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This is the accepted version of a paper published in *Physical Therapy Reviews*. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the original published paper (version of record):

Nyberg, A., Lindström, B., Wadell, K. (2013)

Evidence for single-limb exercises on exercise capacity, quality of life, and dyspnea in patients with chronic obstructive pulmonary disease or chronic heart failure.

Physical Therapy Reviews, 18(3): 157-172

<http://dx.doi.org/10.1179/1743288X13Y.0000000072>

Access to the published version may require subscription.

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RESEARCH PAPER

Evidence for single-limb exercises on exercise capacity, quality of life, and dyspnea in patients with chronic obstructive pulmonary disease or chronic heart failure

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KEYWORDS

Chronic heart failure, Chronic obstructive pulmonary disease, Evidence, GRADE, Single limb exercises

Abstract

Background: Although single limb exercise (SLE) has been used for patients with chronic obstructive pulmonary disease (COPD) and for patients with chronic heart failure (CHF), the evidence for SLE has not been evaluated systematically and remains unclear.

Objectives: Determine the evidence for the effect of SLE compared to any comparator on outcome measurements for exercise capacity, quality of life (QoL) or dyspnea in patients with COPD or CHF.

Methods: PubMed, PEDro and CENTRAL databases were searched from inception until May 31, 2011. Searches started April 1, 2011. English language randomized controlled trials (RCTs) were included. Extraction of data was performed by two review authors. Data and evidence for SLE were summarized in accordance with Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines. Authors of included studies were contacted for missing data.

Results: Six RCTs (two COPD and four CHF) were included. Low to very low quality evidence indicates that SLE significantly improved exercise capacity, but not dyspnea, in patients with COPD, and significantly improved exercise capacity outcomes compared to a control in patients with CHF. However, when SLE was compared to non-SLE regimes in patients with CHF, positive effects were found irrespective of training regime regarding exercise capacity and QoL.

Conclusions: SLE appears to be effective in both conditions especially regarding exercise capacity, and might be included in exercise programs in patients with COPD or CHF. However, the evidence is low to very low according to GRADE and more clinical studies of high quality are required.

Keywords: Chronic heart failure, chronic obstructive pulmonary disease, evidence, GRADE, single limb exercises

Introduction

Exercise intolerance with increased dyspnea and leg fatigue are key disabling factors in chronic obstructive pulmonary disease (COPD).¹ Increased dyspnea during physical activity is also associated with a lower quality of life (QoL).² Another common disease with similar symptoms is chronic heart failure (CHF). Patients with CHF primarily suffer from a circulatory limitation, while patients with COPD are mostly ventilatory limited.²⁻⁴ However, coexisting COPD and CHF is common as approximately 20-30% of patients with COPD have CHF.⁵ The reduced exercise capacity in patients with COPD as well as those with CHF can to some extent be explained by muscle atrophy and weakness, which are determinants seen in both disorders.⁶ In these patients, exercise intolerance has a great impact on QoL.⁷

Exercise training was found to be effective in both patients with COPD and patients with CHF, and is thus recommended to be included in the treatment according to treatment guidelines.^{2,8,9}

Training intensity is an important determinant of the physiological response to exercise training, and there is moderate scientific evidence that indicates that training at a higher exercise intensity produces greater physiological benefits compared to lower intensity exercises in patients with COPD.¹⁰ The primary methods of exercise training within pulmonary rehabilitation have traditionally been different types of exercises incorporating a large amount of muscle mass, such as walking and cycling exercise regimens. However, the chronic airflow limitation in patients with COPD leads to dynamic hyperinflation and increased dyspnea during these whole body/large muscle mass exercises. This causes many patients with COPD to stop exercising before their cardiovascular system or skeletal muscles are maximally stressed.¹¹ In turn, the result is that many patients with COPD are restricted to low-intensity exercises¹² and thereby obtain less physiological effects compared to if a

higher intensity was reached.¹⁰ Training using a reduced muscle mass is a way of dealing with this issue. This was found to give a higher metabolic rate in the exercising muscle due to less stress placed on the respiratory system compared to whole body exercises.¹³ A reduced ventilatory demand during exercise might allow for a higher amount of maximal work and more intense exercise training, leading to greater training effects compared to traditional bilateral exercises.^{11,13}

Studies have demonstrated a higher amount of maximal work (per unit of muscle mass) using a reduced simultaneous muscle mass by the use of single limb exercises (SLE) (i.e. training using one leg/arm at a time) in patients with COPD. The results were explained by decreased stress on the respiratory system as ventilation is reduced in comparison to whole body exercises.^{3,13} Similar to patients with COPD, patients with CHF have demonstrated positive effects of SLE.¹⁴ The positive effects of SLE in patients with CHF have been explained by a maintained peripheral blood flow and muscle perfusion compared to exercise involving a major muscle mass.¹⁵

If the stress on the respiratory and circulatory systems could decrease by the use of SLE regimes, the local work load in the peripheral muscles during training would increase which may lead to better muscle specific training responses compared to training regimes incorporating a larger amount of muscle mass.^{13,14}

There is an increasing demand in healthcare that the interventions applied should be supported by scientific evidence.¹⁶ Although SLE regimes have been used as exercise training in both patients with COPD and patients with CHF, the evidence to support the use of these interventions has not been evaluated systematically, and thus remains unclear.

The result of this systematic review will determine the current evidence for SLE regimes and present implications for practice and future research.

Purpose

To determine the evidence for SLE regimes, we systematically reviewed randomized controlled trials that assessed the efficacy of these interventions, compared to any comparator, on any relevant outcome measurement for exercise capacity, QoL and dyspnea in patients with COPD or CHF.

Methods

Protocol and registration

On March 1, 2011 searches were performed in the Database of Abstract of Reviews of Effects and the Cochrane Database of Systematic Reviews to check whether there were already existing or ongoing reviews. A review protocol was created in accordance with the Centre for Reviews and Dissemination guidelines¹⁷ as recommended in the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.¹⁸ Registration: PROSPERO 2011:CRD42011001050. Updates to the trial protocol are presented in Appendix 1. Online publication of the review protocol is available at: http://www.crd.york.ac.uk/PROSPEROFILES/1050_PROTOCOL.pdf.

Eligibility criteria

Participants

Studies were included if they were studies of adult participants with a clinical diagnosis of stable COPD according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria² or studies of participants with CHF according to NYHA (New York Heart Association).¹⁹ Studies that included a mixed population where COPD and/or CHF were not the primary diagnosis (at least 90% of study population within inclusion criteria) were excluded.

Interventions

Studies examining SLE, supervised or unsupervised in both in- and out-patient populations were included. SLE was defined as any exercise intervention using one arm or one leg at a time (50% or more of the training had to consist of SLE). Studies not fulfilling these criteria were excluded.

Comparators

Studies comparing the SLE regimes with any intervention, no intervention or placebo interventions were included. No exclusions were made with regard to comparator used.

Outcome measures

Pre-decided outcomes were used in this systematic review. A ranking of the importance of these outcomes has been constructed in collaboration with experts in COPD and CHF rehabilitation. The ranking is based on the importance for patients in accordance with GRADE²⁰ for both patients with COPD and patients with CHF (Figure 1).

Figure 1 about here

Primary outcomes

Exercise capacity

- (1) Cycle ergometer: Maximal oxygen consumption (VO_{2max}), submaximal oxygen consumption (submax VO_2), maximal minute ventilation (V_{Emax}), submaximal minute ventilation (submax V_E), peak Watts (W).
- (2) Meters walked: 6-minute walk test (6MWT), 12-minute walk test (12MWT), incremental shuttle walk test (ISWT), endurance shuttle walk test (ESWT).
- (3) Muscle function, maximal and/or endurance, measured by functional or laboratory tests.

Quality of life (QoL) (disease specific QoL questionnaires)

- (1) St. George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRQ), Medical Outcomes Study Short Form-36 (SF-36), or Clinical COPD Questionnaire (CCQ) for COPD.

- (2) Sickness of impact profile (SIP), Sense of coherence (SOC) scale or Minnesota Living with heart failure questionnaire (LiHfe) for CHF.

Secondary outcomes

Dyspnea

- (1) Measured by Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI), Medical Research Council (MRC) Scale or Borg-scale (CR-10).

Studies with outcome measurements not relevant for exercise capacity and/or QoL were excluded. Dyspnea was, despite importance, defined as a secondary outcome because of the likely lack of reporting in studies.

Studies

Only peer reviewed English language randomized controlled trials (RCTs) have been included in this systematic review. Unpublished studies, ongoing studies, studies with only abstract available, or studies with no statistical comparison between groups were excluded. No restrictions regarding publication date were imposed.

Information sources

Electronic searches

The Cochrane Central Register of Controlled Trials (CENTRAL), the Physiotherapy Evidence Database (PEDro), and PubMed were searched for relevant studies. Searches started on April 1, 2011 and all databases were searched from inception to May 31, 2011. In CENTRAL the Cochrane Airways Group and the Cochrane Heart Group specialized register of trials were searched. To ensure that as many relevant papers as possible were retrieved, a

comprehensive search strategy was constructed and both index terming (mesh terms) and “free text” terms and synonyms were used. The search strategy was designed in accordance with the PubMed database and altered for use in other databases. The full search strategy used in PubMed, including hits, is shown in Appendix 2. EndNote was used to manage references of included trials. The search process and the results have been consistently documented. Development, conduction and documentation of search and search strategy were performed by one of the review authors with the assistance of the search coordinators of the Cochrane Airways and Heart groups.

Searching other resources

The related articles function in PubMed was used on included studies from the electronic searches. Reference lists of these included studies and other potentially relevant primary studies, as well as review articles, were searched for further RCTs. In addition, authors of included studies from all searches were contacted about their related studies or knowledge of additional studies.

Data collection and analysis

Selection of studies

Inclusion and exclusion of studies were carried out in three steps using a standardized sheet based on eligibility criteria. These steps were: 1) all titles were read and examined by one author and irrelevant studies were excluded; 2) the abstracts were independently read and examined by two reviewers and irrelevant studies were excluded; 3) entire articles were independently read and studies not meeting inclusion criteria were excluded. Data extraction was performed individually. If unsure, or if only one of the reviewers had approved the study, a decision was reached through discussion between the reviewers. If agreement could not be

reached, a third independent reviewer was involved and a majority decision was taken. Agreement between review authors on study inclusion was measured using Kappa statistics.

Data extraction

Data extraction was individually performed by two review authors with a standardized and pilot tested (on two potentially relevant randomly selected studies during preliminary searches) data extraction form as recommended.²¹ All authors of included studies were contacted to obtain sufficient data for analysis of evidence grade, including test of heterogeneity, according to GRADE (Grading of Recommendations Assessment, Development and Evaluation).²²⁻²⁶

Data items

Pre-specified information regarding PICOS (Participants, Intervention, Comparator(s), Outcome(s), and Study) was extracted – further specifications are presented in Table 1. In addition, recommended items to identify possible duplicate publications to minimize risk for biased results were extracted, if available.²¹

Assessment of risk of bias in individual studies

The methodological study quality of included RCTs was then measured by the PEDro scale²⁷ and the Cochrane risk of bias tool²¹ in an unblinded manner at both study and outcome level. Both scales were used to give a broader judgment of study quality. We graded the risk of bias in each domain as low (-), high (+) or unclear (?). On the PEDro scale, the 10 internal validity items were rated ‘1/0 (Yes/ No)’ giving a sum score of 0–10. First the articles were rated independently and consensus was reached after discussion.

Quality of evidence

The results of included RCTs were then compiled and evidence graded by two review authors using the GRADE-system.²²⁻²⁶ Evidence based on RCTs starts as high, although the evidence may be decreased for one or more of the following reasons: study limitations, inconsistency of results, indirectness of evidence, or imprecision or reporting bias.^{22,24} The Domains of GRADE were rated NA, 0, ?, -1 or -2; a further description is found in Appendix 3. Meta-analyses were not performed because heterogeneous interventions and outcome measurements were used. Results are presented for COPD and CHF separately. The primary outcome measures were difference in effect on pre-specified exercise capacity outcomes and disease specific QoL questionnaires. Assessments of heterogeneity were performed in accordance to GRADE guidelines, if sufficient information was available. No additional analyses were performed.

Results

The high-sensitivity search strategy used in this review resulted in a total of 5257 potentially relevant studies. Nine articles met inclusion criteria.^{14,28-35} However, of these nine studies, three groups were identified as duplicate studies (Gordon 1996²⁸ & Tyni-Lenné 1996³¹, Gordon 1999¹⁴ & Tyni-Lenné 1999³⁰ and Bjørgen 2009³⁴ & Bjørgen 2009³⁵). In these instances, according to PICOS characteristics, the study with the largest amount of information was included and any additional outcomes data reported in the other studies were incorporated into the review. There were a total of six unique studies that met all eligibility criteria, and were thus included in this systematic review. A flowchart of the search strategies used is presented in Figure 2. The agreement between review authors on study inclusion was $\kappa=0.94$.

Figure 2 about here

Description of studies

Characteristics of the included studies are described below and presented separately in Table 1. The reasons for exclusion of trials are presented in Appendix 4.

Included studies

Methods/study: The six included studies were all English language RCT publications.²⁹⁻³⁴ Two studies involved patients with COPD^{33,34}, and four studies involved patients with CHF.²⁹⁻³²

Participants: The included studies consisted of 130 adult participants, 41 (15 male) patients with COPD^{33,34} and 89 (63 male) patients with CHF.²⁹⁻³² In the COPD trials, disease severity was at least moderate (stage II) COPD (GOLD criteria)², and in the CHF trials, disease severity was between stage I-III (NYHA criteria).¹⁹

Interventions: Different SLE regimes were used in the six included studies. One-legged cycling on a cycle ergometer (OneLegCycl) ^{33,34} was used in the COPD studies. Single limb strength training using weights (SingLimbSW) ³² or elastic resistance (SingLimbSE) ²⁹ and one-legged knee-extensor training on a modified cycle ergometer (OneLegKneeExt) ^{30,31} were used in CHF studies. The frequency was three times a week for 7-8 weeks in COPD trials ^{33,34}, and three times a week for 8-12 weeks in CHF trials ²⁹⁻³². Percentage of peak heart rate ³⁴ and percentage of peak power ³³ were used to determine the intensity in the COPD trials. Percentage of peak workload ³⁰⁻³² and perceived exertion (according to Borg RPE scale ²⁹) were used in the CHF trials. The duration of the exercises varied: COPD OneLegCycl (16-30 min work) ^{33,34}, CHF SingLimbSW/E (20-60 min) and OneLegKneeExt (39-45 min). ^{30,31}

Comparator: The COPD SLE regime was compared to two-legged cycling. ^{33,34} The CHF SLE regimes were compared to no intervention ^{29,31}, two legged knee-extensor training on a modified cycle ergometer ³¹, and two-legged cycle ergometer training. ^{30,32}

Outcomes: All pre-decided outcomes (Figure 1) except local muscle endurance and sub maximal minute V_E were incorporated in at least one trial. The primary outcome exercise capacity was evaluated in all six trials ²⁹⁻³⁴ and QoL was evaluated in three CHF trials. ²⁹⁻³¹ The secondary outcome, dyspnea, was evaluated in one COPD study. ³³ All outcome assessments were evaluated pre- and directly post-intervention with no additional follow-up.

Excluded studies

The majority of studies were excluded during the screening of titles. The major reasons for exclusion during screening of abstracts and full-text studies were that the studies did not fulfill the intervention inclusion criteria (n=30) or that they were not RCTs (n=14).

Table 1 about here

Risk of bias in included studies

The risk of bias and the study quality were measured by the Cochrane risk of bias tool ²¹ and the PEDro scale. ²⁷ An overview of judgments is provided in Figure 3, and a detailed description is given in Appendix 5.

Figure 3 about here

Syntheses of results

Due to heterogeneous interventions and outcome measures used in the six included studies in this systematic review a narrative description of results was selected. The absolute difference between groups is presented in the text to aid in determining the relevance of the magnitude of effect. Quality assessment, summary of findings and evidence grade for each outcome based on GRADE are presented in Table 2.

Exercise capacity

One-legged cycling (OneLegCycl)

Maximal exercise capacity during an incremental cycle ergometer test was measured in both COPD trials. ^{33,34} An absolute difference of 12.3 W, 0.152 L/min (peak VO₂) and 3.1L/min (peak V_E) (p<0.05) were found in favor of OneLegCycl. In addition, peak VO₂ (mL/kg⁻¹/min⁻¹) and submaximal VO₂ (mL/kg^{-0.67}/min⁻¹) were measured in the trial by Bjørgen et al. ³⁴ with significantly better results (1.3 mL/kg⁻¹/min⁻¹ and 5.3 mL/kg^{-0.67}/min⁻¹(p<0.05)) in favor of the OneLegCycl group.

Single limb strength training (SingLimbSW and SingLimbSE)

The effects of single limb strength training on exercise capacity were evaluated in two studies. ^{29,32} In the study by Bouchla et al. ³² the SingLimbSW regime was combined with

two-legged cycling compared to two-legged cycling alone. A maximal strength (2RM) difference of 10 kg ($p < 0.05$) was in favor of SingLimbSW. In comparison to a control group, the SingLimbSE group improved peak Watts with 16W ($p < 0.02$), peak VO_2 with $2.7 \text{ mL/kg}^{-1}/\text{min}^{-1}$ ($p < 0.05$) and walked 55 m further on the 6 min walk test (6MWT) ($p < 0.02$).²⁹

One-legged knee extensor training (OneLegKneeExt)

OneLegKneeExt was compared to cycle ergometer training, two-legged knee extensor training and to a control group.^{30,31} Significantly better results for OneLegKneeExt were found regarding peak Watts (15 W), peak VO_2 ($2.5 \text{ mL/kg}^{-1}/\text{min}^{-1}$) ($p < 0.05$), and peak VO_2 (0.24 L/min^{-1}) ($p < 0.04$) in comparison with cycle ergometer during a cycle ergometer test. The absolute difference in meters walked on 6MWT was 35 m ($p < 0.01$) in favor of two-legged knee extension compared to OneLegKneeExt. Compared to a control group the absolute difference on meters walked on 6MWT was 28 m, significantly ($p < 0.01$) better for OneLegKneeExt.³¹

Quality of life

Single limb strength training

The absolute difference between groups in the CHF study by Tyni-Lenné et al.²⁹ on QoL measured with the LiHfe could not be presented due to insufficient information. However, the result was significantly better in favor of SingLimbSE compared to a control group ($p < 0.001$).

One-legged knee extensor training (OneLegKneeExt)

Effects on QoL after OneLegKneeExt were compared to cycle ergometer training, two-legged knee extensor training and a control group with contradictory results.^{30,31} Significant results were only found in favor of OneLegKneeExt in comparison with a control group on sickness

impact profile (SIP) overall (-4) and subscales physical (-5), psychosocial (-4) and sleep & rest (-2) ($p < 0.05$). Compared to two-legged knee extensor training the absolute difference was (-6) on SIP subscales sleep & rest, and (-10) ($p < 0.05$) on home management in favor of the two-legged knee extensor group.³¹ A lower score on SIP indicates higher QoL.

Dyspnea

One-legged cycling (OneLegCycl)

No significant difference was found on dyspnea when comparing one-legged to two-legged cycling.³³

Risk of bias across studies

No test of the risk of bias across studies was performed due to lack of sufficient information. All authors were contacted, but only one³² provided sufficient information. All outcomes in the CHF trials were measured in one study only, making heterogeneity analyses not applicable. No additional analyses were performed.

Table 2 about here

Discussion

The aim of the systematic review was to determine the current evidence for SLE regimes in patients with COPD and in patients with CHF. Six unique RCTs were identified, and the current strength of the overall evidence ranges from low to very low, to support the use of SLE regimes compared to non-SLE regimes or control groups receiving no intervention. The low methodological quality of included studies is the major reason for the current evidence for SLE regimes in patients with COPD or CHF.

In patients with COPD, low to very low quality scientific evidence supports the use of OneLegCycl compared to two-legged cycling regarding exercise capacity outcome measures and low quality scientific evidence indicates no difference on dyspnea. These results are applicable in patients with COPD (\geq stage II), training in hospital settings. QoL was not reported in any COPD study.

In patients with CHF, low quality scientific evidence indicates improved muscle strength using SingLimbSW combined with two-legged cycling compared to using two-legged cycling alone. SingLimbSE improved exercise capacity compared to a control receiving no intervention. Furthermore low quality scientific evidence also indicates that OneLegKneeExt is more effective than both two-legged cycle ergometer training and control groups on a majority of exercise capacity outcomes. However, two-legged knee extensor training is more effective for improving meters walked and some portions of QoL. SingLimbSE and OneLegKneeExt are significantly better for improving QoL compared to control groups, but no significant differences were found compared to two-legged cycle ergometer training. These results are applicable in patients with CHF (stage I - III). Dyspnea was not reported in any CHF trial.

As stated in GRADE²²⁻²⁶, the low evidence rating indicates that further research is very likely to have an important impact in our confidence in the estimate of effect and is likely to change the estimate. The very low evidence rating indicates that any estimate of effect is very uncertain. In Sweden, the Swedish Council on Technology Assessment in Health Care (SBU)¹⁶ states that a low GRADE rating²²⁻²⁶ may be sufficient for implementing an exercise regimen in the clinical setting if other demands are met such as reasonable cost effectiveness. SBU is an independent public authority, consisting of a network of specialists, established by the Swedish government to critically appraise established and new medical methods used in prevention, diagnosis, and treatment of health problems.¹⁶

Exercise capacity

In both patients with COPD and patients with CHF, SLE regimes demonstrated superior results on exercise capacity outcomes compared to control groups receiving no intervention and two-legged cycle ergometer training. In patients with COPD, this might be explained by the results in the study by Richardson et al. who found increased blood flow and reduced ventilation by using a reduced simultaneous muscle mass.³ For patients with CHF, maintained peripheral blood flow and muscle perfusion have been demonstrated when involving only one limb at a time, (i.e. a reduced simultaneous muscle mass is involved), but was not seen when involving a major muscle mass.³⁰ This might be one reason for the positive results of SLE compared to two-legged cycling in patients with CHF. In patients with CHF, two-legged knee extensor training showed better results on meters walked during 6MWT compared to the SLE regime OneLegKneeExt.³¹

Quality of life

SLE is more effective than a control receiving no intervention (passive comparator) regarding improvements in QoL in patients with CHF. However, if an SLE regime is compared to active comparators, e.g. cycle ergometer training and two-legged knee extension, the between group differences no longer appear. As one of the included studies declared, it could be argued that the positive effects seen on QoL after SLE compared with control groups is not the result of physical training, but of other placebo effects such as the training situation, attention, supervision and peer support.³¹

Dyspnea

Dyspnea is considered one of the most important symptoms in patients with COPD and often the major reason for exercise intolerance.³⁶ Dyspnea is also associated with a lower QoL². Dyspnea was only evaluated in one COPD study and no differences between groups were found.³³ None of the included CHF trials²⁹⁻³² reported any outcome measure for dyspnea.

Quality of studies

The major limitations of the included studies are the low methodological quality (average PEDro score: 4.83 (0.41) out of 10) and the small sample sizes. Lack of reporting in trials resulted in an overall unclear risk of bias; as many as 33 out of 42 components were rated as unclear according to Cochrane risk of bias tool.²¹ One way to enhance the reporting in trials is to follow current guidelines such as the CONSORT (Consolidate Standards of Reporting Trials) statement³⁷ for RCTs. Furthermore, the low number of studies investigating each outcome in combination with insufficient information from authors of the included trials made heterogeneity analyses across studies impossible.

Methodological considerations

This review was constructed in accordance with PRISMA guidelines.¹⁸ The strength of this review is the high-sensitivity search strategy used to minimize the risk of missing potentially relevant studies and the randomized designs of included studies. However, the decision to only include RCTs in combination with the limitation to only include English language publications may have resulted in potentially relevant studies being omitted. The lack of homogeneity in the included studies on SLE strategies and outcome measures used prevented the pooling of data and the execution of meta-analyses.

Conclusions

Implications for practice

Incorporating SLE regimes in rehabilitation programs for patients with COPD and patients with CHF might be of benefit. The findings of this systematic review indicate that SLE regimes have positive effects on exercise capacity in patients with COPD and on exercise capacity and QoL in patients with CHF. The positive effects of SLE regimes in both conditions were seen on exercise capacity outcomes considered important or critical for decision making. The evidence at this time is presented in Table 3. However, the strength of these conclusions is considered low to very low in accordance with GRADE, and further research is very likely to have an important impact in our confidence in the estimate of effect. Nevertheless a low GRADE rating²²⁻²⁶ may be sufficient for implementing an exercise regimen in clinical settings if other demands are met.¹⁶

Table 3 about here

Implications for future research

There is a lack of well described high-quality studies especially comparing the effects of one SLE regime over another for both patients with COPD and patients with CHF. To increase the quality of RCTs the CONSORT guidelines³⁸ should be followed. Future studies should focus on involving both upper and lower extremity muscles since the positive physiological effects of exercise training only occur in the involved muscle(s). In this systematic review, only the studies by Tyni-Lenné²⁹ and Bouchla³² have incorporated both upper and lower extremity exercises. Furthermore, most outcomes used within included trials were considered important for decision making. Future studies should incorporate outcome measures on walking ability, local muscle endurance, dyspnea, and QoL, outcomes considered critical for decision making in assessment of SLE regimes for both patients with COPD and CHF.

Funding

The study was funded with grant support from The Swedish Research Council and the Medical Faculty Umeå University. The funders had no role in review design, conduction, data collection and analysis, decision to publish, preparation or reporting of the systematic review.

Disclosure statement

No conflict of interest exists

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Importance of outcomes		
Meters walked, QoL, Dyspnea	9	} Critical to decision making
Local muscle endurance	8	
	7	
Submax VO_2 , submax V_E^a , max muscle strength	6	} Important but not critical to decision making
	5	
VO_2^{\max} , $V_E^{\max^a}$, peak Watts	4	} Not important to decision making of lower importance
	3	
	2	
	1	
	1	

Figure 1. Hierarchy of outcomes according to their importance to assess the effect of single limb exercises in patients with COPD or CHF. ^a Only relevant for COPD patients; QoL, Quality of life; VO_2 , Oxygen consumption; V_E , Minute ventilation.

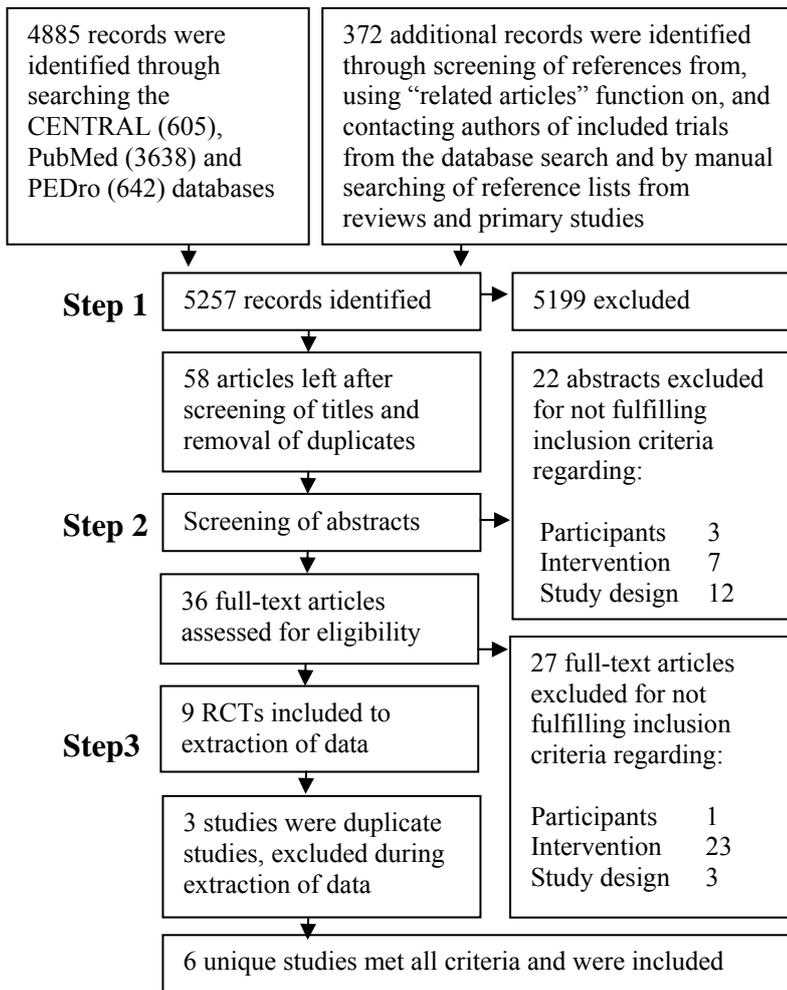


Figure 2 Flowchart of included studies

Table 1. Characteristics of included studies

Study	Participants	Intervention	Comparators	Outcomes	Study	Results
Bouchla 2011 ³²	<p>Total number: 20 participants, 10 in each group</p> <p>Age: 50.5 ± 11.4</p> <p>aerobic training group, 56.7 ± 7.2</p> <p>combined training group</p> <p>Gender: 16 male (9 in aerobic group, 7 in combined group)</p>	<p>G1: Strength: leg extension, leg curls, arm curls and lateral arm abduction. Each limb trained separately</p> <p>Two legged cycling: aerobic interval training (30 seconds exercise, 60 seconds rest) on electromagnetic cycle ergometer</p> <p>Frequency: 12 weeks, 3 times a week</p> <p>Intensity: Strength: Leg extension: 55% - 65% of 2 RM-test, leg curl at: 0.5-1kg from leg extension. Upper extremity: 10 RM. 3 sets of 10-12 repetitions.</p> <p>Two-legged cycling: 50 % of peak workload from “step ramp test”</p> <p>Duration: 20 minutes strength + 20 minutes two-legged cycling</p>	<p>G2: Two legged cycling in the form of aerobic interval training (30 seconds exercise, 60 seconds rest)</p> <p>Frequency: 12 weeks, 3 times a week</p> <p>Intensity: aerobic: 50 % of peak workload from “step ramp test”</p> <p>Duration: 40 minutes</p>	<p>Exercise capacity</p> <p>Peak Watts, peak VO2 (mL * kg-1 * min-1), during cycle ergometer test, sum of 2RM (kg) for quadriceps</p> <p>Quality of life: Not reported</p> <p>Dyspnea: Not reported</p>	<p>Setting: Not reported</p> <p>Date and duration (follow up): 2011, 12 weeks (no follow up)</p> <p>Study design: RCT</p> <p>Language: English</p>	<p>Better result for G1 on 2RM (kg) for quadriceps (P < 0.05). NS difference between groups on peak Watts and peak VO2 (mL * kg-1 * min-1) during cycle ergometer test.</p>
Tyni-Lenné 2001 ²⁹	<p>Total number: 24 participants, 16 in intervention group, 8 in control group</p> <p>Age: 62 ± 11 in control group, 63 ± 9 in intervention group</p> <p>Gender: 13 male (5 in control group, 8 in intervention group).</p>	<p>G1: One muscle group at a time was trained with rest during the other side training different arm, leg and trunk muscles using elastic resistance</p> <p>Frequency: 8 weeks, 3 times a week</p> <p>Intensity: 2*25 repetitions for each side of each limb at 70 b.p.m. Central exertion ≤ 13, and peripheral exertion from 13 to 16 on Borg RPE scale.</p> <p>Duration: 6 minute warm-up, 45 minutes work, 9 minutes cool-down</p>	<p>G2: Control group</p> <p>Frequency: Not applicable</p> <p>Intensity: Not applicable</p> <p>Duration: Not applicable</p>	<p>Exercise capacity</p> <p>Peak Watts, peak VO2 (mL * kg-1 * min-1) during cycle ergometer test, 6min walk test (m).</p> <p>Quality of life: Minnesota living with heart failure questionnaire (LiHfe)</p> <p>Dyspnea: Not reported</p>	<p>Setting: Not reported</p> <p>Date and duration (follow up): 2001, 8 weeks (No follow up)</p> <p>Study design: RCT</p> <p>Language: English</p>	<p>G1 had better results on 6min walk test (m) (P < 0.02), peak VO2 (mL/kg/min), peak Watts during cycle ergometer test (P < 0.05) and QoL (LiHfe score) (P < 0.001)</p>

Table 1. Characteristics of included studies

Study	Participants	Intervention	Comparators	Outcomes	Study	Results
Tyni-Lenné 1996 ³¹	Total number: 21 participants, 7 in each group Age: 57 ± 10 in two-leg training group, 60 ± 10 in one-leg training group and 63 ± 6 in control group Gender: 21 male	G1: One legged knee-extensor training on a modified cycle ergometer. Only active extension Frequency: 8 weeks, 3 times a week Intensity: 60 kicks per minute, 35% of two-leg peak work rate from knee-extensor ergometer test Duration: 6 minute warm-up, 30 minutes work (15min /leg), 3 minute cool down	G2: Two legged knee-extensor training on a modified cycle ergometer. Frequency: 8 weeks, 3 times a week Intensity: 60 kicks per minute, 70% of peak work rate from knee-extensor ergometer test Duration: 6 minute warm-up, 15 minutes work (both legs), 3 minute cool down G3: Control group, normal daily activities Frequency: Not reported Intensity: Not reported Duration: Not reported	Exercise capacity 6 minute walk test (m) Quality of life: SIP: subscales: Overall, Phy and Psy dim, S&R and HM. Dyspnea: Not reported	Setting: Not reported Date and duration (follow up): 1996, 8weeks (no follow up) Study design: RCT Language: English	Better result on distance walked for G2 compared to G1 and G3 (p=0.01). G1 better than G3 on distance walked (p=0.01), overall SIP, Phy Dim, Psy Dim, and S&R (p<0.05). NS on HM. G2 better results on all dimensions compared to G3 (p<0.01 – 0.05). NS between G1and G2 on overall SIP, Phy Dim, Psy Dim. G2 S better on S&R and HM (p<0.05).
Tyni-Lenné 1999 ³⁰	Total number: 24 participants, 8 in each group Age: 62 ± 11 in cycle group, 64 ± 12 in one-legged training group and 61 ± 7 in control group Gender: 13 male (5 in cycle group, 4 in knee extensor group, 4 in control group).	G1: One-legged knee-extensor training on a modified cycle ergometer. Only active extension Frequency: 8 weeks, 3 times a week Intensity: 60 kicks per minute, 50% of peak work rate from 1-leg knee-extensor ergometer test Duration: 6 minute warm up, 16-18 minutes per leg work and 3 minute cool-down	G2: Two-legged cycle ergometer training Frequency: 8 weeks, 3 times a week Intensity: 50% of peak work rate from cycle ergometer test Duration: 6 minute warm up, 20 minutes work and 3 minute cool-down G3: Control group Frequency: Not reported Intensity: Not reported Duration: Not reported	Exercise capacity Peak Watts and peak VO ₂ (mL * kg ⁻¹ * min ⁻¹ and L/min) during cycle ergometer test and knee extensor test. 6min walk test (m), self-paced and high speed. Quality of life: LiHfe (subscales: Total, Phys, Em) SIP: (subscales Amb, SI, S&R, HM),SOC Dyspnea: Not reported	Setting: Outpatient, Karolinska University Hospital in Huddinge , Sweden Date and duration (follow up): 1999, 8 weeks (No follow up) Study design: RCT Language: English	G1 had better results on peak Watts (p<0.05), peak VO ₂ (L/min ⁻¹) (p<0.04), and peak VO ₂ (mL/kg ⁻¹ /min ⁻¹) (p<0.05) during cycle ergometer. NS differences on meters walked, (self paced and high speed), peak watts, peak VO ₂ (L/min ⁻¹), peak VO ₂ (mL/kg ⁻¹ /min ⁻¹) during knee extensor and QoL (LiHfe score), SIP and SOC. All of the above results are in comparison to G2. No outcome data presented for G3

Table 1. Characteristics of included studies

Study	Participants	Intervention	Comparators	Outcomes	Study	Results
Bjørgen 2009 ³⁴	Total number: 23 participants, 12 in one-leg group, 11 in two-leg group. 19 completed, 4 dropped out from the two leg group Age: 61± 4 one-leg group, 62 ± 8 two-leg group Gender: 7 male (5 in one-leg group, 2 in two-leg group)	G1: One-legged cycling Frequency: 8 weeks, 3 times a week Intensity: 4*4 minute intervals. 85-95% of one leg peak heart rate, alternating between the two legs giving a total number of eight intervals Duration: 10 minute warm up, 16 minute work	G2: Two-legged cycling Frequency: 8 weeks, 3 times a week Intensity: 4*4 min intervals. 85-95% of two leg peak heart rate with a 3 minute active rest period at 60-70% of peak heart rate in between intervals Duration: 10 minute warm up, 16 minutes work 9 minutes rest in between intervals	Exercise capacity Peak Watts, peak VO ₂ (L/min), and Peak VE during two-legged cycle ergometer test. Quality of life: Not reported Dyspnea: Not reported	Setting: St Olav University Hospital in Trondheim, Norway Date and duration (follow up): 2009, 8weeks (No follow up) Study design: RCT Language: English	G1 had better results on peak watts, peak VO ₂ (L/min ⁻¹), peak VO ₂ (mL/kg ⁻¹ /min ⁻¹), and submax VO ₂ (mL/kg ⁻¹ /min ⁻¹) (p<0.05), during two-legged cycle ergometer. NS differences between groups on peak V _E (L/min) during two-legged cycle ergometer.
Dolmage 2008 ³³	Total number: 18 participants, 9 in each group Age: 62± 8 one-leg group, 63 ± 14 two-leg group Gender: 8 male (3 in one-leg group, 5 in two leg group)	G1: One-legged cycling Frequency: 7 weeks, 3 times a week Intensity: 50% of peak power attained on baseline incremental test Duration: 30 minutes	G2: Two-legged cycling Frequency: 7 weeks, 3 times a week Intensity: 70% of peak power attained on baseline incremental test. Duration: 30 minutes	Exercise capacity Peak Watts, peak VO ₂ (L/min), Peak V _E during two-legged cycle ergometer Quality of life: Not reported Dyspnea: Modified Borg scale	Setting: West Park Healthcare Center in Toronto, Canada Date and duration (follow up): 2008, 7 weeks (no follow up) Study design: RCT Language: English	G1 had better results on peak Watts, peak VO ₂ (L/min ⁻¹) and peak V _E (L/min) (p<0.05) during cycle ergometer test. NS differences on modified Borg scale between groups.

Abbreviations: Amb; Ambulation (SIP subscale), CHF; Chronic heart failure, Em; Emotional (LiHfe subscale), COPD; Chronic obstructive pulmonary disease, G; group, GOLD; Global initiative for chronic obstructive lung diseases, HM; Health Management (SIP subscale), LiHfe; Minnesota living with heart failure questionnaire, NS; Non significant, NYHA; New York heart association, PEDro; Physiotherapy evidence database, Phy Dim; Physical Dimension (SIP subscale), Phys; Physical (LiHfe subscale), Psy Dim; Psychosocial Dimension (SIP subscale), RM; Repetitions maximum, S; significant, SI; Social Interaction (SIP subscale), SIP; Sickness Impact profil, S&R; Sleep and rest (SIP subscale), SOC; Sense of coherence scale V_E; Minute ventilation, VO₂; Oxygen consumption

	Sequence generation	Allocation concealment	Blinding Patients, Personnel	Blinding Outcome assessors	Incomplete outcome data	Selective outcomes	Other concerns about bias:	PE德罗 score
Bjørgen 2009 ³⁴	?	?	-	?	-	?	?	4
Bouchla 2011 ³²	?	?	?	?	?	?	?	5
Dolmage 2008 ³³	+	?	?	-	?	?	?	5
Tyni-Lenné 1996 ³¹	?	?	?	?	-	?	?	5
Tyni-Lenné 1999 ³⁰	?	?	-	?	-	-	?	5
Tyni-Lenné 2001 ²⁹	?	?	?	?	?	-	?	5

Figure 3. Judgment of risk of bias. +: low risk of bias; -:high risk of bias; ?:unclear risk of bias

Table 2. Quality assessment, summary of findings and evidence grade for each outcome based on GRADE

Outcome, no of studies (ref)	Limitations	Quality assessment according to GRADE				Participants		Summary of findings		
		Consistency	Directness	Precision	Publication bias	G1	G2	Significance	Quality	Importance
Objective: Effects of OneLegCycl (G1) versus two-legged cycling (G2) in patients with COPD										
Exercise capacity		<u>Peak Watts, peak VO₂ (L/min⁻¹) during cycle ergometer</u>								
2 ^{33,34}	-1	0	0	0	?	21	16	S better result for G1 (P < 0.05) in both studies	++ ¹	Important
		<u>Peak VO₂ (mL/kg⁻¹/min⁻¹), submax VO₂ (mL/kg^{-0.67}/min⁻¹) during cycle ergometer</u>								
1 ³⁴	-1	NA	0	0	-1	12	7	S better result for G1 (P < 0.05)	++ ²	Important
		<u>Peak V_E (L/min) during cycle ergometer test</u>								
2 ^{33,34}	-1	?	0	-1	?	21	16	S better for G1 in one study ³³ (P<0.05), NS in other ³⁴	+ ³	Important
Quality of life		<u>Breathlessness using modified Borg scale</u>								
1 ³³	-1	NA	0	?	-1	9	9	NS difference between groups	++ ⁴	Critical
Objective: Effects of SinglimbSW + two-leg cycl (G1) vs to two-leg cycl alone (G2) in patients with CHF										
Exercise capacity		<u>Peak Watts, peak VO₂ (mL/kg⁻¹/min⁻¹), submaximal VO₂ (mL/kg^{-0.67}/min⁻¹) during cycle ergometer</u>								
1 ³²	-1	NA	0	?	-1	10	10	NS difference between groups	++ ⁵	Important
		<u>Maximal muscle strength (2RM)</u>								
1 ³²	-1	NA	0	0	-1	10	10	S better result for G1 (P<0.05)	++ ⁶	Important
Objective: Effects of SinglimbSE (G1) compared to control (G2) in patients with CHF										
Exercise capacity		<u>Peak Watts, peak VO₂ (mL/kg⁻¹/min⁻¹) during cycle ergometer and Meters walked</u>								
1 ²⁹	-1	NA	0	0	-1	16	8	S better result for G1 (P < 0.05)	++ ⁷	Imp-Critical
Quality of life		<u>LiHfe score</u>								
1 ²⁹	-1	NA	0	0	-1	16	8	S better result for G1 (P < 0.001)	++ ⁷	Critical

¹ Both trials had a lack of blinding and sparse data. Missing outcome data in one trial and only two small trials with few events.

² No blinding of participants and missing outcome data, one study only and sparse data.

³ Both trials had a lack of blinding and sparse data. Missing outcome data in one and only two small trials with few events. Contradictory results.

⁴ No blinding of outcome assessors, one study only and sparse data.

⁵ Unclear judgment of risk of bias in combination with low Pedro score, sparse data, one study only and few events.

⁶ Unclear judgment of risk of bias in combination with low Pedro score, one study only and few events.

⁷ Selective outcomes reported, unclear judgment of risk of bias in combination with low Pedro score, one study only, few events and sparse data.

Table 2. Quality assessment, summary of findings and evidence grade for each outcome based on GRADE, continued

Outcome, no of studies (ref)	Limitations	Quality assessment according to GRADE				Participants		Summary of findings		
		Consistency	Directness	Precision	Publication bias	G1	G2	Significance	Quality	Importance
Objective: Effects of OneLegKneeExt (G1) compared to a control (G2) in patients with CHF										
Exercise capacity	<u>Meters walked on 6minute walk test</u>									
1 ³¹	-1	NA	0	0	-1	7	7	S better result for G1(P < 0.01)	++ ⁸	Critical
Quality of life	<u>SIP overall, SIP physical, SIP psychosocial, SIP Sleep & rest</u>									
1 ³¹	-1	NA	0	0	-1	7	7	S better result for G1(P < 0.05)	++ ⁸	Critical
	<u>SIP Home Management</u>									
1 ³¹	-1	NA	0	0	-1	7	7	NS difference between groups	++ ⁸	Critical
Objective: Effects of OneLegKneeExt (G1) compared to Two-legged knee extension (G2) in patients with CHF										
Exercise capacity	<u>Meters walked on 6minute walk test</u>									
1 ³¹	-1	NA	0	0	-1	7	7	S better result for G2 (P < 0.01)	++ ⁹	Critical
Quality of life	<u>SIP sleep and rest, SIP home management</u>									
1 ³¹	-1	NA	0	?	-1	7	7	S better result for G2 (P < 0.05)	++ ⁹	Critical
	<u>SIP overall, SIP physical, SIP psychosocial</u>									
1 ³¹	-1	NA	0	0	-1	7	7	NS difference between groups	++ ⁹	Critical
Objective: Effects of OneLegKneeEx (G1) compared to cycle ergometer training (G2) in patients with CHF										
Exercise capacity	<u>Peak watts, peak VO₂ (L/min⁻¹) and (mL/kg⁻¹/min⁻¹) during cycle ergometer</u>									
1 ³⁰	-1	NA	0	0	-1	8	8	S better result for G1(P < 0.05)	++ ¹⁰	Important
	<u>Peak watts, peak VO₂ (L/min⁻¹) and (mL/kg⁻¹/min⁻¹) during knee extensor and meters walked on 6 minute walk test self paced, and high speed</u>									
1 ³⁰	-1	NA	0	?	-1	8	8	NS difference between groups	++ ¹⁰	Important
Quality of life	<u>LiHfe Total, LiHfe Physical, LiHfe Emotional, SIP ambulation, SIP social interaction, SIP sleep and rest, SIP home management and SOC</u>									
1 ³⁰	-1	NA	0	?	-1	8	8	NS difference between groups	++ ¹⁰	Critical

⁸ Incomplete outcome data, unclear judgment of risk of bias in combination with low Pedro score, one study only, few events and sparse data

⁹ Unclear judgment of risk of bias in combination with low Pedro score, one study only, few events and sparse data.

¹⁰ No blinding of participants and personnel, incomplete outcome data, selective outcomes reported, one study only, few events and sparse data

Table 3. Evidence for SLE regimes in COPD and CHF patients

COPD	
(i)	OneLegCycl is significantly more effective than two-legged cycling regarding peak Watts, peak VO ₂ (L/min), and peak VO ₂ (mL/kg/min), during cycle ergometer (low ++) (important)
(ii)	There is no significant between group difference on peak V _E (L/min) (very low +) (important) and dyspnea (modified Borg scale) between OneLegCycl and two-legged cycling (low ++) (critical)).
CHF	
(iii)	SingLimbSW combined with aerobic training is significantly more effective than aerobic training alone to improve maximal strength (2RM) (low ++) (important)
(iv)	No significant differences between SingLimbSW combined with aerobic training and aerobic training alone was found on peak Watts, peak VO ₂ (mL/kg ⁻¹ /min ⁻¹), and submaximal (anaerobic threshold) VO ₂ (mL/kg/min) (++) (important).
(v)	SingLimbSE is significantly more effective than a control group regarding peak Watts, peak VO ₂ (mL/kg/min) meters walked and QoL LiHfe scale in CHF patients (low ++) (important-critical).
(vi)	OneLegKneeExt is significantly more effective than cycle ergometer training regarding peak Watts, peak VO ₂ (L/min) and peak VO ₂ (mL/kg/min) during cycle ergometer tests (++) (important).
(vii)	No significant differences between OneLegKneeExt and cycle ergometer training was found on peak Watts, peak VO ₂ (L/min), peak VO ₂ (mL/kg/min) during knee extension test and QoL scales LiHfe (total, physical, emotional), SIP (ambulation, social interaction, sleep and rest, home management) and SOC (low ++) (important-critical).
(viii)	Two-legged knee extension training is significantly more effective than OneLegKneeExt on meters walked and SIP subscales sleep & rest and home management (low ++) (critical)
(ix)	No significant differences between two-legged knee extension and OneLegKneeExt were found on QoL scales SIP (overall, physical, and psychosocial) (low++) (critical).
(x)	OneLegKneeExt is significantly more effective than a control group on meters walked and QoL scale SIP (overall, physical, psychosocial and sleep and rest) (++) (critical)
(xi)	No significant differences between OneLegKneeExt and a control group were found on QoL scales SIP (home management) (++) (critical).

Abbreviations: LiHfe; Minnesota living with heart failure questionnaire, OneLegCycle; One legged cycling, OneLegKneeEx; One-legged knee-extensor training, QoL; Quality of life, RM; Repetitions maximum, SingLimbSE; Single limb strength training using elastic resistance, SingLimbSW; Single limb strength training using weights, SIP; Sickness Impact profil, SOC; Sense of coherence scale, V_E; Minute ventilation, VO₂; Oxygen consumption