

Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH)

ExTraMATCH Collaborative

Abstract

Objective To determine the effect of exercise training on survival in patients with heart failure due to left ventricular systolic dysfunction.

Design Collaborative meta-analysis.

Inclusion criteria Randomised parallel group controlled trials of exercise training for at least eight weeks with individual patient data on survival for at least three months.

Studies reviewed Nine datasets, totalling 801 patients: 395 received exercise training and 406 were controls.

Main outcome measure Death from all causes.

Results During a mean (SD) follow up of 705 (729) days there were 88 (22%) deaths in the exercise arm and 105 (26%) in the control arm. Exercise training significantly reduced mortality (hazard ratio 0.65, 95% confidence interval, 0.46 to 0.92; log rank $\chi^2 = 5.9$; $P = 0.015$). The secondary end point of death or admission to hospital was also reduced (0.72, 0.56 to 0.93; log rank $\chi^2 = 6.4$; $P = 0.011$). No statistically significant subgroup specific treatment effect was observed.

Conclusion Meta-analysis of randomised trials to date gives no evidence that properly supervised medical training programmes for patients with heart failure might be dangerous, and indeed there is clear evidence of an overall reduction in mortality. Further research should focus on optimising exercise programmes and identifying appropriate patient groups to target.

Introduction

Exercise training is known to reduce the debilitating symptoms of chronic heart failure, such as breathlessness and fatigue, through effects on the cardiovascular and musculoskeletal systems.¹⁻³ Despite this, it is not widely utilised, perhaps because data on its effect on survival are limited.⁴

Randomised controlled trials have focused largely on symptomatic benefits and on surrogate markers of prognosis, including neurohormonal balance, variability in heart rate, and peak oxygen consumption.¹ Individual trials have mostly been small. Meta-analyses of randomised trials can provide more reliable estimates of treatment effect than individual trials because they have greater statistical power. When based on data

from individual patients they have several important advantages over those based solely on published data.⁵

We report a collaborative meta-analysis, based on individual patient data, of randomised controlled trials comparing exercise training with usual care in patients with chronic heart failure due to left ventricular systolic dysfunction. We aimed to obtain reliable and precise estimates of overall treatment benefit on death and on the secondary end point of death or admission to hospital.

Methods

A collaborative group was established, coordinated from the Heart Failure Unit of the Imperial College School of Medicine, London. A prospective protocol was written and agreed by the collaborative group before data collection, specifying the methods to be used, the main prespecified analyses, and a common dataset of collected variables.

We searched Medline for randomised controlled trials since 1990 of exercise training in patients with chronic congestive heart failure or left ventricular dysfunction. The characteristics of trials to be included were that they should be randomised parallel group controlled trials and should evaluate exercise training without any other simultaneous intervention that could confound the results, should study patients with stable heart failure (three months or more of stability) due to left systolic ventricular dysfunction (left ventricular ejection fraction less than 50%), should have an exercise programme lasting eight weeks or more, should utilise training involving at least both legs, and should have survival follow up of three months or more.

Initial screening identified 101 potential reports of which 41 were non-overlapping datasets. Nine met the eligibility criteria.

After formal agreement, all principal investigators were asked to provide datasets in the form of anonymised predefined individual patient data for each patient originally randomised. Only the first clinical event other than death was recorded. The number of events in this meta-analysis may differ slightly from

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those reported by the trials because follow up is now more complete.

We examined the potential for publication bias by constructing a funnel plot⁶ applying a regression method⁷ and the Kendall tau method.

The primary end point was time to death (from any cause). A secondary end point was death or time to admission to hospital (for any reason). Time to death was available for all studies, and time to death or admission to hospital was available for eight of the nine studies. The treatment arms were combined into one arm as were the placebo arms.

The effect of exercise was also assessed in prespecified subgroups—males versus females, New York Heart Association functional class I-II versus III-IV, ischaemic versus non-ischaemic causes, age, peak oxygen uptake (< 15 ml/kg/min *v* ≥ 15ml/kg/min), left ventricular ejection fraction (< 27% *v* ≥ 27%), and duration of training programme (< 28 weeks *v* at least 28 weeks). The continuous variables were each dichotomised at their corresponding median values over the whole dataset. For each subgroup we tested for interaction.

Results

Nine prospective studies met the criteria for the meta-analysis (see bmj.com).^{2, 4, 8-15} Tables 1 and 2 present the characteristics of the trials and patients. We found no evidence of publication bias.

Overall, there were 88 deaths in the exercise arm (median time to event, 618 days) and 105 in the control arm (421 days). Mortality was significantly lower in the exercise group ($P=0.015$). The hazard ratio for mortality was 0.65 (95% confidence interval 0.46 to

0.92) (figure). These results would imply a number needed to treat of 17 to prevent one death in two years.

The secondary end point of death or admission to hospital occurred in 127 patients in the exercise arm and 173 in the control arm. The median time to admission to hospital was 426 days in the exercise arm and 371 days in the control arm ($P=0.011$, figure). The hazard ratio for the combined end point was 0.72 (0.56 to 0.93).

In each subgroup (and for each end point) there was no significant interaction term between treatment allocation and subgroup (see bmj.com). No evidence was therefore found of a subgroup specific treatment effect.

Discussion

Exercise training significantly improves survival time in patients with chronic heart failure due to left ventricular systolic dysfunction. The mechanism on survival remains unknown. Observational studies in chronic heart failure are essentially unanimous in confirming a strong relation between exercise capacity and survival.¹⁶ Indeed, observational work in the general healthy population has shown that exercise capacity, even if assessed without metabolic measurements, is a more powerful prognostic indicator than traditional risk factors such as smoking, high blood pressure, blood cholesterol level, and diabetes.¹⁷

One explanation, applicable to patients with ischaemic causes, is that exercise training improves myocardial perfusion by alleviating endothelial dysfunction and therefore dilating coronary vessels and by stimulating new vessel formation by way of intermit-

Table 1 Characteristics of studies included in meta-analysis

Study	Location	No in groups (training, control)	Duration of training programme (days)	Mean (SD) duration of follow up (days)	Description of training programme	Intensity of programme
Belardinelli et al, 1999 ⁴	Italy	50, 49	420	1144 (461)	Supervised cycling, 60 minutes three days a week for eight weeks, then two days a week	60% peak oxygen consumption
Dubach et al 1997 ^{9, 10}	Switzerland	24, 26	56	261 (106)	Supervised walking, two hours daily; supervised cycling 40 minutes four days a week	80% peak oxygen consumption
Giannuzzi et al, 1997 ¹¹	Italy	46, 42	168	206 (35)	Supervised cycling, 30 minutes three days a week for two months, then home based 30 minutes for three days a week and walking for 30 minutes	80% peak heart rate
Hambrecht et al, 1995 ¹²	Germany	34, 35	168	159 (22)	Supervised and home based walking, calisthenics, cycling 40-60 minutes a day	70% peak oxygen consumption
Kiilavuori et al, 2000 ¹³	Finland	12, 15	182	2284 (1213)	Supervised cycling 30 minutes three days a week for three months, then home based training (walking, cycling, rowing, and swimming)	50-60% peak oxygen consumption
McKelvie et al, 2002 ²	Canada	90, 91	364	557 (219)	Supervised aerobic (cycling, treadmill, arm) and resistance training 30 minutes three days a week for three months, then home based aerobic training three days a week	60-70% peak heart rate
Zanelli et al, 1997 ¹⁴	Italy	76, 79	364	304 (140)	Supervised aerobic (cycling, treadmill, arm) and resistance training 30 minutes two days a week and home based cycling three days a week for two months, then only home based aerobic training five days a week	70% peak oxygen consumption
Wielenga et al, 1999 ¹⁵	Netherlands	41, 39	84	1440 (917)	Supervised cycling, walking, ball game 30 minutes three days a week for eight weeks, then two days a week	60% peak heart rate
Willenheimer et al, 1998 ¹⁶	Sweden	22, 30	112	1623 (797)	Supervised interval cycling training (90 second exercise and 30 second rest) for 15-45 minutes two days a week	80% peak oxygen consumption or grade 15 Borg scale
Total		395, 406	213 (135)	705 (729)		

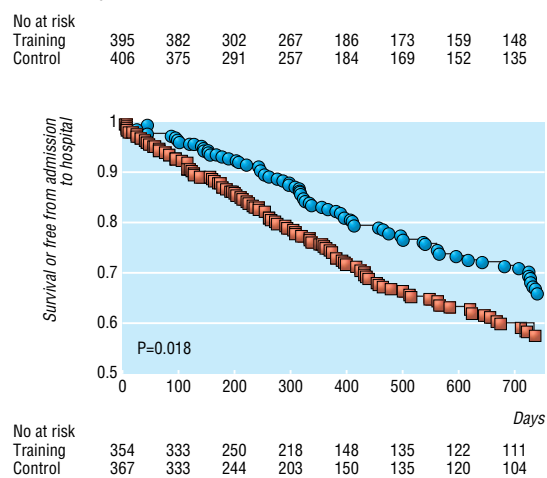
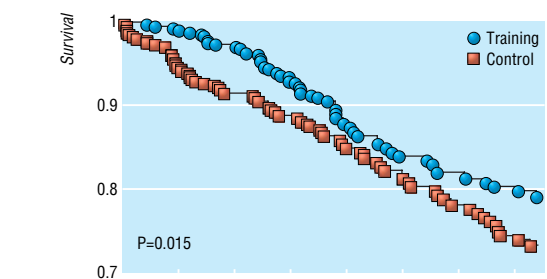
tent ischaemia.^{18 19} Ventricular remodelling has been shown to be attenuated by exercise training.¹¹

Even when the amount of time spent exercising as part of a programme is small, supervised and encouraged exercise is likely to lead to a more active lifestyle, so that the effective “dose” of exercise may be considerably greater than that directly prescribed. Arguably, this contrasts with pharmacotherapy.

Study limitations

One trial that met all the validity criteria was not included because its raw data could not be obtained.²⁰ This was a small trial (12 cases, 13 controls), and its results were of a net benefit of exercise training in exercise tolerance and quality of life. It is unlikely that the principal findings of our meta-analysis would have been altered if the raw data had been available.

Exercise training can necessarily only be trialled in open design studies, and it is important to consider the possibility that there may have been more vigorous prognostic pharmacotherapy in one arm than in the other. At baseline there was no significant difference in treatment pattern between groups. To assess the plausibility of changes in medical therapy as a cause for the reduction in mortality, we asked all the investigators about changes in drugs during the trial. Investigators in six of the nine trials, covering two thirds of the patients, were able to provide information. They stated that there was no change in angiotensin converting enzyme inhibitor, β blocker, or antialdosterone therapies during the trial period. As is normal clinical practice, however, patients were allowed to vary their dosage of loop diuretic, but comprehensive data on this are not available.



Kaplan-Meier cumulative two year survival (top) and Kaplan-Meier cumulative two year survival or free from admission to hospital (bottom)

Table 2 Characteristics of patients included in meta-analysis. Values are numbers (percentages) unless indicated otherwise

Characteristics	Training (n=395)	Control (n=406)
Male	88.4	87.2
Mean (SD) age (years)	60.5 (9.3)	59.7 (13.2)
Mean (SD) NYHA class	2.6 (0.6)	2.5 (0.6)
Ischaemic heart disease	59.7	58.7
Mean (SD) left ventricular ejection fraction (%)	27.9 (8.3)	27.0 (8.6)
Mean (SD) peak oxygen uptake (ml/kg/min)	15.4 (4.0)	15.2 (3.9)
Mean (SD) renal function (laboratory findings)*:		
Serum creatinine (mg/dL)	1.4 (0.4)	1.4 (0.5)
Urea (mg/dL)	61.3 (40)	63.7 (38)
Drugs†:		
Angiotensin converting enzyme inhibitors	73.4	73.2
Anticoagulant	40.0	36.9
Aspirin	30.1	30.8
Amiodarone	10.9	12.8
β adrenergic blockade	12.2	14.5
Digitalis	50.4	47.8
Diuretics	68.9	69.5
Nitrate	40.0	31.0

NYHA=New York Heart Association.

*Renal function known for 146 patients.

†Drugs known for 655 patients.

What is already known on this topic

Exercise training reduces the debilitating symptoms of chronic heart failure through effects on the cardiovascular and musculoskeletal systems

Exercise training is not widely used because data on its effect on survival are not compelling

What this study adds

Mortality and admission to hospital are significantly reduced after exercise training in patients with chronic heart failure due to left ventricular systolic dysfunction

This benefit was not restricted to any particular subgroup of patients

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- 1 European Heart Failure Training Group. Experience from controlled trials of physical training in chronic heart failure. *Eur Heart J* 1998;19:466-75.
- 2 McKelvie RS, Teo KK, Roberts R, McCartney N, Humen D, Montague T, et al. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). *Am Heart J* 2002;144:23-30.
- 3 Hambrecht R, Niebauer J, Fiehn E, Kalberer B, Hauer K, 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.
- 4 Belardinelli R, Georgiou D, Cianci D, 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.
- 5 Stewart LA, Parmar MKB. Meta-analysis of the literature of individual patient data: is there a difference? *Lancet* 1993;341:418-22.
- 6 Begg CB. Publication bias. In: Cooper H, Hedges LV, eds. *The handbook of research synthesis*. New York: Russell Sage Foundation, 1994:400-9.
- 7 Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
- 8 Dubach P, Myers J, Dziekan G, Goebels U, Reinhart W, Muller P, et al. Effect of high intensity exercise training on central hemodynamic responses to exercise in men with reduced left ventricular function. *J Am Coll Cardiol* 1997;29:1591-8.
- 9 Myers J, Wagner D, Schertler T, Beer M, Luchinger R, Klein M, 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;104:719-25.
- 10 Giannuzzi P, Temporelli PL, Corra U, Gattone M, Giordano A, Tavazzi L. Attenuation of unfavorable remodeling by exercise training in postinfarction patients with left ventricular dysfunction: results of the Exercise in Left Ventricular Dysfunction (ELVD) trial. *Circulation* 1997;96:1790-7.
- 11 Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure. A randomized trial. *J Am Med Assoc* 2000;283:3095-101.
- 12 Kilavuori K, Naveri H, Salmi T, Harkonen M. The effect of physical training on skeletal muscle in patients with chronic heart failure. *Eur J Heart Fail* 2000;2:53-63.
- 13 Zanelli E, Volterrani M, Scalvini S, Musmeci G, Campana M, Zappa C, et al. Multidisciplinary non-pharmacological intervention prevents hospitalization, improves morbidity rates and functional status in patients with congestive heart failure. *Eur Heart J* 1997;18(abstract suppl):647.
- 14 Wielenga RP, Huisveld IA, Bol E, Dunselman PH, Erdman RA, Baselier MR, et al. Safety and effects of physical training in chronic heart failure. Results of the chronic heart failure and graded exercise study (CHANGE) *Eur Heart J* 1999;20:872-9.
- 15 Willenheimer R, Erhardt L, Cline C, Rydberg E, Israelsson B. Exercise training in heart failure improves quality of life and exercise capacity. *Eur Heart J* 1998;774-81.
- 16 Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;83:778-86.
- 17 Myers J, Prakash M, Froelicher V, Partington S, Atwood E. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;346:793-801.
- 18 Laughlin MH, McAllister RM. Exercise training-induced coronary vascular adaptation. *J Appl Physiol* 1992;73:2209-25.
- 19 White FC, Roth DM, McKirnan D, Carroll SM, Bloor CM. Exercise induced coronary collateral development: a comparison to other models of myocardial angiogenesis. In: Schaper W, Schaper J, eds. *Collateral circulation*. Norwell, MA: Kluwer Academic; 1993:261-89.
- 20 Quittan M, Sturm B, Wiesinger GF, Pacher R, Fialka-Moser V. Quality of life in patients with chronic heart failure: a randomised controlled trial of changes induced by a regular exercise program. *Scand J Rehabil Med* 1999;31:223-8.

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Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial

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Abstract

Objective To compare the effectiveness of an electrocautery strategy with ovulation induction using recombinant follicle stimulating hormone in patients with clomiphene resistant polycystic ovary syndrome.

Design Randomised controlled trial.

Setting Secondary and tertiary hospitals in the Netherlands.

Participants 168 patients with clomiphene citrate resistant polycystic ovary syndrome: 83 were allocated electrocautery and 85 were allocated recombinant follicle stimulating hormone.

Intervention Laparoscopic electrocautery of the ovaries followed by clomiphene citrate and recombinant follicle stimulating hormone if anovulation persisted, or induction of ovulation with recombinant follicle stimulating hormone.

Main outcome measure Ongoing pregnancy within 12 months.

Results The cumulative rate of ongoing pregnancy after recombinant follicle stimulating hormone was 67%. With only electrocautery it was 34%, which increased to 49% after clomiphene citrate was given.

Subsequent recombinant follicle stimulating hormone increased the rate to 67% at 12 months (rate ratio 1.01, 95% confidence interval 0.81 to 1.24). No complications occurred from electrocautery with or without clomiphene citrate. Patients allocated to electrocautery had a significantly lower risk of multiple pregnancy (0.11, 0.01 to 0.86).

Conclusion The ongoing pregnancy rate from ovulation induction with laparoscopic electrocautery followed by clomiphene citrate and recombinant follicle stimulating hormone if anovulation persisted, or recombinant follicle stimulating hormone, seems equivalent to ovulation induction with recombinant follicle stimulating hormone, but the former procedure carries a lower risk of multiple pregnancy.

Introduction

Polycystic ovary syndrome is characterised by oligomenorrhoea or amenorrhoea, infertility, hirsutism,



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