Systematic review of the effect of aerobic and resistance exercise training on systemic brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients

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CRD summary
This review concluded that exercise training had a favorable effect on brain natriuretic peptide and N-terminal pro-BNP in heart failure patients. Uncertainty of over parts of the review process, some methodological shortcomings in the included studies and significant variability across studies mean the authors' conclusions should be interpreted with caution.

Authors' objectives
To assess the effect of exercise training on brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP) levels in patients with left ventricular dysfunction.

Searching
MEDLINE (1950 to July 2008), EMBASE (from 1974), Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (from 1981) and Web of Science (from 2000) were searched without language restrictions to February 2009. Conference proceedings and journals not yet available on electronic databases were searched. Search terms were reported. Reference lists of included studies were searched.

Study selection
Randomised controlled trials (RCTs) of aerobic and/or resistance exercise training that measured BNP and/or pro-BNP in heart failure patients were eligible for inclusion provided they reported changes in BNP and NT-pro-BNP (primary outcomes). Secondary outcomes included changes in functional capacity and energy expenditure.

In the included studies, most participants were male (79.7% in the exercise group and 75.4% in the control group). Age ranged from 53 to 75 years. New York Heart Association Class ranged from I to III. The most frequent exercise was cycling; studies also included walking and aerobic and resistance exercises. Training frequency varied from two to seven sessions per week (30 to 50 minutes duration) over three to nine month programmes. Intensity ranged from 50% to 70% of maximum peak VO$_2$.

Two reviewers independently screened articles for inclusion. Discrepancies were resolved through consultation with a third reviewer.

Assessment of study quality
Study quality was assessed based on criteria of methods of randomisation and recruitment, outcome reporting, exercise adherence and reporting changes in drug therapy (maximum possible score 5).

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Post-exercise change in BNP and NT-pro-BNP were extracted as mean differences with 95% confidence intervals (CIs). Where possible, total work completed during the cycle ergometry portions of the exercise training programs (kcal) and mean weekly calorie expenditure were calculated to determine a dose-response relationship with change in BNP or NT-pro-BNP, disease severity and clinical characteristics of participants with congestive heart failure.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Mean differences and 95% CIs were pooled in a meta-analysis using a random-effects model. Statistical heterogeneity was assessed using a Cochran Q test. Sensitivity analyses were undertaken to assess the impact of removing studies with large standard deviations in measurements of BNP and NT-pro-BNP.

Results of the review
Nine RCTs (n=463) were included in the review. Study quality varied: two studies scored 1, one study scored 2, five studies scored 3 and one study scored 4. Only two studies reported the randomisation method in sufficient detail. Recruitment was unclear in five studies. Details of exercise adherence were not reported in six studies. In three studies changes in drug therapy were stable.

Exercise training significantly lowered BNP (MD -79pg/mL, 95% CI -141 to -17, $I^2=73\%$; five studies) and NT-pro-BNP (MD -621pg/mL, 95% CI -844 to -398, $I^2=75\%$; six studies); significant heterogeneity was noted for both comparisons.

Sensitivity analysis showed changes in BNP and NT-pro-BNP (four studies) remained statistically significant. Significant heterogeneity was noted for both comparisons ($I^2=77\%$ and $I^2=84\%$).

Authors' conclusions
Exercise training had a favorable effect on BNP and NT-pro-BNP in heart failure patients.

CRD commentary
The objectives and inclusion criteria of the review were clear. Relevant sources were searched without language restrictions, which reduced the likelihood of language bias. Study selection was carried out with efforts to reduce error and bias; the authors did not report whether such methods were applied to data extraction and validity assessment. Study quality was assessed using appropriate criteria; methodological shortcomings were present for most studies. It appeared that appropriate techniques were used to combine data, assess heterogeneity and explore differences between trials. Given the considerable statistical heterogeneity for all analyses it was questionable whether it was appropriate to pool these data.

Uncertainty of over parts of the review process, some methodological shortcomings in the included studies and significant variability across studies mean the authors' conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that suitably powered long-term studies should be undertaken to demonstrate a link between exercise-induced BNP/NT-pro-BNP decrease and morbidity, healthcare costs and mortality in chronic heart failure patients. Short-term (less than 12 months) studies should be conducted to investigate changes in BNP and NT-pro-BNP with improved myocardial function, functional capacity and blunted neurohormonal responses at rest.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.