

Mechanistic evaluation of two approaches to oxygen therapy in critical care (MecROX)

Submission date 14/01/2023	Recruitment status No longer recruiting	<input type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 27/03/2023	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 15/08/2024	Condition category Surgery	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

Plain English summary of protocol

Background and study aims

Although oxygen is necessary, excess oxygen can be harmful, especially to those requiring artificial ventilation. Usually, lungs are kept open by a detergent-like material in the lungs called "surfactant" so they can work properly. However, too much oxygen can kill the cells that make surfactant or increase surfactant breakdown. This can cause the lung to become damaged and fill with fluid instead of air, causing unnecessary harm. Too much oxygen can also cause powerful chemical reactions (called oxidative stress) that can damage cells around the body, causing major organs to fail. This can lead to the worsening of a patient's condition.

Aims: Intensive Care Patients (ICU) are often given oxygen via artificial ventilation through a breathing machine. Giving too much oxygen is harmful and can damage the lungs. We want to improve patient outcomes by understanding how excess oxygen causes lung damage. In this study, we aim to determine whether using a lower oxygen target in patients on a breathing machine reduces lung damage.

What does the study involve?

A national research study (UK-ROX, <https://www.isrctn.com/ISRCTN13384956>) is looking to find out whether giving less oxygen to patients in ICU will improve their survival compared to standard care (more oxygen). UK-ROX trial will not be able to assess how exactly the excess oxygen may cause harm. Therefore, this study will run in parallel with UK-ROX to look in more detail at how excess oxygen might affect the lungs.

We will take blood and lung fluid samples from these participants three times during the study. We will take blood from a small catheter already in place as part of their standard ICU treatment. Lung fluid samples will be taken through a small suction tube attached to the breathing tube already in their windpipe.

Who can participate?

Anyone aged 18 years or above who requires mechanical ventilation (breathing machine) to support their breathing in an intensive care unit setting. We intend to recruit 100 patients from the UK-ROX trial and conduct this detailed sub-study to determine whether surfactant and

oxidative stress play a role in excess oxygen-induced lung damage. Half of the participants will be recruited from the low oxygen group of UK-ROX and the other half from the standard oxygen group.

What are the possible benefits and risks of participating?

No direct benefit will accrue for participants. However, this study will improve the understanding of how oxygen causes damage to the lungs and may lead to the development of treatments that benefit patients with similar diseases.

Where is the study run from?

The study is conducted in two NHS centres, University Hospital Southampton and University Hospital Plymouth (UK)

When is the study starting, and how long is it expected to run for?

December 2022 to July 2025

Who is funding the study?

The NIHR Efficacy and Mechanism Evaluation Programme (UK)

Who is the main contact?

MecROX study team (mecrox@soton.ac.uk)

Chief Investigator, Dr A Dushianthan (a.dushianthan@soton.ac.uk)

Contact information

Type(s)

Principal investigator

Contact name

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Additional identifiers

Clinical Trials Information System (CTIS)

Nil known

Integrated Research Application System (IRAS)

320671

ClinicalTrials.gov (NCT)

Nil known

Protocol serial number

IRAS 320671, CPMS 54827

Study information

Scientific Title

Oxidative stress, redox status and surfactant metabolism in mechanically ventilated patients receiving different approaches to oxygen therapy

Acronym

MecROX

Study objectives

We hypothesise that both hyperoxia and hyperoxemia increase alveolar and systemic oxidative stress and adversely impact surfactant metabolism. Specifically, in mechanically ventilated patients: (i) Administration of high inspired oxygen concentrations will contribute to increased alveolar and systemic oxidative stress; (ii) increased alveolar and systemic oxidative stress will result in adverse changes in surfactant metabolism. We will characterise these metabolic phenotypes according to surfactant metabolism and alveolar and systemic oxidative stress.

This is a sub-study of the UK-ROX interventional randomised controlled trial. <https://www.isrctn.com/ISRCTN13384956>

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 19/12/2022, London-Bromley Ethics Committee (Temple Quay House 2 The Square Temple Quay Bristol BS1 6PN, UK; +44 207 104 8118; bromley.rec@hra.nhs.uk), ref: 22/LO/0877

Study design

Prospective observational study

Primary study design

Observational

Study type(s)

Other

Health condition(s) or problem(s) studied

Mechanically ventilated patients from hypoxic respiratory failure.

Interventions

Participants from UK-ROX will be enrolled. They will receive methyl-D9 choline infusion followed by endotracheal aspirate, and blood sampling will be done 0, 48 and 72 hours after the study initiation.

Intervention Type

Procedure/Surgery

Primary outcome(s)

The difference of percentage of DPPC (PC32:0) in relation to total phosphatidylcholine composition (% of total PC in surfactant) at 48 hours between conservative and usual oxygen target groups.

Key secondary outcome(s)

1. Surfactant index: This is a composite PC surfactant molecular index calculated from surfactant specific PC molecules (PC32:0, PC32:1 and PC30:0) and unsaturated surfactant PC34:1. This index will give a composite measure of surfactant PC alterations, which will provide a measure of surfactant PC status for the two different targets after 48 hours of oxygen therapy. This outcome is a measure of surfactant specific PC composition. Surfactant index = $\{32:0+32:1+30:0\}$ 34:1
2. Surfactant phosphatidylcholine concentration (urea corrected) at 48 hours. This outcome is a measure of endogenous surfactant level.
3. Systemic oxidative stress: Total free thiols, lipid peroxides and total surfactant oxidation products. This outcome will measure whole-body oxidative stress.

Secondary explanatory outcomes

1. Surfactant total phosphatidylcholine and PC32:0 methyl-D9choline enrichment at 48 hours. Measure of endogenous surfactant synthesis. This will measure the surfactant PC synthesis via the CDP-Choline pathway.
2. Surfactant total lysoPC and lysoPC16:0 concentrations, composition and methyl-D9 choline enrichment at 48 hours. This outcome is a measure of endogenous surfactant breakdown. This will help to assess dynamic surfactant PC breakdown through hydrolysis.
3. Surfactant oxidised PC composition and concentrations at 48 hours. Measure of endogenous surfactant breakdown. This will help to assess dynamic surfactant breakdown by oxidation.
4. Whole- body redox balance by quantifying stable products of ROS (e.g., isoprostanes), RNS (e.g., nitrite, nitrate, nitrosation products) and RSS (e.g., total free thiols, thiosulfate, low molecular weight thiols including sulfide) at 48 hours from tracheal aspirates and plasma. Measure of lung and systemic redox status.
5. Comparison of clinical outcomes (ICU mortality, hospital mortality, 90-day mortality, ICU, and hospital length of stay) in relation to surfactant abnormalities.
6. Comparison of clinical outcomes (ICU mortality, hospital mortality, 90-day mortality, ICU, and hospital length of stay) in relation to specific markers of oxidative stress.

Completion date

01/07/2025

Eligibility

Key inclusion criteria

1. Enrolled in UK-ROX study
2. Aged greater or equal to 18 years

3. Receiving invasive mechanical ventilation in the ICU for hypoxaemic respiratory failure
4. Receiving supplemental oxygen (fractional inspired concentration of oxygen ($FiO_2 > 0.21$ at the time of enrolment)
5. Anticipated to be mechanically ventilated for a minimum of 72 hours

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 years

Sex

All

Key exclusion criteria

1. Currently receiving extra corporeal membrane oxygenation (ECMO)
2. The treating clinician considers that one UK-ROX trial intervention arm is either indicated or contraindicated

Date of first enrolment

01/02/2023

Date of final enrolment

01/08/2024

Locations**Countries of recruitment**

United Kingdom

England

Study participating centre

University Hospital Southampton

Southampton University Hospital

Tremona Road

Southampton

United Kingdom

SO16 6YD

Study participating centre

University Hospitals Plymouth NHS Trust
Derriford Hospital
Derriford Road
Derriford
Plymouth
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PL6 8DH

Sponsor information

Organisation

University Hospital Southampton NHS Foundation Trust

ROR

<https://ror.org/0485axj58>

Funder(s)

Funder type

Government

Funder Name

Efficacy and Mechanism Evaluation Programme

Alternative Name(s)

NIHR Efficacy and Mechanism Evaluation Programme, Efficacy and Mechanism Evaluation (EME), EME

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and or analysed during the current study are/will be available upon request from Dr Ahilanandan Dushianthan (a.dushianthan@soton.ac.uk)

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		08/07/2024	15/08/2024	Yes	No