

# BMJ Open Physiological responses to arm versus leg activity in patients with chronic obstructive pulmonary disease: a systematic review protocol

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## ABSTRACT

**Introduction** Compared with healthy older adults, people with chronic obstructive pulmonary disease (COPD) have reduced capacity and increased symptoms during leg and arm activities. While the mechanisms underlying limitations and symptoms during leg activities have been investigated in detail, limitations and symptoms during arm activities are not well understood, and the potential differences between physiological responses of leg and arm activities have not been systematically synthesised. Determining physiological responses and symptoms of arm activities compared with physiological responses and symptoms of leg activities will help us understand the mechanisms behind the difficulties that people with COPD experience when performing physical activities, and determine how exercise training should be prescribed.

Thus, the aim of this systematic review is to compare the physiological responses and symptoms during activities involving the arms relative to activities involving the legs in people diagnosed with COPD.

**Methods and analyses** This protocol is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols. Potentially relevant studies will be identified from CINAHL, EMBASE, PEDro, Cochrane Central Register of Controlled Trials and PubMed databases. The Population, Exposure, Comparator, Outcomes, and Study characteristics framework will be used to systematise the process of selecting and extracting data from relevant studies. Assessment of the methodological quality of the studies will be done by using the 14 most relevant components from the checklist by Downs and Black. The result will be presented with a narrative synthesis, and if appropriate with meta-analyses.

**Ethics and dissemination** Ethical approval is not required as this study is a systematic review. It is our intention to submit the results of our review for peer-reviewed publication.

**PROSPERO registration number** CRD42017074476.

## BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a disease characterised by persistent respiratory symptoms and airflow limitation.<sup>1</sup> In addition to this central limitation, a common peripheral consequence of

## Strengths and limitations of this study

- This protocol is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols, and the systematic review will be reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.
- This protocol includes a wide search strategy and inclusion criteria which will result in a comprehensive narrative synthesis of the current evidence.
- The exclusion of papers written in languages not known by the research group might leave relevant studies out of the review.

COPD is limb muscle dysfunction.<sup>2</sup> Compared with healthy individuals, people with COPD have intrinsic muscle structural changes that include mitochondrial dysfunction,<sup>3</sup> a shift from muscle fibre type I towards fibre IIx,<sup>4</sup> as well as poor oxidative capacity.<sup>5</sup> Furthermore, during activities involving the legs, people with COPD present reduced aerobic capacity,<sup>6</sup> reduced mechanical efficiency (ME; work per unit oxygen consumed),<sup>7</sup> a greater amount of fatigue for the same absolute oxygen consumption ( $VO_2$ )<sup>8</sup> and changes in quadriceps metabolism at a lower work load.<sup>9</sup>

Arm activities are also poorly tolerated by many individuals with COPD, particularly when the arms are unsupported and raised above shoulder height.<sup>10</sup> Compared with healthy individuals, people with COPD have demonstrated increased hyperinflation and increased perceived dyspnoea, despite lower cardiorespiratory responses during peak arm exercises.<sup>11</sup> These differences can, at least partially, be explained by the fact that arm elevation increases the functional residual capacity and the elastic load of the inspiratory muscles, while reducing their force-generating capacity.<sup>12</sup> Moreover, during unsupported arm activities, the accessory

muscles of respiration have been shown to be less available to assist with ventilation, as they are recruited for postural support.<sup>13</sup>

Determining physiological responses and symptoms of arm activities compared with physiological responses and symptoms of leg activities will help us understand the mechanisms behind the difficulties that people with COPD experience when performing physical activities, and determine how exercise training should be prescribed.

Previous research has demonstrated similar or higher ME during arm cycling compared with leg cycling in people with COPD.<sup>14 15</sup> These findings are in contrast to what was observed in healthy controls where ME during arm cycling was lower than the ME observed in leg cycling.<sup>14 15</sup> In addition, another study showed that at a given  $\text{VO}_2$ , dyspnoea response is comparable during arm and leg cycling in individuals with COPD.<sup>16</sup> These findings show that arm cycling may be as demanding as leg cycling in individuals with COPD and could be as effective as leg cycling to maximise the physiological benefits of endurance exercise.<sup>17</sup> However, a different study showed that at a given  $\text{VO}_2$ , dyspnoea and hyperinflation are greater during arm exercises than during leg exercises in individuals with COPD.<sup>18</sup>

These seemingly contradictory messages highlight the need for a systematic comparison of studies that have evaluated physiological responses and symptoms during arm and leg activities in individuals with COPD to provide a comprehensive synthesis of the current evidence.

## Objectives

The primary objective of the systematic review is to compare the physiological responses during activities involving the arms relative to activities involving the legs in people diagnosed with COPD.

The secondary objective of the systematic review is to compare the exertional symptoms during activities involving the arms relative to activities involving the legs in people diagnosed with COPD.

## METHODS

This systematic review protocol is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols.<sup>19</sup> The systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 4 September 2017 (registration number: CRD42017074476).

### Eligibility criteria for inclusion of studies

#### Study designs

We will include studies that present a cross-sectional comparison of physiological responses and/or symptoms of arm versus leg activities in individuals with COPD. We will consider all prospective and retrospective study designs, including but not limited to cross-sectional, cohort, case-control and experimental study designs. For

studies with multiple measurement points (eg, intervention studies), baseline data will be used.

#### Participants

We will consider any study including people with a diagnosis of COPD confirmed by spirometry following published guidelines (eg, European Respiratory Society,<sup>20 21</sup> the American Thoracic Society,<sup>21 22</sup> the British Thoracic Society<sup>23</sup> and the Global Initiative for Chronic Obstructive Lung Disease).<sup>1</sup> Studies that include a mixed population where people with COPD are not the primary diagnosis will be excluded if data cannot be attained separately for people with COPD.

#### Exposure

Exposure will include any type of upper limb/arm activity, either unsupported or supported including but not limited to aerobic and/or resistance training/activities targeting the upper limbs/arms. Activities involving the whole body or upper limbs/arms and lower limbs/legs simultaneous will be excluded.

#### Comparators

Comparators will include any type of lower limb/leg activity including but not limited to aerobic and/or resistance training/activities targeting the lower limbs/legs.

#### Outcomes of interest, including but not limited to

Cardiorespiratory and metabolic responses: heart rate (HR), peripheral capillary oxygen saturation ( $\text{SpO}_2\%$ ),  $\text{VO}_2$ , carbon dioxide production ( $\text{VCO}_2$ ) and concentration of blood lactate.

Lung volumes: tidal volume (Vt), minute ventilation (VE), breathing frequency (BF), VE and maximum voluntary ventilation (MVV) ratio, dynamic hyperinflation (DH), end-expiratory lung volume (EELV), end-inspiratory lung volume (EILV), and inspiratory capacity (IC).

Biomechanics: muscle activity, chest wall kinematics, ME, peak load and total workload.

Symptoms: subjective ratings of exertional symptoms (ie, dyspnoea and fatigue) measured with Borg's rating of perceived exertion, the revised category-ratio 0–10 scale (Borg CR10)<sup>24</sup> or another scale with similar properties.

#### Setting

No exclusions will be made due to settings.

#### Language

Only studies written in English, Swedish, Spanish or Portuguese will be considered for this systematic review.

#### Time span

There will be no restriction related to year of publication, all articles from inception to 1 October 2017 of selected databases will be considered.

#### Search methods

Potentially relevant studies will be identified from CINAHL (EBSCO interface, 1981 onwards), EMBASE (OVID interface, 1980 onwards), PEDro (Neuroscience

Research Australia 1929 onwards), PubMed (US National Library of Medicine, 1946 onwards) and Cochrane Central Register of Controlled Trials (Wiley, 2010 onwards).

A search for 'grey' literature will be performed through ClinicalTrials.gov, where observational studies and randomised controlled trials can be registered. In addition, before submitting this protocol for a systematic review, we searched the Cochrane Database of Systematic Reviews (CDSR) and PROSPERO to identify existing or ongoing reviews on the topic.

We will include relevant conference abstracts if all information can be retrieved; if information is missing we will contact the study leaders for additional information. If sufficient information is provided, conference abstracts will be included in the analyses; if not, they will be excluded. Also, the study leaders of identified unpublished and studies in progress will be contacted to establish whether published literature was missed.

### Search strategy

The search strategy will be developed with the assistance of a health science librarian and reviewed by experts in the fields of physiotherapy and lung diseases. To ensure literature saturation, comprehensive searches will be constructed of both index terming (MeSH terms), 'free text' terms and synonyms. A draft of the search strategy in PubMed can be found in online supplementary file 1. We will also hand-search the reference lists of included studies or relevant reviews identified through the search. Lastly, the 'related articles' function in PubMed will be used on included studies or relevant reviews.

### Study records

#### Data management

The results from the literature searches will be uploaded to Covidence, an internet-based software program that facilitates management of studies, including removal of duplicates and collaboration among reviewers during the study-selection process. The research team will develop and test screening questions and forms for phase 1 and 2 assessments based on the inclusion and exclusion criteria. The search process will be documented, including:

- the name of the database searched
- the name of the database provider/system used
- the date when the search was run
- the years covered by the search
- the search terms used, hits per search term and number of articles retrieved.

#### Selection process

The inclusion of articles will be performed in three steps. If necessary, we will seek additional information from study authors to resolve potential questions regarding eligibility or missing data. None of the review authors will be blind to the journal titles, the study authors or institutions. The selection process will be visualised by

a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart diagram.

At each phase, the articles will be classified into three groups.

Phase 1: screening of titles (one reviewer)

- Article appears to meet inclusion criteria, included to phase 2.
- Article clearly does not meet inclusion criteria, excluded.
- If unsure, article is included to phase 2.

Phase 2: examination of abstracts (two reviewers)

- Article appears to meet inclusion criteria, included to phase 3.
- Article clearly does not meet inclusion criteria, excluded.
- If unsure, article is included to phase 3.

Phase 3: individual examination of full text article (two reviewers)

- Yes: article meets all inclusion criteria according to both reviewers, included to systematic review.
- No: article clearly does not meet inclusion criteria according to both reviewers, excluded.
- Maybe: if unsure, or if only one reviewer has given the article a yes, decision will be reached through discussion between reviewers. If disagreement could not be resolved by consensus, a third reviewer will be consulted and a majority (2/1) rule will be used.

Agreement between assessors will be assessed mathematically using a Kappa statistic (K value). Special attention to identify possible duplicates will be taken to minimise risk for biased results.

#### Data extraction

A standardised data-extraction form will be used by two reviewers to extract data independently from full text copies of all included studies. The form will be pilot tested on two to three potentially eligible articles. Disagreement will be solved by consensus. When disagreement cannot be resolved by consensus, a third reviewer will be consulted, and a majority (2/1) rule will be used. All data will be double checked with the included studies by a third reviewer.

#### Study characteristics

Study: author(s) name, title, publication year, inclusion and exclusion criteria, setting and identification of measurements taken without prior intervention.

Participants: age, gender, diagnosis of COPD, forced expiratory volume in 1 s, body mass index, comorbidities, sample size and missing values.

Exposure (arm activity): type of activity, number of participants, intensity and duration.

Comparator (leg activity): type of activity, number of participants, intensity and duration.

#### Outcomes of interest, including but not limited to

Cardiorespiratory and metabolic responses: HR,  $\text{SpO}_2\%$ ,  $\text{VO}_2$ ,  $\text{VCO}_2$  and concentration of blood lactate.

Lung volumes Vt, VE, BF, VE/MVV ratio, DH EELV, EILV and IC.

Biomechanics muscle activity, chest wall kinematics, ME, peak load and total workload.

Symptoms: subjective ratings of exertional symptoms (ie, dyspnoea and fatigue) measured with Borg CR10<sup>24</sup> or another scale with similar properties.

### Study quality assessment

Assessment of the methodological quality of the studies will be done by using the 14 most relevant components from the checklist by Downs and Black.<sup>25</sup> The components are:

- ▶ Is the hypothesis/aim/objective of the study clearly described?
- ▶ Are the main outcomes to be measured clearly described in the introduction or methods section?
- ▶ Are the characteristics of the patients included in the study clearly described?
- ▶ Are the distributions of principal confounders in each group of subjects to be compared clearly described?
- ▶ Are the main findings of the study clearly described?
- ▶ Does the study provide estimates of the random variability in the data for the main outcomes?
- ▶ Have the characteristics of patients lost to follow-up been described?
- ▶ Have actual probability values been reported (eg, 0.035 rather than <0.05) for the main outcomes except where the probability value is <0.001?
- ▶ Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
- ▶ Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
- ▶ Were the statistical tests used to assess the main outcomes appropriate?
- ▶ Were the main outcome measures used accurate (valid and reliable)?
- ▶ Were losses of patients to follow-up taken into account?
- ▶ Did the study have sufficient power to detect a clinically important effect/difference where the probability value for a difference being due to chance is less than 5%?

The checklist by Downs and Black has been recommended for the assessment of methodological quality for randomised controlled trials and non-randomised trials, including cross-sectional studies.<sup>26</sup> The 14 components are appropriate for non-randomised trials and were used previously in a review that investigated differences in physiological responses during arm activities between healthy controls and people with COPD.<sup>11</sup>

A standardised data form for study quality will be used by two independent reviewers. The form will be pilot tested on two to three potentially eligible articles. Disagreement will be resolved by consensus. When disagreement cannot be resolved by consensus, a third reviewer will be consulted, and a majority (2/1) rule will be used. The

result from the quality analyses will be included in the synthesis, no study will be excluded due to poor quality.

If applicable, to determine whether selective outcome reporting was present within included studies, we will compare methods and outcomes reported in protocols and the published article. If no protocol is available, we will compare outcomes reported in the methods and result sections.

### Synthesis

We anticipate that there will be limited scope for meta-analysis because of the range of different outcomes measured across the small number of existing trials. However, where studies have used the same type of exposure and comparator, with the same outcome measure, we will pool the results using a random-effects meta-analysis, with standardised mean differences for continuous outcomes, and calculate 95% CI and two-sided P values for each outcome.

A systematic narrative synthesis will be presented in text and tables to summarise the characteristics of all included studies. The narrative synthesis will report the findings found both within and between the included studies, in line with guidance from the PRISMA statement.<sup>27</sup>

A suitable subgroup analysis will be used to determine the impact of the type of arm activity performed (eg, supported vs unsupported, resistance training vs aerobic arm cranking, etc) in the comparison of physiological responses and symptoms relative to the responses during leg activities

### DISCUSSION

The results of the systematic review will help us better understand the physiological responses during different arm and leg activities in individuals with COPD and the potential impact these responses have on their performance in everyday activities and on exercise training. This knowledge is useful when screening for exercise tolerance and prescribing training interventions in people with COPD with the intention to maximise gains and minimise symptom limitation.

To maintain high methodological quality, our systematic review will follow the PRISMA statement. The use of a wide search strategy and inclusion criteria will result in a thorough narrative synthesis of the current evidence regarding physiological responses and symptoms during arm and leg activities for people with COPD.

A potential limitation of the systematic review is the exclusion of papers written in languages not known by the research group which may leave relevant studies out of the review.

### ETHICS AND DISSEMINATION

Ethical approval is not required as this study is a systematic review. It is our intention to submit the results of our review for peer-reviewed publication and to present our findings at national and international meetings and conferences.

## Amendments

In case of amendments, we will provide the date of each amendment and a description of the change and its rationale in this section. No changes will be incorporated in the protocol. AN and TJ-F will be responsible for approving, documenting and implementing the amendments.

**Contributors** AN and TJ-F are the guarantors for the protocol and contributed equally to the development of the protocol. EF and AN drafted the protocol. EF, VPL, TJ-F and AN contributed to the development of the eligibility criteria, the risk of bias assessment strategy, search strategy and data-extraction criteria. EF, VPL, TJ-F and AN read, provided feedback and approved the final protocol.

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**Competing interests** None declared.

**Patient consent** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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