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Comparing the effects of high-intensity interval training (HIIT) with different oxygen delivery methods in patients with pulmonary fibrosis

Submission date
22/05/2023

Recruitment status
No longer recruiting

Registration date
21/06/2023

Overall study status
Completed

Last Edited
10/09/2024

Condition category
Respiratory

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Interstitial lung disease (ILD) refers to a range of lung conditions that cause inflammation and damage. People with ILD experience a drop in their blood oxygen levels during physical activity, which limits their ability to carry out daily tasks. Pulmonary rehabilitation (PR) is a treatment for ILD patients, but the decrease in oxygen levels poses a challenge to achieving favorable outcomes. Therefore, we aim to investigate whether a combination of High-Intensity Interval Training (HIIT) and High Flow Nasal Oxygen (HFNO) can enhance exercise capacity in ILD patients. We believe that this training method, along with increased oxygen supply, may mitigate the decline in blood oxygen levels and improve exercise tolerance. This approach could serve as an alternative during pulmonary rehabilitation, potentially leading to better treatment results.
The primary objective of this study is to assess the impact of an 8-week program involving HIIT with HFNO on the exercise capacity of ILD patients compared to standard PR. We will evaluate exercise capacity using a bicycle exercise test at a constant work rate, set at 75% of the maximum workload achieved from a previous Cardiopulmonary Exercise Test (CPET). The secondary objectives include examining the effects of this training on daily physical activity levels, quadriceps muscle strength, quality of life using the St George's Respiratory Questionnaire (SGRQ), anxiety and depression levels using the Hospital Anxiety and Depression Scale (HADS), dyspnea sensation, and lung function. Furthermore, we will explore the impact on specific blood biomarkers associated with fibrosis, selected from the ELFMEN study, which have been linked to disease progression. Additionally, we will compare the results of patients receiving antifibrotic medications with those who are not receiving such treatment.

Who can participate?
All patients affected with interstitial lung diseases referred to the physiotherapy department to receive pulmonary rehabilitation in the Lothian region who are between 18 and 85 years old and with the ability to give informed consent will be able to participate.

What does the study involve?
In general, the study will consist of 8 weeks of intervention in the clinic plus 1 day of evaluations

before and after the intervention. Spending 1 hour per day, three times a week every second day during the intervention and 2 hours during the other 2 days of evaluations approximately. The window between the baseline appointment and the first day of the intervention can be from 1 to 30 days, and the window between the last day of intervention and the post-intervention appointment will be from 8 to 38 days. All the visits will take place in ward 204 (Respiratory Medicine) of the Royal Infirmary of Edinburgh (for participants from Edinburgh) and in the Royal Victoria Infirmary, Newcastle upon Tyne Hospital (for participants from Newcastle).
The following measurements will be conducted:
During the first day before the intervention, a blood test will be taken (only 6 ml) to know the levels of blood biomarkers associated with fibrosis that have been shown to be associated with disease progression (Inc. but not restricted to PAI-1, VEGF-A, PDGF-AA, PDGF-BB, Cystatin-C, Angiopotein-1, HE4/WFDC-2). Additionally, a test called the quadriceps maximal voluntary contraction test (QMVCT) will be taken to measure the strength of the quadriceps muscle. The subjects are studied seated in a chair, with hip and knee flexion of 90 degrees. An inextensible strap is placed around the ankle, and adjusted to ensure the knee remains at 90 degrees flexion. The ankle strap is connected to a strain gauge mounted on the back of the chair. A seatbelt is secured across the subject's hips to stabilise the pelvis. The patient has to do a knee extension and we can measure their strength.
In addition, the shortness of breath will be assessed using the Modified version of the Medical Research Council scale (mMRC).

In addition, height and weight will be taken. Breathing tests will not be performed, because these procedures the participants have already done in the outpatient clinic.

In addition, a Cardiopulmonary Exercise Test (CPET) will be carried out.

Furthermore, a Constant work rate Cycle Test at 75% of the peak work rate (obtained from a maximal exercise test conducted beforehand) will be carried out. The participants will be able to rest for about 20 minutes between each test and we will offer them refreshments.

Physical activity levels in daily life will also be measured using an Actigraph GT3x activity monitor, which will be delivered during the baseline appointment to use in their house for only 1 week before and 1 week after the intervention, this is a belt that the participants will have to use like any other. After the intervention, they should return it to us during their post-intervention appointment.

Moreover, two questionnaires called St George's Respiratory Questionnaire (SGRQ) and the Hospital Anxiety and Depression Scale (HADS), will have to be answered to measure the quality of life and anxiety and depression levels respectively. These tests will be answered at home.

During the first day after the intervention, participants will be undergone exactly the same tests as in the baseline appointment, except for height

Intervention, a group of participants will be submitted to 8 weeks of a PR program based on HIIT plus HFNO and the other group will also be submitted to 8 weeks of a PR program based on HIIT but with conventional oxygen delivery without HFNO. Which group will use HFNO or conventional oxygen will be randomly selected from a sealed envelope.

What are the possible benefits and risks of participating?
The information gained from the participation of the patients may enable us to come up with the most optimal rehabilitation programme in the future, and this may benefit patients with ILD. Their results from the assessments we perform will also be made available to them and their

general practitioner with their consent. We will inform them and their GP if anything with clinical relevance is found. During a CPET, participants might experience the following: breathlessness or leg fatigue. They can stop the test at any time. Other more infrequent symptoms may develop during exercise such as chest pain, a drop in blood oxygen levels, drop or increment in their blood pressure. We will be monitoring these and we may decide to stop the test if we feel this is a risk. A clinician will be available to deal with any problem.

Where is the study run from?
Department of Physiotherapy of the Royal Infirmary of Edinburgh and the Royal Victoria Infirmary (UK)

When is the study starting and how long is it expected to run for?
March 2022 to November 2024

Who is funding the study?
This research study is sponsored by the University of Edinburgh and NHS Lothian and financed by The Chilean National Scholarship Program for Graduate Studies (UK)

Who is the main contact?
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Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
314541

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
AC23014,IRAS 314541

Study information

Scientific Title
A Study to Compare Intergroup Effects of High-Intensity Interval Training (HIIT) with the Addition of High Flow Nasal Oxygen (HFNO) versus HIIT plus oxygen delivered through a nasal cannula (NC) in Patients with Fibrosing Interstitial Lung Disease (FILD)

Study objectives
Will High-Intensity Interval Training (HIIT) combined with High Flow Nasal Oxygen (HFNO) lead to better outcomes (i.e. exercise capacity, quality of life) in comparison to Pulmonary Rehabilitation (PR) delivered without HFNO in patients with Fibrosing Interstitial Lung Disease (FILD)?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/05/2023, South East Scotland REC 01 (Waverley Gate, 2 - 4 Waterloo Place, Edinburgh, EH1 3EG, UK; +44 7814 764 241; sandra.wyllie@nhslothian.scot.nhs.uk), ref: 23/SS/0042

Study design
Randomized controlled multicentre proof-of-concept study

Primary study design
Interventional

Secondary study design
Randomized, controlled, multicentre proof-of-concept study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Fibrosing interstitial lung disease

Interventions
RECRUITMENT, CONSENT AND SCREENING
All Patients affected with interstitial lung diseases referred to the physiotherapy department to receive pulmonary rehabilitation in the Lothian region and Newcastle, also those from the ILD clinic will be invited by a member of the direct care team (Dr Roberto Rabinovich in Edinburgh and Dr Ian Forrest in Newcastle) to participate and will receive a patient's information sheet with an invitation to attend pre-assessment for this study. This appointment should occur at least 3 days after the patient has received the Patient Information Sheet. This is to ensure that the patient has adequate time to consider his or her decision to participate in the study. At pre-assessment, the study will be explained to them and written informed consent will be obtained from those agreeing to participate.

RANDOMISATION
Following confirmation of eligibility by the CI or PI and signature of the informed consent, patients will be randomised using sealed letters to HIIT plus HFNO or HIIT plus nasal cannula. Patients will be sequentially randomised. Randomisation code and sealing of envelopes will be done by the research nurses and stored in a room at RIE and Royal Victoria Infirmary accessible with a key. This will be done before any baseline procedures.

BLINDING
In this open-label study, patients will not be blinded with respect to the modality of oxygen delivery but will not know the dose of oxygen they will be receiving or their SpO2 during the pulmonary rehabilitation program and the tests.

INTERVENTION
The intervention consists of HIIT plus HFNO versus HIIT plus oxygen delivered through a nasal cannula. The oxygen delivered via HFNO will be between 31 and 37°C according to patient preference. To minimize condensation, the heated humidified gas is delivered via heated tubings through a wide-bore nasal prong. Air flow will be 50 L/min and FiO2 will be titrated to maintain SpO2 above 88%. The comparator will be oxygen delivered via nasal cannula titrated to the same SpO2. Both HIIT will be performed at the same workload, which will be progressive throughout the 8 weeks and will be modified during each session in order to achieve a Borg score of 5, starting with high load intervals at 60% of the maximal watts achieved beforehand during a maximal CPET divided by lower load intervals at 40% maximum load during the first week, and finishing with high load intervals at 110% maximum load separated by load intervals at 80% maximum load in the last weeks.
Basically, the participants will have to pedal on a stationary bicycle for 30 minutes, during the other 20 minutes the patients will do exercises for their upper limbs using Thera bands and dumbbells. Muscles of upper limbs to work will be deltoids, pectorals and biceps (3 series of 10 repetitions each). Finally, the participants will receive 10 minutes of respiratory physiotherapy including techniques to eliminate phlegm, breathing exercises and ludic activities to train the

respiratory muscles such as inflating balloons.
Which group will use HFNO or conventional oxygen will be randomly selected from a sealed envelope. Randomized means that all participants will have the same chance of belonging to one group or another, they must choose a sealed envelope and inside it will be written to which group they will belong.

DURATION OF THE STUDY
In general, the study will consist of 8 weeks of intervention in the clinic plus 1 day of evaluations before and after the intervention. Spending 1 hour per day, three times a week every second day during the intervention and 2 hours during the other 2 days of evaluations approximately. The window between the baseline appointment and the first day of the intervention can be from 1 to 30 days, and the window between the last day of intervention and the post-intervention appointment will be from 8 to 38 days. All the visits will take place in ward 204 (Respiratory Medicine) of the Royal Infirmary of Edinburgh (for participants from Edinburgh) and in the Royal Victoria Infirmary, Newcastle upon Tyne Hospital (for participants from Newcastle).
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In addition, the shortness of breath will be assessed using the Modified version of the Medical Research Council scale (mMRC).
In addition, height and weight will be taken. Breathing tests will not be performed, because these procedures the participants have already done in the outpatient clinic.
In addition, a Cardiopulmonary Exercise Test (CPET) will be carried out.
Furthermore, a Constant work rate Cycle Test at 75% of the peak work rate (obtained from a maximal exercise test conducted beforehand) will be carried out. The participants will be able to rest for about 20 minutes between each test and we will offer them refreshments.
Physical activity levels in daily life will also be measured using Actigraph GT3x activity monitor, which will be delivered during the baseline appointment to use in their house for only 1 week before and 1 week after the intervention, this is a belt that the participants will have to use like any other. After of the intervention, they should return it to us during their post-intervention appointment.
Moreover, two questionnaires called St George's Respiratory Questionnaire (SGRQ) and the Hospital Anxiety and Depression Scale (HADS), will have to be answered to measure the quality of life and anxiety and depression levels respectively. These tests will be answered at home.
During the first day after of the intervention, participants will be undergone exactly to the same tests as in the baseline appointment, except height.

Intervention Type
Other

Primary outcome measure

Exercise Capacity, which will be assessed as endurance time (Tlim) during a constant work rate cycle test at 75% of the maximal workload (obtained beforehand from a maximal CPET). This outcome will be measured at baseline and after 8 weeks of the intervention.

Secondary outcome measures
1. Physical activity levels in daily life using Actigraph GT3x activity monitor. This outcome will be measured at baseline and after 8 weeks of the intervention.
2. Quadriceps muscle strength through the quadriceps maximal voluntary contraction test (QMVCT). This outcome will be measured at baseline and after 8 weeks of the intervention.
3. Quality of life using IPF-specific version of the St George's Respiratory Questionnaire (SGRQ). This outcome will be measured at baseline and after 8 weeks of the intervention.
4. Anxiety and depression levels through the Hospital Anxiety and Depression Scale (HADS). This outcome will be measured at baseline and after 8 weeks of the intervention.
5. Dyspnoea through the Modified version of the Medical Research Council scale (mMRC). This outcome will be measured at baseline and after 8 weeks of the intervention.
6. Blood biomarkers associated with fibrosis (Inc but not restricted to PAI-1, VEGF-A, PDGF-AA, PDGF-BB, Cystatin-C, Angiopotein-1, HE4/WFDC-2). This outcome will be measured at baseline and after 8 weeks of the intervention.
7. The number of patients using anti-fibrotic medication will also be assessed.
8. We will also assess if the patients who are in treatment with antifibrotic medicines have better results than those who are not in treatment with antifibrotic medicines.

Overall study start date
01/03/2022

Completion date
30/11/2024

Eligibility

Key inclusion criteria
1. Fibrosing lung disease on HRCT obtained from medical records, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10%, performed within 24 months of screening visit Clinical stability concerning pulmonary infections or acute exacerbations within the previous four weeks of inclusion in the study.
2. Absence of recent Myocardial Infarction (within last 3 months), unstable angina, other significant cardiac problems, systolic blood pressure > 180 mmHg, diastolic blood pressure > 100 mmHg or tachycardia (higher than 100 bpm)
3. Absence of significant orthopaedic, neurological, cognitive and/or psychiatric impairment restricting mobility.
4. Not following any exercise programme in the last 3 months.
5.Participants between 18 and 85 years old will be recruited with the ability to give informed consent.
6. TLCO ≥ 25% and ≤ 80% predicted. FVC (or VC) ≥ 45%
7. Patients that experience a drop in oxygen saturation with the exercise below 90%

Participant type(s)
Patient

Age group

Adult

Lower age limit
18 Years

Upper age limit
85 Years

Sex
Both

Target number of participants
30

Total final enrolment
11

Key exclusion criteria
1. Emphysema greater than extent of fibrosis on high resolution computed tomography (HRCT) of the thorax.
2. FEV1/FVC ratio < 70%.
3. Involvement in the planning and/or conduct of the study.
4. Participants should not be taking part in other interventional studies.
5. Patient is unable to attend the assessment sessions or would like to withdraw from the study.
6. Absolute contraindications for cardiopulmonary exercise testing, which are:
6.1. Unstable angina
6.2. Uncontrolled arrhythmias causing symptoms or hemodynamic compromise.
6.3. Syncope.
6.4. Active endocarditis.
6.5. Acute myocarditis or pericarditis.
6.6. Symptomatic severe aortic stenosis.
6.7. Uncontrolled heart failure.
6.8. Acute pulmonary embolus or pulmonary infarction.
6.9. Thrombosis of lower extremities.
6.10. Suspected dissecting aneurysm.
6.11. Uncontrolled asthma.
6.12. Pulmonary edema.
6.13. Room air desaturation at rest ≤ 85%
6.14. Respiratory failure.
6.15. Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)
6.16. Mental impairment leading to inability to cooperate.

Date of first enrolment
01/09/2023

Date of final enrolment
06/09/2024

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Royal Infirmary of Edinburgh
51 Little France Crescent
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Sponsor information

Organisation
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Sponsor type
University/education

Website
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ROR
https://ror.org/01nrxwf90

Funder(s)

Funder type
Government

Funder Name
Chilean National Scholarship Program for Graduate Studies (ANID)

Results and Publications

Publication and dissemination plan
When the study is completed according to plan, the results may be published in scientific or medical journals or be presented at conferences and written up as part of a doctorate. Participants will get a copy of their results through newsletters.

Intention to publish date
30/07/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to confidentiality.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2.0	14/04/2023	26/05/2023	No	Yes
Protocol file	version 1.0	22/02/2023	26/05/2023	No	No