Exercise-based rehabilitation programmes for pulmonary hypertension (Protocol)

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Exercise-based rehabilitation programmes for pulmonary hypertension

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and safety of exercise-based rehabilitation for people with PH.

BACKGROUND

Description of the condition

Pulmonary hypertension (PH) is a progressive vasculopathy characterised by extensive remodelling of the pulmonary vasculature resulting in a narrowing of the arterial lumen (Casserly 2009). There is a marked increase in the pulmonary vascular resistance resulting in right ventricular remodelling and eventual failure, which, in the majority of cases, results in the patient death (Tuder 2013). Confirmatory diagnosis of PH is made via right heart catheterisation in which the patient has a resting mean pulmonary artery pressure of greater than 25 mmHg (Hoeper 2013). PH may arise in association with a broad range of disease states (over 40) of both known and unknown cause. International guidelines classified PH into the following five clinical groups (Simonneau 2013):

1. pulmonary arterial hypertension (PAH);
2. PH due to left heart disease;
3. PH due to lung diseases and/or hypoxia;
4. chronic thromboembolic PH;
5. PH with unclear multifactorial mechanisms.

Given the evolving definition of PH, the incidence and prevalence of the disease is difficult to define (Strange 2012). One recent study suggested that the incidence and prevalence of PH varies markedly between the five clinical groups. In an observational cohort study of over 10,000 individuals from Armadale and the surrounding region in Western Australia, Strange 2012 reported the minimum indicative prevalence for all groups of PH was 326/100,000, with left heart disease associated with Group 2 being the most prevalent. Registries of prevalent and incident cases from around the world have now been published (McGoon 2013), suggesting an increased global awareness of the disease. Regardless of aetiology, PH is characterised by limited exercise capacity and a progressive increase in breathlessness. Until recently,
treatment options for PH remained limited and patient prognosis poor. One early registry of PH patients reported a median survival time of 2.8 years post diagnosis (D’Alonzo 1991). The development of PH specific drug therapies, targeted at the pulmonary vasculature, has significantly improved prognosis. This improved survival has been reflected in several of the more recently published registries (McGoon 2013). For example, the United States Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) registry of over 3500 prevalent and incident cases recorded between 2006-9, reported five-year survival rates for PAH at 57% (Benza 2010).

Advances in PH-specific therapies has meant that other treatment options aimed at improving outcomes such as exercise capacity and quality of life have been explored. In other chronic heart and lung disease patients, there is strong evidence that exercise training improves functional capacity, quality of life and even long-term survival (Spruit 2013). However, until very recently, exercise reha- bilitation has been actively discouraged in patients with PH for fear it would worsen symptoms and negatively impact on cardiac function (Galie 2013). Whilst new guidelines released in December 2013 recommend exercise training, the guideline authors acknowledge that gaps in the knowledge exist including knowledge of the optimal training dose, characteristics of supervision, mechanisms of adaptation and the impact of exercise training on long-term survival (Galie 2013).

Description of the intervention
Exercise-based rehabilitation programs include aerobic and strength training. Aerobic training involves the activation of a large skeletal muscle mass through cycling or walking exercise whereas strength training programs involve upper and lower body muscle groups (Spruit 2013). Programs are typically offered in an outpatient or inpatient setting, involving two to three sessions per week over at least a four-week period.

How the intervention might work
In healthy young and older patients, exercise training results in improved oxygen transport and uptake at peak exercise through both central and peripheral adaptations. Central adaptations include an increase in maximal cardiac output, through an increase in stroke volume (Ogawa 1992). Central adaptations are the result of volume overload mediated cardiac remodelling that leads to improved cardiac function at rest and during exercise (Ogawa 1992; Pluim 2000). In the periphery, greater skeletal muscle oxidative capacity occurs with an increase in enzymes associated with cellular respiration in particular those involved in the citric acid cycle (the Krebs cycle) and oxidative phosphorylation (Coggan 1992; Gollnick 1973). In addition, there is an increase in the capillary density per myofibril (Coggan 1992; Gollnick 1973). As a result of these central and peripheral adaptations, there is not only an increased delivery of oxygen to the exercising myofibril, there is also increased capacity to metabolise oxygen for the production of adenosine triphosphate. Transition between myofibril types typically occurs with an increase in the fast twitch oxidative and a decrease in fast twitch glycolytic fibres following exercise training (Coggan 1992; Ennion 1995; Gollnick 1973). Moreover, there is an increase in the cross sectional area of slow switch (Type I) and Type IIa fibres in trained individuals (Coggan 1992; Gollnick 1973).

In PH, the factors which contribute to exercise limitation are complex (Fowler 2012). The changes in the pulmonary vasculature associated with PH results in a significant increase in pulmonary artery pressure and right ventricular afterload during exercise (Provencher 2008; Riley 2000). Right ventricular contractility is decreased and there is a reduced capacity for stroke volume and therefore cardiac output to increase during exercise (Fowler 2012). Moreover, PH patients have a reduced heart rate response to exercise (chronotropic incompetence) which further decreases the ability for cardiac output to increase during exercise (Provencher 2006). As a result, people with PH have a blunted increase in cardiac output during exercise that significantly reduces peak oxygen transport. In the periphery, people with PH appear to have marked skeletal muscle dysfunction consistent with a reduced oxidative capacity (Mainguy 2010a). Compared to controls, PH patients had a lower percentage of Type I fibres and increased concentrations of enzymes associated with glycolytic (anaerobic) metabolism (Mainguy 2010a). These central and peripheral changes would result in a substantial reduction in the ability to transport and utilise oxygen during exercise.

In patients with chronic lung disease, lower limb exercise training and strength training have both been demonstrated to increase exercise capacity and quality of life (Spruit 2013). The primary site of adaptation appears to be the skeletal muscle, with little change in cardiac function following exercise training in chronic heart and lung disease patients (Vogiatzis 2013). For example, in patients with chronic obstructive pulmonary disease there is evidence that exercise training results in improved skeletal muscle structure and function with little change in cardiac function (Vogiatzis 2013; Whittom 1998). Whilst preliminary evidence in a small number of subjects suggests that there is some improvement in skeletal muscle function following exercise training in PH (de Man 2009; Mainguy 2010b), it remains unclear if these changes result in improved exercise capacity or if they relate to improved long term outcomes. Currently there is insufficient evidence for any central changes following exercise training in PH.

Why it is important to do this review
The objective of this review is to assess the efficacy and safety of exercise-based rehabilitation for people with PH. In other chronic lung disease populations, for example chronic obstructive pul-
monary disease, this form of rehabilitation is safe and has demonstrable benefits in terms of improvement in exercise capacity, lower limb muscle strength and quality of life (Spruit 2013). Indeed, until recently there had been a reluctance to recommend exercise-based rehabilitation for PH due to the fact that it may worsen the patient’s long term health outcomes (Galie 2009). Given that new international guidelines recommending exercise training in PH (Galie 2013), it is important that the current state of the evidence regarding the efficacy and safety of exercise based rehabilitation is established. The results of this review will provide essential information to clinicians who may consider referring PH patients for exercise-based rehabilitation and help guide decisions on which PH patients may be suitable.

OBJECTIVES
To assess the efficacy and safety of exercise-based rehabilitation for people with PH.

METHODS
Criteria for considering studies for this review

Types of studies
We will include randomised controlled trials (RCTs). We will include studies reported in full or abstract form as well as any relevant, unpublished data.

Types of participants
We will include adults with a diagnosis of PH. We will include all five clinical groups of PH (Simonneau 2013), independent of whether the patients are stable on therapy (i.e. change of therapy over the past three months).

Types of interventions
We will include trials comparing exercise-based rehabilitation with usual care or no exercise-based rehabilitation. Exercise-based rehabilitation of any frequency and duration will be eligible for inclusion and may include inpatient, outpatient or home-based settings. We will include exercise programs of any length; however, we will only include trials in which exercise training is supervised. We will exclude exercise programs that only provide exercise advice. We will include exercise-based programs prescribing aerobic and/or strength training.

We will analyse exercise-rehabilitation that only includes a strength-training program separately. The control group may include individuals randomised to a program of education which has no specific exercise prescription component.

Types of outcome measures

Primary outcomes
- Exercise capacity
  - Measures of exercise capacity would include but not confined to outcomes such as the six minute walk distance, peak exercise capacity (VO$_{2peak}$), peak power (W$_{peak}$) and measures derived during the assessment of exercise capacity such as breathing efficiency (VE/VCO$_2$ slope) and anaerobic threshold
  - Serious adverse events during the intervention period
    - We will use this measure to assess the short-term safety of exercise training in PH
      - mortality;
      - disease progression, defined according to the investigators’ definition;
      - symptoms precluding training, such as illness, light headedness, syncope or presyncope; and
      - discontinuation of the study
- Health-related quality of life measured by a validated generic or disease specific quality of life measure

Secondary outcomes
- Cardiopulmonary haemodynamics
  - These include measures made using echocardiographic, right heart catheter or magnetic resonance imaging techniques
    - Outcome measures would include, but not be confined to indices such as mean pulmonary artery pressure, mean pulmonary vascular resistance, right ventricular systolic pressure, tricuspid annular plane systolic excursion, ventricular ejection fraction, ventricular end diastolic volume and ventricular end systolic volume
- Functional Class measured by the New York Heart Association (NYHA) Classification (NYHA 1994)
- Clinical worsening during the follow-up period.
  - The impact of exercise training on clinical worsening will be assessed using the investigators definition
    - Typically clinical worsening is defined using a combination of outcomes including survival, hospitalisation due to PH, transplantation, requirement for additional pharmacological therapy, a reduction in functional class and or a reduction in the six-minute walk test (Frost 2013)
    - For the purpose of this study, we will treat mortality during the follow-up period as a separate secondary outcome measure.
Mortality during the follow-up period
  - We will record all deaths reported following the exercise intervention.
  - We will treat these deaths separately to those that occurred during the exercise training period, which will be recorded by the primary outcome measure, serious adverse events.

- B-type natriuretic peptide
  - A commonly used marker of right ventricular dysfunction in PH that is correlated with survival (Casserly 2009).
  - We will examine changes in B-type natriuretic peptide following exercise-based rehabilitation.

Reporting one of more of the outcomes listed here in the trial is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches
We will identify trials from searches of the following databases:

- the Cochrane Airways Group Register of Trials (all years);
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library) (latest issue);
- MEDLINE (Ovid) (1950 to date);
- EMBASE (Ovid) (1974 to date);
- Physiotherapy Evidence Database (PEDro) (all years).

The proposed MEDLINE strategy is listed in Appendix 1. We will adapt it for use in the other databases. We will search all databases from their inception to the present, and there will be no restriction on language or type of publication. We will identify handsearched conference abstracts and grey literature from the CENTRAL database.

We will also conduct a search of ClinicalTrials.gov (http://clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources
We will check reference lists of all primary studies and review articles for additional references. We will search for errata or retractions from included studies published in full-text on PubMed and report the date this was done within the review.

Data extraction and management
We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. Two review authors (NM and AH) will extract study characteristics from included studies.

We will extract the following study characteristics.
1. Methods: study design, total duration of study, details of any ‘run in’ period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: number enrolled, mean age, age range, gender, severity of condition, diagnostic criteria, baseline echocardiography and right heart catheter data, baseline lung function, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, training dose (intensity, frequency and duration of exercise training), comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

We will note in the ‘Characteristics of included studies’ table if outcome data was not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (FK). One review author (NM) will transfer data into the Cochrane Collaboration’s statistical software, Review Manager 2014. We will double-check that data is entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (AH) will spot-check study characteristics for accuracy against the trial report.

Data collection and analysis

Selection of studies

Assessment of risk of bias in included studies
Two review authors (NM and AH) will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).
We will resolve any disagreements by discussion or by involving another author (FK).

We will assess the risk of bias according to the following domains:
1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment in a 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

**Unit of analysis issues**

Where studies randomly allocate the participants to either the exercise-based rehabilitation or control, we will consider the participant as the unit of analysis. We will exclude cross-over trials due to the potential carry over effects of exercise training.

**Dealing with missing data**

We will contact trial investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

**Assessment of heterogeneity**

We will use the $I^2$ statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis.

**Assessment of reporting biases**

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study and publication biases.

**Data synthesis**

We will perform a pooled quantitative synthesis where the trials are clinically homogeneous. We will pool data using a random-effects model to incorporate between study heterogeneity into the meta-analysis. Where the trials are clinically heterogeneous, we will perform a narrative synthesis. We will use RevMan HAL, developed by the Cochrane Schizophrenia Group (http://szg.cochrane.org/revman-hal), to construct a first draft of the results section.

**Summary of findings table**

We will create a 'Summary of findings' table using the following outcomes: exercise capacity, serious adverse events, cardiopulmonary haemodynamics, quality of life, functional class, mortality and clinical worsening during follow up. We will use the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions using GRADEpro software (GRADEpro 2008; Higgins 2011). We will justify...
all decisions to down- or up-grade the quality of studies in the 'Footnotes' section of the 'Summary of findings' table, and we will make comments to aid reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity
We plan to carry out the following subgroup analyses.
- Type of PH:
  - we will analyse data separately for patients with PAH only (Group 1).
- Severity of PH:
  - we will compare the outcomes of less severe disease classification (NYHA Class I/II) with those with more severe disease classification (NYHA Class III/IV).

We will use the following outcomes in subgroup analyses:
- exercise capacity;
- serious adverse events;
- health-related quality of life.

We will use the formal test for subgroup interactions in Review Manager 2014.

Sensitivity analysis
We will perform sensitivity analyses to examine the effects of methodological quality on the pooled estimate by removing studies that are at high or unclear risk of bias for the domains of blinding and incomplete outcome data.

ACKNOWLEDGEMENTS
Rebecca Normansell was the Editor for this review and commented critically on the review.

REFERENCES

Additional references

Benza 2010

Cassery 2009

Coggan 1992

D’Alonzo 1991

de Man 2009

Ennion 1995

Fowler 2012

Frost 2013

Galie 2009

Galie 2013

Gollnick 1973
Exercise-based rehabilitation programmes for pulmonary hypertension (Protocol)

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GRADEpro 2008
Jan Brozek, Andrew Oxman, Holger Schünemann.

Higgins 2011

Hoeper 2013

Mainguy 2010a

Mainguy 2010b

McGoon 2013

NYHA 1994

Ogawa 1992

Pluim 2000

Provencher 2006

Provencher 2008

Review Manager 2014

Riley 2000

Simonneau 2013

Spruit 2013

Strange 2012

Tuder 2013

Vogiatzis 2013

Whittom 1998

* Indicates the major publication for the study
APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Hypertension, Pulmonary/
2. Pulmonary Heart Disease/
3. (pulmonary adj3 hypertens$).ti,ab.
4. pulmonary vascular disease.ti,ab.
5. or/1-4
6. exp Exercise/
7. exp Exercise Therapy/
8. Exercise Tolerance/
9. Physical Fitness/
10. Physical Exertion/
11. exp Ergometry/
12. Bicycling/
13. Weight Lifting/
14. Muscle Strength/
15. exercis$.ti,ab.
16. (conditioning or ergometry or treadmill or endurance or “upper limb” or “lower limb”).ti,ab.
17. (walk$ or swim$ or cycle$ or cycling or bicycl$ or jog$).ti,ab.
18. ((strength$ or resistance$ or weight$) adj3 train$).ti,ab.
19. aerobic$.ti,ab.
20. rehabilitat$.ti,ab.
21. or/6-20
22. 5 and 21
23. (controlled clinical trial or randomized controlled trial).pt.
24. (randomized or randomised).ab,ti.
25. placebo.ab,ti.
26. randomly.ab,ti.
27. trial.ab,ti.
28. groups.ab,ti.
29. or/23-28
30. Animals/
31. Humans/
32. 30 not (30 and 31)
33. 29 not 32
34. 22 and 33

CONTRIBUTIONS OF AUTHORS

NM drafted the protocol with the assistance from AH and FK.
DECLARATIONS OF INTEREST

The authors reported no conflict of interest with regard to the content of this review.

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- Queensland Health, Australia.
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External sources
- No sources of support supplied