The effectiveness of supplemental oxygen during exercise training in patients with chronic obstructive pulmonary disease who show severe exercise-induced desaturation: a protocol for a meta-regression analysis and systematic review

Shohei Kawachi

Shinshu Daigaku <https://orcid.org/0000-0002-5093-5125>

Shuhei Yamamoto

Shinshu Daigaku Igakubu Fuzoku Byoin

Kenichi Nishie

Shinshu Daigaku

Takayoshi Yamaga

Health science university, Yamanashi, Japan

Manaka Shibuya

Kitasato Daigaku Byoin

Yasunari Sakai

Shinshu Daigaku Igakubu Fuzoku Byoin

Keisaku Fujimoto (✉ keisaku@shinshu-u.ac.jp)

Department of Clinical Laboratory Sciences, Shinshu University School of Health Sciences, Japan

<https://orcid.org/0000-0002-6512-1757>

Protocol

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Abstract

Background: Supplemental oxygen during exercise training has been used to prevent hypoxemia or allow toleration of higher intensity training in patients with chronic obstructive pulmonary disease (COPD) who show exercise-induced desaturation. Although some meta-analyses examined the efficacy of supplemental oxygen during exercise training, these studies concluded that it does not further improve exercise tolerance compared to exercise training alone. However, supplemental oxygen during exercise training may be effective to improve exercise tolerance in COPD patients with severe desaturation during exercise under breathing room air or compressed air. Therefore, this study will be performed to elucidate the efficacy of supplemental oxygen during exercise training and the relationship between its efficacy and severity of desaturation during exercise at baseline.

Methods: We will first assess the effectiveness of supplemental oxygen during exercise training in COPD. The main outcome is the change in exercise tolerance before and after the intervention, indicated by 6-minute walking distance or shuttle walking distance, and analyzed as the standardized mean difference (SMD). The quality and risk of bias in individual studies will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system and risk-of-bias tool (RoB ver.2). If statistical heterogeneity in effectiveness of exercise tolerance is shown, we will conduct meta-regression analyses to examine the association between efficacy of exercise training with supplemental oxygen and severity of desaturation at baseline.

Discussion: One strength of this study is that it is a systematic review with meta-regression analysis to elucidate the effectiveness of supplemental oxygen during exercise training in patients with COPD who show severe exercise-induced desaturation. However, the quality and number of studies included meta-analysis may be low.

Systematic review registration: Registration number, UMIN000039960.

Description Of The Condition

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities caused by exposure to harmful particles or gases.¹ An epidemiological study estimated that COPD has an incidence of 384 million in 2020, with a prevalence of 11.7% worldwide.² Globally, 3 million people die from COPD annually.³

As it has been reported that exercise training in rehabilitation improves exercise tolerance, which is related to mortality in COPD,⁴ the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria recommend rehabilitation regardless of severity of COPD.¹ However, as COPD patients who show exercise-induced desaturation are not able to tolerate high-intensity training, its effectiveness in such cases is limited. In COPD, exercise-induced desaturation is caused by decreases of diffusion capacity and

ventilation perfusion mismatch due to alveolar destruction and airflow obstruction, respectively.^{5,6} Furthermore, patients with severe COPD have more severe exercise-induced desaturation as a result of worsening alveolar hypoventilation by dynamic lung hyperinflation related to airflow limitation on exertion.^{7,8} As exercise-induced desaturation is involved in adverse sequelae and higher risk of mortality in COPD,^{9,10} supplemental oxygen during exercise training has been prescribed in COPD patients who show severe desaturation.

The efficiency of combined supplemental oxygen and exercise training remains unclear. Previous studies showed a twofold increase in exercise training load in the supplemental oxygen group compared to the control group, and therefore the supplemental oxygen group also showed improvements in exercise tolerance, dyspnea, and depressive symptoms.^{11,12} However, other studies failed to show significant improvements in exercise tolerance with supplemental oxygen.^{13,14} In 2007 and 2019, meta-analyses were conducted to elucidate the efficacy of supplemental oxygen during exercise training.^{15,16} The meta-analysis in 2019 concluded that supplemental oxygen during exercise training does not further improve exercise tolerance compared to exercise training alone.¹⁶ However, especially in COPD patients with severe desaturation at rest and on exertion, supplemental oxygen during exercise training may be effective to improve exercise tolerance. A previous study reported that patients with desaturation by more than 4% and to less than 90% on exertion, and who walked 10% or more further with ambulatory oxygen on endurance shuttle walk test showed significant improvements in exercise tolerance by a 6 – 7-week exercise training program with supplemental oxygen.¹⁷ In moderate to severe COPD patients with SpO₂ during exercise $\geq$ 90%, endurance training three times/week resulted in significant improvements in quality of life (QOL) and exercise capacity independent of oxygen supplementation, and there were no further benefits of supplemental oxygen from 12 to 24 weeks despite progressively increased training loads.¹⁸ Therefore, we will also conduct meta-regression analyses to examine the association between efficacy of exercise training with supplemental oxygen and severity of desaturation under breathing room air at baseline.

Objectives

The objective of this systematic review and meta regression analysis is to elucidate the efficacy of supplemental oxygen during exercise training and the relationship between its efficacy and severity of desaturation in COPD.

Methods And Analyses

This systematic review will be conducted according to the Cochrane Handbook for Systematic Review of Interventions, the Preferred Reporting Items for Systematic Reviews, Meta-Analyses (PRISMA) statement.^{19,20} The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system will be used to assess the evidence in cumulative evidence.²¹ This protocol paper was prepared according to PRISMA-P checklist which was uploaded as a supplementary material.²²

Type of study

Randomized controlled trials (RCTs) regardless of cluster or individual randomization between January 1, 1980 and May 31, 2020 will be included restricted to those published in English. In addition, full-text studies, those published as abstracts only, and unpublished data are eligible for inclusion. We will only include RCTs with supplemental oxygen during exercise training for COPD and exclude RCTs related to ambulatory oxygen or long-term oxygen therapy.

Type of participants

We will include participants 18 years of age or older, with a diagnosis of COPD diagnosed according to the GOLD criteria.¹ We will exclude participants with other respiratory diseases.

Type of intervention and comparators

The active treatment group will receive supplemental oxygen during exercise training using wall oxygen units in a hospital or clinic, portable oxygen cylinders, liquid oxygen canisters, and oxygen concentrators.

The control group will be provided sham gas, such as compressed air, through a wall unit or cylinders or will receive no intervention under room air.

The exercise training performed in both groups is defined as a supervised or unsupervised inpatient, outpatient, home-based intervention that includes some form of exercise training applied to COPD patients.

Types of outcome

Primary outcome

1. Exercise capacity: 6-minute walking distance (6MWD: m) or shuttle walking distance (SWT: m) or other measures, e.g., peak oxygen consumption. (Peak VO_2 : mL/kg/min)
2. Maximum exercise load of exercise training, e.g., workload (Watts).
3. Dyspnea scores at the end of the exercise test, e.g. Borg score.
4. Health-related QOL assessed by questionnaires, e.g., 36-item Short Form Health Survey (SF-36).

Search methods for identification of studies

Electronic searches

This meta-analysis will be carried out according to the PRISMA Statement.¹⁹ We will conduct searches for studies with inception dates up to May 31, 2020 in the Cochrane Central Register of Controlled Trials (CEN-TRAL), MEDLINE, and EMBASE electronic databases. We will also search abstracts and meeting presentations utilizing the same search terms from Medical Subject Headings (MeSH). The search

strategy will be based on discussions with an information specialist, and will be modified appropriately for each database. The search strategy includes a combination of free text words, words in titles/abstracts, and medical subject headings, such as “pulmonary disease, chronic obstructive,” “supplemental oxygen,” “oxygen inhalation therapy,” and “exercise.” Searches are limited to peer-reviewed research involving human participants. The detailed strategy and details of the formula that will be used to search the databases are shown in table 1.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. Further, we will contact experts in the field to ask if they know of any ongoing or unpublished trials.

Selection of studies

Two review authors (SK and SY) will independently screen the titles and abstracts of all potentially relevant studies identified by the search, and code them as “retrieve” (eligible or potentially eligible/unclear) or “do not retrieve.” In the case of disagreements, other review authors will be asked to arbitrate (KN and TY). SK and SY will retrieve the full text reports/publications, and independently screen the full texts and identified studies for inclusion. SK and SY will also identify and record reasons for the exclusion of ineligible studies. Any disagreements will be resolved by discussion or by consulting other review authors (KN and TY) when necessary. The review authors will identify and exclude duplicates, and collate multiple reports of the same study so that the unit of interest in the review will be each study, rather than each report. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and “Characteristics of excluded studies” table. A data collection form piloted in at least one study in the review will be used to record study characteristics and outcome data. Two review authors (SK and SY) will extract characteristics from the included studies as follows:

1. Methods: study design, total duration of study, duration of follow-up, number of subjects, study setting, and date of study.
2. Participants: sample size, mean age, sex, history of smoking, history of oxygen therapy, forced expiratory volume in 1 s (FEV₁) after bronchodilator administration, and arterial partial pressure of oxygen (PaO₂) at baseline.
3. Interventions: type of supplemental oxygen device, oxygen supplemental settings, such as continuous flow or demand delivery systems, and their flow rates, type of intervention as control, such as compressed air (and the flow rate), or room air, type of exercise training as frequency, duration, and contents.
4. Outcomes: exercise capacity, maximum exercise load of exercise training, dyspnea scores at the end of exercise test, health-related QOL assessed by questionnaire survey.
5. Notes: funding for trial and conflicts of interest of the trial authors.

Data collection of studies

Two review authors (SK and SY) will independently extract outcome data from the included studies and check each other's data extraction. One review author (SK) will transfer data into the Review Manager 5.3 file (RevMan 2019) and the EZR statistical program.²³ SK and SY will double-check that data have been entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (KN) will spot-check the study characteristics for accuracy against the trial report.

Assessment of risk of bias

Two review authors (SK and SY) will independently assess risk of bias for each study using the criteria outlined in the (RoB version 2) in the Cochrane Handbook for Systematic Reviews of Interventions.¹⁹ Any disagreements will be resolved by discussion, by involving other review authors (KN and YT), or by contacting the authors of the included studies. We will assess risk of bias according to the following domains:

1. Bias arising from the randomization process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result

We will grade each potential source of bias as low risk, some concerns, or high risk and provide a quote from the study report together with a justification for our judgment in the "Risk of bias" table. We will summarize the risk of bias judgments across different studies for each of the domains listed.

Measures of treatment effect

We will analyze continuous data as the mean difference (MD) or standardized mean difference (SMD) with 95% confidence interval (95% CI). The MD is the absolute difference between the mean change before and after the intervention in a trial. The SMD is used as a summary statistic in the meta-analysis when the studies all assessed the same outcome but measured it in a variety of ways. We will enter data presented as a value with a consistent direction of effect. When the standard deviation (SD) for change from the baseline is not available, we will calculate the SD using Review Manager (RevMan) version 5.3. All CIs have two-sided probability coverage of 95%. A p -value < 0.05 will be considered significant. We will carry out sensitivity analysis when there is a high risk of bias that could affect the results.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis with Tau^2 , I^2 , and Chi^2 statistics following the Cochrane Handbook for Systematic Reviews.¹⁹ We regard heterogeneity as substantial with $I^2 > 0\%$ and either the Tau^2 is $> \text{zero}$ or $p < 0.10$ in the c^2 test for heterogeneity. Data from each study will be

pooled with fixed-effects modeling when there is no heterogeneity ($p > 0.1$, $I^2 \leq 40\%$). We will perform meta-analyses with random-effects models when there is heterogeneity ($p < 0.1$, $I^2 > 40\%$).

Subgroup analysis

We plan to carry out the following subgroup analyses for primary outcomes if we obtain an I^2 score $> 50\%$.

1. Severity of hypoxemia of rest at baseline ($\text{PaO}_2 \leq 60\text{Torr}$ or $\text{PaO}_2 > 60\text{Torr}$)
2. Severity of exercise-induced desaturation at baseline (exercise induced desaturation: either decrease of $\text{SpO}_2 \geq 4\%$ and nadir SpO_2 during exercise $\leq 88\%$ or not-exercise induced desaturation)
3. Severity of airflow limitation ($\%FEV_1 \geq 50\%$ or $\%FEV_1 < 50\%$)

We plan to explore differences in outcomes in these subgroups if the number of collected studies is sufficient.

Sensitivity analysis

We plan to carry out sensitivity analysis for primary outcomes if the high risk of bias of some of the included studies affected the results. We will define “high risk” in each study as at least one domain evaluated as “high risk” or some domains are allocated as “some concern” that can decrease the reliability of the results.¹⁸ We plan to carry out the following sensitivity analyses.

Meta-regression

If there is any statistically heterogeneity or methodological heterogeneity, we will perform meta-regression using PaO_2 at baseline (Torr) and decreases of SpO_2 in exercise tests as covariates to investigate whether the severity of desaturation at baseline affects the effectiveness of exercise tolerance.

Assessment of reporting biases

When 10 or more studies are included in a meta-analysis, we will create a funnel plot and examine its asymmetry visually to explore any publication bias.

Assessment of evidence in individual study

We will use the GRADE criteria to assess the quality of evidence for each outcome according to four levels (high, moderate, low, or very low).²¹ The quality of evidence will be reduced by any one of the following limitations: risk of bias, inconsistency, indirectness, imprecision and publication bias. Two investigators (SK, SY) will independently conduct those assessment. Investigators will resolve disagreements between the two investigators through discussion, with a third reviewer available for adjudication (KN).

Discussion

As exercise-induced desaturation is involved in adverse sequelae and higher risk of mortality in COPD, supplemental oxygen during exercise training has been prescribed in COPD patients who show severe desaturation. The meta-analysis in 2019 concluded that supplemental oxygen during exercise training does not further improve exercise tolerance compared to exercise training alone. However, especially in COPD patients with severe desaturation at rest and on exertion, supplemental oxygen during exercise training may be effective to improve exercise tolerance. A previous study reported that patients only who show exercise induced-desaturation in COPD, and who walked 10% or more further with ambulatory oxygen on shuttle walking test showed significant improvements in exercise tolerance by an exercise training program with supplemental oxygen. Therefore, we will conduct meta-regression analyses to examine the association between efficacy of exercise training with supplemental oxygen and severity of desaturation at baseline. However, the quantity and quality of the trials will possibly be the main limitation of this research.

Abbreviations

COPD: chronic obstructive pulmonary disease

SMD: standardized mean difference

GRADE: grading of recommendations assessment, development, and evaluation

GOLD: global initiative for chronic obstructive lung disease

QOL: quality of life

PRISMA: preferred reporting items for systematic reviews, meta-analyses

RCT: randomized controlled trial

6MWD: 6-minute walking distance

SWT: shuttle walking distance

Peak VO_2 : peak oxygen consumption

SF-36: 36-item short form health survey

CEN-TRAL: cochrane central register of controlled trials

MeSH: medical Subject Headings

FEV_1 : forced expiratory volume in 1 s

PaO₂: arterial partial pressure of oxygen

MD: mean difference

95% CI: 95% confidence interval

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

SK and SY contributed to the conception of the study. KN, TY, SM and YS designed the methods of the systematic review and KF will supervise those design and analysis. All authors were involved in the critical revision, for the intellectual content, and read and approved the final manuscript.

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Tables

Table 1. The detailed strategy and details of formula for search in databases

(A). MEDLINE

1. Lung Diseases [MeSH Terms]
2. Lung Diseases, Obstructive [MeSH Terms]
3. Pulmonary Disease, Chronic Obstructive [MeSH Terms]
4. Bronchial Diseases [MeSH Terms]
5. Emphysema [MeSH Terms]
6. Hypoxia [MeSH Terms]
7. Hypoxemia [MeSH Terms]

8. COPD [All Fields]
9. COAD [All Fields]
10. COBD [All Fields]
11. exercise induced-desaturation [Title/Abstract])
12. #1OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
13. supplemental oxygen [Title/Abstract]
14. oxygen Inhalation Therapy [MeSH Terms]
15. oxygen supplementation [Title/Abstract]
16. oxygen supply [Title/Abstract]
17. Oxygen [MeSH Terms]
18. #13 OR #14 OR #15 OR #16 OR #17
19. exercise [MeSH Terms]
20. resistance Training [MeSH Terms]
21. exercise Therapy [MeSH Terms]
22. high-Intensity Interval Training [MeSH Terms]
23. physical Therapy Modalities [MeSH Terms]
24. physical Conditioning, Human [MeSH Terms]
25. rehabilitation [MeSH Terms]
26. #19 OR #20 OR #21 OR #22 OR #23 OR #24
27. randomized Controlled Trial [Title/Abstract]
28. trial [Title/Abstract]
29. randomized [Title/Abstract]
30. randomized [Title/Abstract]
31. randomly [Title/Abstract])
32. placebo [Title/Abstract]
33. #27 OR #28 OR #29 OR #30 OR #31 OR #32
34. Animals [Title/Abstract])
35. #33 NOT #34
36. #12 AND #18 AND #26 AND #35

(B). Embase

1. lung diseases
2. obstructive lung diseases

3. chronic obstructive pulmonary disease
4. bronchial diseases
5. emphysema
6. hypoxia
7. hypoxemia
8. COPD: ab
9. exercise induced-desaturation
10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. oxygen inhalation therapy
12. supplemental oxygen
13. oxygen supplementation
14. oxygen supply
15. #11 OR #12 OR #13 OR #14
16. exercise
17. resistance training
18. exercise therapy
19. interval training
20. physical therapy
21. rehabilitation
22. physical conditioning
23. exercise training
24. #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25. randomized controlled trial
26. ab
27. ab
28. ab
29. placebo
30. #25 OR #26 OR #27 OR #28 OR #29
31. ab
32. #30 NOT #31
33. #10 AND #15 AND #24 AND #32

(C). Cochrane Central Register of Controlled Trials

1. MeSH descriptor: [Lung Diseases] explode all trees
2. MeSH descriptor: [Lung Diseases, Obstructive] explode all trees
3. MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
4. MeSH descriptor: [Bronchial Diseases] explode all trees
5. MeSH descriptor: [Emphysema] explode all trees
6. MeSH descriptor: [Hypoxia] explode all trees
7. Hypoxemia
8. COPD: ti,ab,kw OR COAD: ti,ab,kw OR COBD: ti,ab,kw OR exercise induced-desaturation: ti,ab,kw
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. MeSH descriptor: [Oxygen Inhalation Therapy] explode all trees
11. supplemental oxygen
12. oxygen supplementation
13. oxygen supply
14. MeSH descriptor: [Oxygenators] explode all trees
15. #10 OR #11 OR #12 OR #13 OR #14
16. MeSH descriptor: [Exercise] explode all trees
17. MeSH descriptor: [Resistance Training] explode all trees
18. MeSH descriptor: [Exercise Therapy] explode all trees
19. MeSH descriptor: [High-Intensity Interval Training] explode all trees
20. MeSH descriptor: [Physical Therapy Modalities] explode all trees
21. MeSH descriptor: [Physical Conditioning, Human] explode all trees
22. Rehabilitation
23. #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24. Randomized Controlled Trial: pt OR trial: ti,ab,kw OR randomized: ti,ab,kw OR placebo: ti,ab,kw OR randomly: ti,ab,kw
25. animals
26. #24 NOT #25
27. #9 AND #15 AND #23 AND #26