 3 sessions/wk, 12 wk | 50%–75% max oxygen consumption; 60% of 1 repetition max | 0% strength; 8% aerobic | 3 months | 50% BB<br>90% ACE |
| European Heart Failure Training Group (48) | Crossover | | 134 | 20 min, 4–5 sessions/wk, 8 wk | 70%–80% maximum heart rate; aerobic | 13% | 6–16 wk | 0% BB<br>79% ACE |
| Harris (84) | Longitudinal | | 24 | 30 min, 5 sessions/wk, 6 wk | 70% maximum heart rate; aerobic | 4% | 6 wk | 38% BB<br>92% ACE |
| Kavanagh (32) | Controlled nonrandom | 9 | 21 | 45 min, 5 sessions/wk, 52 wk, 10–21 km weekly | 50%–60% max oxygen consumption; aerobic | 17% | 52 wk | 0% BB<br>ACE no data |
| Kemppainen (85) Finland | Controlled nonrandom | 7 | 9 | 45 min, 3 sessions/wk, 20 wk | 70% max oxygen consumption; aerobic + strength | 27% | 20 wk | 78% BB<br>78% ACE |
| Keteyian (86) | Longitudinal | | 15 | 40 min, 3 sessions/wk, 14–24 wk | 60%–80% heart rate reserve; aerobic | 14% | 24 wk | 33% BB<br>93% ACE |
| McConnell (87) | Longitudinal | | 24 | 60 min, 3 sessions/wk, 12 wk | 70%–85% maximum heart rate; aerobic + strength | 8% | 12 wk | 50% BB<br>70% ACE |
| Maiorana (49) | Crossover | | 13 | 60 min, 3 sessions/wk, 8 wk | 55%–85% of 1 repetition max; 70% maximum heart rate; aerobic + strength | 13% | 8 wk | 15% BB<br>92% ACE |
| Magnusson (43) | Longitudinal | | 11 | 45 min, 3 sessions/wk, 8 wk | 80% of 1 repetition max; aerobic + strength 65%–75% max workload | 5% overall; 4% strength; 7% aerobic | 8 wk | 9% BB<br>73% ACE |
| Otsuka (88) | Longitudinal | | 52 | 50–90 min, 3–5 sessions/wk, 12 wk | 50%–60% heart rate reserve; aerobic | 17% | 12 wk | 42% BB<br>8% ACE |
| Owen (36) | Crossover | | 19 | 60 min, 1 session, 12 wk | <70% maximum heart rate; strength + aerobic | 6-minute walk distance | 12 wk | 17% BB<br>75% ACE |

**Table 3.** continued

| First Author (Reference) | Design | Controls (n) | Exercise Training Subjects (n) | Training Time, Frequency, Duration | Intensity and Nature of Training | Change in Oxygen Consumption | Follow-up | Drug Therapy |
|---|---|---|---|---|---|---|---|---|
| Stolen (89) | Controlled nonrandomized | 11 | 9 | 45 min, 3 sessions/wk, 20 wk | 50%–70% max oxygen consumption; aerobic + strength | 27% | 20 wk | 78% BB<br>78% ACE |
| Taylor (90) | Crossover | | 8 | 30 min, 3 sessions/wk, 8 wk | 45%–70% maximum heart rate; aerobic | Exercise time | 8 wk | No data BB<br>100% ACE |
| Webb-Peploe (47) | Crossover | | 12 | 20 min, 5 sessions/wk, 8 wk | 70%–80% maximum heart rate; strength + aerobic | Indirect | 8 wk | No BB<br>100% ACE |
| Malfatto (91) | Controlled nonrandomized | 15 | 30 | 60 min, 5 sessions/wk, 12 wk | 40%–50% max oxygen consumption; aerobic | 18% | 12 wk | 48% BB<br>100% ACE |
| Agnosti (92) | Longitudinal | | 14 | 90 min, 3 sessions/wk, 26 wk | 75% maximum heart rate; aerobic | Change in workload | 26 wk | 0% BB<br>100% ACE |
| Ali (93) | Longitudinal | | 15 | 35 min, 3 sessions/wk, 12 wk | 70%–85% maximum heart rate; aerobic | 7% | 12 wk | 100% ACE<br>0% BB |
| Conn (94) | Longitudinal | | 10 | 35–45 min, 3–5 sessions/wk, 1 wk | 70%–80% maximum heart rate; aerobic | METS; treadmill | 12 months | 0% BB<br>0% ACE |
| Delagardelle (39) | Longitudinal | | 14 | 60 min, 3 sessions/wk, 26 wk | 75% max oxygen consumption; aerobic + strength | 10% | 26 wk | 29% BB<br>79% ACE |
| Demopoulos (5) | Longitudinal (investigated drug effects) | 8 heart failure | 15 | 15–60 min, 4 sessions/wk, 12 wk | 50% max oxygen consumption; aerobic | 24% | 12 wk | 8 Carvedilol<br>7 Propanolol<br>100% ACE |
| Demopoulos (95) | Longitudinal | | 16 | 60 min, 4 sessions/wk, 12 wk | 50% max oxygen consumption; aerobic | 30% | 12 wk | 0% BB<br>100% ACE |
| Digenio (3) | Longitudinal | | 38 | 30–45 min, 3 sessions/wk, 26 wk | 70–85% maximum heart rate; aerobic | 14% | 26 wk | 24% BB<br>29% ACE |
| Ehsani (4) | Longitudinal | | 8 | 3–5 sessions/wk, 52 wk, | 60%–85% max oxygen consumption; aerobic | 25% | 52 wk | No data |
| Forissier (6) | Longitudinal | | 38 | 30 min, 3–5 sessions/wk, 4 wk | Anaerobic threshold; aerobic + strength | 17% | 4 wk | 63% BB<br>100% ACE |
| Hedback (51) | Longitudinal | | 21 | 40 min, 2 sessions/wk, 52 wk | Aerobic | Change in workload | 52 wk | 38% BB<br>0% ACE |
| Hornig (41) | Longitudinal | 7 healthy | 12 | 30 min, 7 sessions/wk, 4 wk | 70% max work rate; strength | Change in workload | 4 wk | No BB<br>100% ACE |
| Meyer (50) | Crossover | | 18 | 30 min, 3 sessions/wk, 3 wk | 50% max work rate; aerobic | 20%; intermittent | 3 wk | 72% BB<br>89% ACE |
| Kellerman (96) | Longitudinal | | 11 | 20 min, 2 sessions/wk, 104 wk | 90% max work rate; aerobic | Submaximal test | 104 wk | 0% BB<br>No data ACE |
| Larsen (37) | Longitudinal | 15 healthy | 15 | 30 min, 3 sessions/wk, 12 wk | 80% maximum heart rate; aerobic | 11% | 12 wk | No BB<br>87% ACE |

**Table 3.** continued

| First Author (Reference) | Design | Controls (n) | Exercise Training Subjects (n) | Training Time, Frequency, Duration | Intensity and Nature of Training | Change in Oxygen Consumption | Follow-up | Drug Therapy |
|---|---|---|---|---|---|---|---|---|
| Lee (97) | Longitudinal | | 18 | 20–45 min, 2–6 sessions/wk, 52 wk | 70%–85% maximum heart rate; aerobic | Change in workload | 52 wk | No BB No ACE |
| Letac (98) | Longitudinal | | 8 | 65 min, 3 sessions/wk, 8 wk | 80% maximum heart rate; aerobic | Change in workload | 8 wk | No data |
| Mancini (99) | Longitudinal | | 8 | 90 min, 3 sessions/wk, 12 wk | 30% maximum inspiratory effort; inspiratory | 16% | 12 wk | No data BB 100% ACE |
| Minotti (44) | Longitudinal | | 5 | 24 min, 7 sessions/wk, 4 wk | 1.9 kg; strength | Indirect | 4 wk | No BB 80% ACE |
| Pietila (7) | Longitudinal | | 31 | 30 min, 6 sessions/wk, 26 wk | 60%–85% maximum heart rate; aerobic | 13% | 26 wk | 65% BB 65% ACE |
| Radzewitz (100) | Longitudinal | | 88 | 25 min, 3 sessions/wk, 4 wk | 60%–80% max oxygen consumption; aerobic + strength | 11% | 4 wk | 83% BB 85% ACE |
| Santoro (101) | Longitudinal | | 6 | 90 min, 3 sessions/wk, 16 wk | 50%–60% max oxygen consumption; 50% of 1 repetition max; aerobic + strength | 18% | 16 wk | No drug data |
| Scalvini (102) | Longitudinal | | 12 | 20 min, 5 sessions/wk, 5 wk | 70% max workload; aerobic | 17% | 5 wk | No BB No ACE |
| Shepherd (103) | Longitudinal | | 17 | 30–45 min, 5 sessions/wk, 16 wk | 60%–70% max oxygen consumption; aerobic | 17% | 16 wk | No data |
| Sullivan (104) | Longitudinal | | 12 | 60 min, 3–5 sessions/wk, 16–24 wk | 75% max oxygen consumption; aerobic | 23% | 24 wk | No BB 25% ACE |
| Tavazzi (105) | Longitudinal | | 95 | 70 min, 7 sessions/wk, 4 wk | 85%–95% maximum heart rate; aerobic | Change in workload | 4 wk | 8% BB No ACE |
| Testa (106) | Controlled nonrandomized | 5 CHF | 10 | 40 min, 4 sessions/wk, 12 wk | 50% max oxygen consumption; aerobic | 24% | 12 wk | 50% BB 100% ACE |
| Tyni-Lenne (46) | Longitudinal | | 24 | 15 min, 3 sessions/wk, 8 wk | 65%–75% max work rate; aerobic | 13% | 8 wk | 38% BB 88% ACE |
| Tyni-Lenne (107) | Longitudinal | | 16 | 15 min, 3 sessions/wk, 8 wk | 65%–75% max work rate; strength | 20% | 8 wk | 50% BB 75% ACE |
| Vibarel (108) | Longitudinal | | 10 | 46 min, 3 sessions/wk, 8 wk | 70%–80% max oxygen consumption; aerobic | 22% | 8 wk | No data |
| Whellan (61) | Longitudinal | | 70 | Unknown | Aerobic | Change in workload | 12 wk | No data |

ACE = angiotensin-converting enzyme [inhibitor]; BB = beta-blocker; METS = metabolic equivalents.

**Table 4.** Characteristics of Randomized Controlled Trials that Reported Deaths or Adverse Events in Training or Follow-up Periods

| First Author (Reference) | New York Heart Association Class | Ejection Fraction | Duration of Training or Follow-up | Events* | |
|---|---|---|---|---|---|
| | | | | Exercise | Control |
| Belardinelli (31) | II to IV | 28.2% | 173 ± 8 weeks | 9 deaths, 8 events | 20 deaths, 17 events |
| Brosseau (63) | II and III | <35% | 8 weeks | 0 deaths or events | 1 death, 0 events |
| Cider (38) | II and III | <40% | 22 weeks | 0 deaths, 1 event | 0 deaths or events |
| Cider (64) | II and III | <35% | 8 weeks | 0 deaths, 1 event | 0 deaths or events |
| Giannuzzi (66) | NA | 34% | 26 weeks | 0 deaths, 1 event | 1 death, 1 event |
| Giannuzzi (67) | II and III | 35% | 26 weeks | 0 deaths, 4 events | 1 death, 7 events |
| Gielen (68) | II and III | <40% | 26 weeks | 0 deaths, 1 event | 0 deaths or events |
| Hambrecht (69) | I to III | 27% | 28 weeks | 3 deaths, 2 events | 2 deaths, 2 events |
| Hambrecht (18) | II and III | <40% | 26 weeks | 1 death, 0 events | 1 death, 0 events |
| Johnson (35) | II and III | <40% | 8 weeks | 0 deaths, 2 events | 1 death, 1 event |
| Keteyian (71) | II and III | 22% | 24 weeks | 0 deaths, 3 events | 1 death, 1 event |
| Kiilavuori (33) | II and III | 25% | 26 weeks | 0 deaths or events | 0 deaths, 1 event |
| McKelvie (53) | I to III | <40% | 52 weeks | 9 deaths, 3 events | 8 deaths, 2 events |
| Quittan (74) | II and III | <30% | 12 weeks | 0 deaths, 1 event | 0 deaths, 1 event |
| Tyni-Lenne (77) | II and III | 28% | 9 weeks | 0 deaths, 1 event | 0 deaths or events |
| Wielenga (78) | II and III | 26.5% | 12 weeks | 1 death, 2 events | 3 deaths, 1 event |
| Willenheimer (29) | I to III | 35% | 43 weeks | 3 deaths, 0 events | 2 deaths, 0 events |

* Adverse events include hospitalization or events causing temporary or permanent withdrawal from the exercise program (see Methods).
NA = not applicable.

exceeded that in 13 combined aerobic and strength programs (15.0% ± 10.6%, $P = 0.64$), and the sole study on inspiratory training reported an increment of 16%. Only seven of the 81 studies used an intermittent aerobic protocol, of which only two reported directly measured changes in peak oxygen consumption of 10% to 20%, which were comparable with the 16.5% overall change in aerobic studies ($P = 0.82$).

## *Safety*

No exercise-related deaths were reported in patients during more than 60,000 patient-hours of exercise training, comparing favorably with exercise in normal and cardiac populations.

## *Outcome Measures*

During exercise testing, training, or follow-up periods in randomized controlled trials (Table 4), there were 30 adverse events among 622 exercising patients, compared with 34 adverse events among 575 control subjects, an odds ratio (OR) of 0.83 (95% CI: 0.50 to 1.39; $P = 0.49$) for adverse events (Figure 1). A composite analysis of adverse events and deaths revealed 56 combined endpoints in the exercise groups and 75 such events in the control groups (Figure 2), an odds ratio of 0.98 (95% CI: 0.61 to 1.32; $P = 0.60$).

During the training and follow-up periods (mean, 5.9 months) for the 30 randomized parallel group trials,

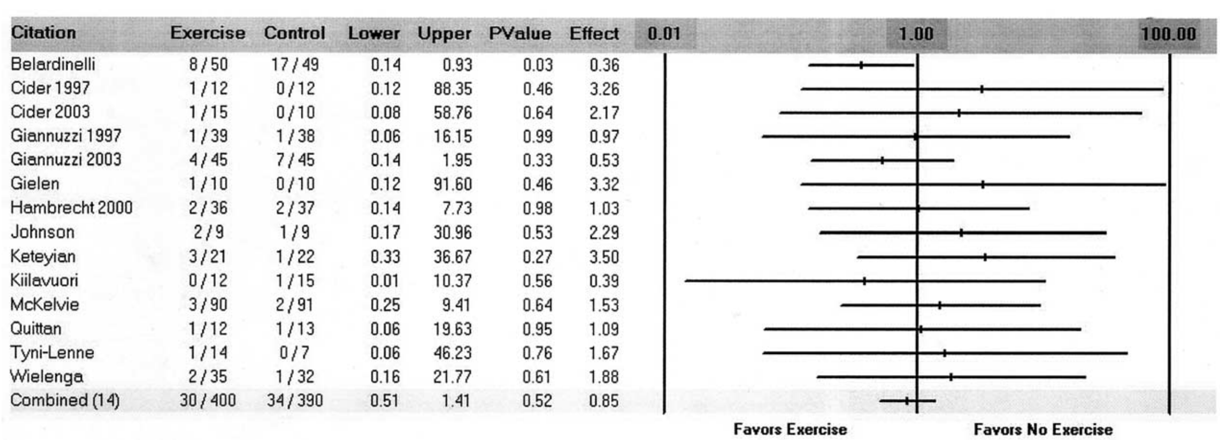


**Figure 1.** Odds ratios (with 95% confidence intervals) for adverse events in 14 trials reporting adverse events and no mortality.

| Citation | Exercise | Control | Lower | Upper | PValue | Effect |
|---|---|---|---|---|---|---|
| Belardinelli | 17/50 | 37/49 | 0.07 | 0.40 | 0.00 | 0.17 |
| Brosseau | 0/12 | 1/12 | 0.01 | 8.31 | 0.46 | 0.31 |
| Cider 1997 | 1/12 | 0/12 | 0.12 | 88.35 | 0.46 | 3.26 |
| Cider 2003 | 1/15 | 0/10 | 0.08 | 58.76 | 0.64 | 2.17 |
| Giannuzzi 1997 | 1/39 | 2/38 | 0.04 | 5.45 | 0.54 | 0.47 |
| Giannuzzi 2003 | 4/45 | 8/45 | 0.13 | 1.62 | 0.21 | 0.45 |
| Gielen | 1/10 | 0/10 | 0.12 | 91.60 | 0.46 | 3.32 |
| Hambrecht 1998 | 1/10 | 1/10 | 0.05 | 18.57 | 1.00 | 1.00 |
| Hambrecht 2000 | 5/36 | 4/37 | 0.33 | 5.41 | 0.69 | 1.33 |
| Johnson | 2/9 | 2/9 | 0.11 | 9.23 | 1.00 | 1.00 |
| Keteyian | 3/21 | 2/22 | 0.25 | 11.13 | 0.60 | 1.67 |
| Kiilavuori | 0/12 | 1/15 | 0.01 | 10.37 | 0.56 | 0.39 |
| McKelvie | 12/90 | 10/91 | 0.51 | 3.05 | 0.63 | 1.25 |
| Quittan | 1/12 | 1/13 | 0.06 | 19.63 | 0.95 | 1.09 |
| Tyni-Lenne | 1/14 | 0/7 | 0.06 | 46.23 | 0.76 | 1.67 |
| Wielenga | 3/35 | 4/32 | 0.14 | 3.19 | 0.60 | 0.66 |
| Willenheimer | 3/17 | 2/20 | 0.28 | 13.16 | 0.50 | 1.93 |
| Combined (17) | 56/439 | 75/432 | 0.46 | 1.00 | 0.05 | 0.68 |

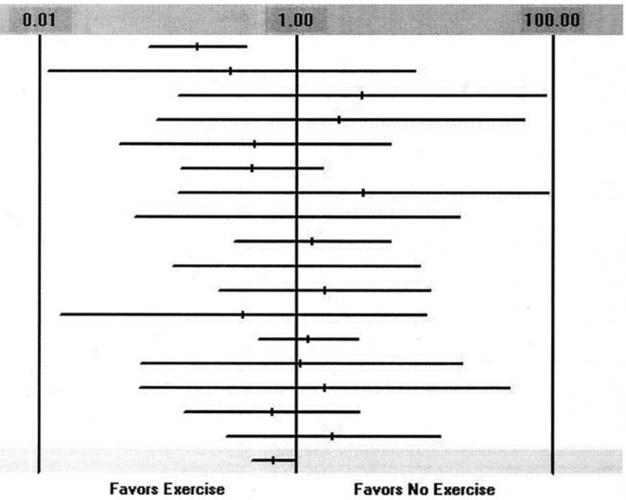


**Figure 2.** Odds ratios (with 95% confidence intervals) for the composite endpoint of mortality and adverse events in 17 trials reporting adverse events.

there were 26 deaths among the 622 subjects in the exercise group and 41 deaths among the 575 sedentary control subjects. The odds ratio of death during the activity or follow-up period was 0.71 (95% CI: 0.37 to 1.02; $P = 0.06$) in exercising versus control patients (Figure 3). Only two studies demonstrated a sizable number of deaths, and analysis of these two studies yielded a relative risk of 0.62 (95% CI: 0.36 to 1.07; $P = 0.09$) with exercise training.

## DISCUSSION

The results of this systematic review indicate that exercise training for patients with heart failure is safe and associated with a meaningful increment in peak oxygen consumption. There is also evidence of a reduction in the composite endpoint of death and adverse events, as well as a possible survival benefit following exercise training. The optimal form of training remains undefined, and although intermittent aerobic exercise appears to be effective, strength training alone may not be as effective as the standard approach of continuous aerobic exercise.

Although therapeutic advances have improved mortality in heart failure patients, impaired quality of life due to exercise intolerance remains an ongoing burden. Reduced functional capacity has been shown to be related to impaired quality of life (21,31–34), although this relation is more tenuous in studies lacking quantitative measures of functional capacity (35,36). On these grounds, an improvement in exercise capacity might be expected to improve quality of life, a contention that is supported by others (35). Furthermore, since the direct analysis of the effects of different training programs on quality of life is complicated by the variety of assessment methods, a more feasible approach is to examine change in functional capacity.

Maximal oxygen consumption is the most commonly reported measure of functional capacity in heart failure

| Citation | Exercise | Control | Lower | Upper | PValue | Effect |
|---|---|---|---|---|---|---|
| Belardinelli | 9/50 | 20/49 | 0.13 | 0.80 | 0.01 | 0.32 |
| Brosseau | 0/12 | 1/12 | 0.01 | 8.31 | 0.46 | 0.31 |
| Giannuzzi 1997 | 0/39 | 1/38 | 0.01 | 8.01 | 0.46 | 0.32 |
| Giannuzzi 2003 | 0/45 | 1/45 | 0.01 | 8.22 | 0.47 | 0.33 |
| Hambrecht 1998 | 1/10 | 1/10 | 0.05 | 18.57 | 1.00 | 1.00 |
| Hambrecht 2000 | 3/36 | 2/37 | 0.25 | 10.13 | 0.62 | 1.59 |
| Johnson | 0/9 | 1/9 | 0.01 | 8.35 | 0.46 | 0.30 |
| Keteyian | 0/21 | 1/22 | 0.01 | 8.65 | 0.49 | 0.33 |
| McKelvie | 9/90 | 8/91 | 0.42 | 3.13 | 0.78 | 1.15 |
| Wielenga | 1/35 | 3/32 | 0.03 | 2.88 | 0.26 | 0.28 |
| Willenheimer | 3/17 | 2/20 | 0.28 | 13.16 | 0.50 | 1.93 |
| Fixed Combined (11) | 26/364 | 41/365 | 0.37 | 1.02 | 0.06 | 0.61 |

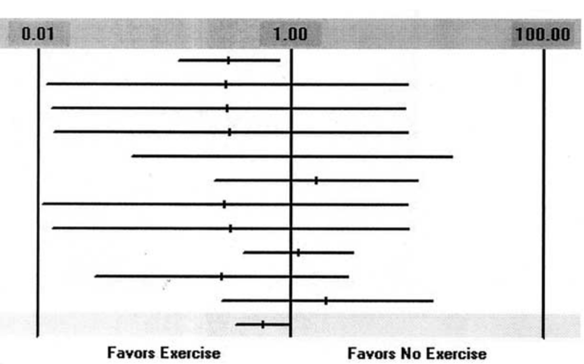


**Figure 3.** Odds ratios (with 95% confidence intervals) for mortality in 11 trials reporting deaths in treatment or control groups.

patients; however, it is rarely achieved in the execution of daily activities. The relative success of an exercise-training program is commonly determined by comparing the increment between baseline and post-training maximal oxygen consumption. In our study, we examined studies that used directly measured maximal oxygen consumption. However, there were other studies (Tables 2 and 3) without maximal oxygen consumption data that used other parameters such as 6-minute walks or submaximal tests, which show variable correlation with maximal oxygen consumption in different persons and therefore were considered insufficiently reliable for analysis.

Perhaps the most important issue that remains undefined regarding the role of exercise training in heart failure is program design. Traditionally, exercise-training programs have followed the standard prescription of continuous aerobic exercise used in cardiac rehabilitation, with resistance exercise sometimes added. Continuous aerobic exercise may not optimally stress the peripheral muscles, which are atrophied and have fewer muscle fibers, oxidative enzymes, and capillaries in heart failure patients (37). Several studies (34,36,38–47) have examined the extent to which strength training might reverse skeletal muscle wasting that is due to reduced cardiac function. The European Heart Failure Training Group (48) suggested that a combined strength and endurance training program, similar to the program by Maiorana et al (49), may be the optimal exercise prescription. Our analysis suggests a greater increment in functional capacity with aerobic exercise than with strength training, but the numbers were too small to attain statistical significance. Moreover, our findings may reflect the use of aerobic testing as the marker of efficacy. There may be other benefits of strength training, and the optimal program may involve a combination of both forms of exercise, which was the format of several studies in our review.

Intermittent aerobic exercise (29,36,39,43,49–52) allows rest breaks that lower total cardiac stress, and therefore allow patients with compensated heart failure to complete short work periods at a higher intensity than would be possible with a continuous protocol. In this review, only two of the seven studies using an intermittent protocol yielded acceptable functional capacity measures (39,50), with increments comparable with those of continuous aerobic programs. These results are consistent with similar changes in functional capacity that have been demonstrated with intermittent and continuous exercise training in healthy, older men (52).

The effect of the exercise "dose" on the efficacy of training is not known. Morris et al (52) suggested that the volume of exercise rather than the method of delivery determined improvement in functional capacity, whereas other studies have suggested that program duration may have more influence. The European Heart Failure Training Group (48) reported that improvements in functional capacity after 12 weeks were greater than those after 6 weeks, and changes after 24 weeks were even greater. Similarly, two studies demonstrated that changes can be maintained for more than 12 months (31,32). However, a recent large study has suggested that initial fitness gains are not improved further after 3 months, and that exercise adherence deteriorates once the patient adopts a home program (at 3 to 12 months) (53). We found no clear relation between the dose parameters (frequency, intensity, duration, session time) of the exercise programs and change in functional capacity, suggesting that other factors may influence the conditioning response to exercise.

Although a few studies have suggested that some subgroups benefit particularly from training (48–54), our results indicate otherwise. Patients with ischemia may respond differently; indeed, one study reported changes in functional capacity to be lower in patients with ischemia than in those without (48). In this study, patients with ischemia were also younger and had a lower New York Heart Association functional class and functional capacity at baseline. Mortality may also be higher in patients with ischemia (31).

Age should not be a contraindication to training, although changes may be smaller in patients older than 70 years (48). Exercise training may be beneficial in the elderly, who have the highest incidence of heart failure, but many elderly patients are intimidated by the prospect of exercise training. Younger patients are less likely to participate in an exercise program due to work commitments. In the few studies that reported on exercise adherence (13,48), compliance was generally good.

Sex may also affect the rate and extent of responses to exercise training, although with the underrepresentation of women in most studies this issue remains unclear. Still, the incidence of heart failure in men and women is reported to be similar (55).

Although a positive effect of exercise training may be fewer hospitalizations, it is difficult to ascertain whether adverse events were directly attributable to exercise. Heart failure patients are prone to clinical events, but on the basis of previous data, it appears that patients undergoing exercise testing or training would experience a clinical event every 3700 hours, suggesting that training does not increase the rate of adverse events. No exercise-related deaths were reported in heart failure patients during more than 60,000 patient-hours of exercise training, which compares favorably with outcomes in healthy and cardiac populations (56,57).

The majority of studies reported that patients had been stable on medications for at least 3 months before recruitment. The incorporation of beta-blockers in standard therapy for heart failure is a relatively recent development (58,59), and many studies in our review precede this era. Improvements in cardiac function and functional capacity in the existing trials are therefore incremental to standard therapy, and some studies have documented the ongoing efficacy despite beta-blocker therapy (6). Moreover, the location of most studies at specialized centers suggests that access to other heart failure therapies was available.

Several studies have shown home exercise programs to be effective in the short-term treatment of heart failure (60); although their safety is not established, early evidence is encouraging (55). A cost-effective, safe, long-term, supervised maintenance model has yet to be developed. A home program would eliminate the time and 'ease of access' constraints to participation, although it would introduce problems of supervision for safety and adherence purposes.

Only five studies recorded follow-up data after the completion of the exercise program (4,11,29,31,61), although a number of studies did involve long-term training programs (and therefore follow-up). Only two studies (31,53) demonstrated a sizable number of deaths. However, the effects of training were disparate; the relative risk of death was about 3.6-fold higher in the McKelvie study (53) than in the Belardinelli study (31). The most likely explanation for this difference is that the Belardinelli study had an extended (4-year) follow-up, and although patients were not instructed to follow an exercise regimen during this period, many may have done so.

In conclusion, despite these unresolved questions, the data show that the composite endpoint of mortality and adverse events may be reduced in exercising subjects compared with sedentary controls. Exercise training is safe and effective and should be part of the standard treatment of heart failure patients, but further studies are required to determine whether there is any survival benefit.

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