ISRCTN17381278 https://doi.org/10.1186/ISRCTN17381278

Inhalation challenge to assess inducible laryngeal obstruction (ILO)

Submission date
27/06/2018

Recruitment status
No longer recruiting

Registration date
28/08/2018

Overall study status
Completed

Last Edited
30/07/2024

Condition category
Respiratory

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

Plain English summary of protocol

Background and study aims
Inducible laryngeal obstruction (ILO) is when the voice box (larynx) closes and obstructs breathing. The closure is usually sudden and often happens in response to a trigger. ILO causes breathing difficulties, which are reversible, but can be severe, meaning patients go to Emergency Departments and intensive care units. No standard test has been established to diagnose ILO. This study aims to develop a way of assessing whether someone has ILO. Patients report similar triggers for ILO and idiopathic chronic cough (ICC, a long-lasting cough with no clear cause). Citric acid (CA) may be a reliable trigger to provoke ILO. In order to see if this is correct, changes in larynx opening when someone inhales CA are compared to a control solution and this response is compared between people who have ICC, people who have ILO and a healthy control group.

Who can participate?
ILO patients, ICC patients and healthy volunteers

What does the study involve?
Each participant attends a hospital visit on three occasions over a period of 14 days. On the first two visits participants are asked to complete a standard cough challenge (where an increasing amount of challenge solution is inhaled through a mouthpiece) at the same time as having a laryngoscopy (a small flexible tube passed through a nostril to rest just above the voice box). Participants wear two bands around their chest to monitor breathing movements and a microphone to record sounds. The challenge agent given on each visit is determined by random allocation and the person doing the test and the participant do not know which is being administered. Before and after the challenge, simple breathing tests and questionnaires are completed. After each dose challenge, questions are asked about throat and breathing symptoms. On the final visit, some questionnaires are filled out and a simple breathing test is performed.

What are the possible benefits and risks of participating?
There are no direct benefits to volunteers participating in this study. Citric acid challenges are safe, but there is a slight risk that they may cause chest tightness and breathlessness in some people. In the event that this does happen there is a clinician available to administer a

bronchodilator, a medicine which relieves chest tightness. Lung function tests are performed before and after challenges to ensure that there is no ill effect of inhaling the citric acid.

Where is the study run from?
The study is being run in the North West Lung Centre at Manchester NHS Foundation Trust, Wythenshawe Hospital and The Royal Brompton and Harefield NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
September 2017 to May 2025

Who is funding the study?
The North West Lung Centre Charity (UK)

Who is the main contact?
Jemma Haines
cough.research@manchester.ac.uk

Contact information

Type(s)
Public

Contact name
Mrs Jemma Haines

Contact details
Cough Research Team
Manchester NHS Foundation Trust
Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT
+44 (0)161 291 5031
cough.research@manchester.ac.uk

Additional identifiers

Integrated Research Application System (IRAS)
250025

Protocol serial number
18/CHILO/001, IRAS 250025

Study information

Scientific Title
Inhalation challenge to assess inducible laryngeal obstruction (ILO)

Acronym
CH-ILO

Study objectives
Inducible laryngeal obstruction (ILO) is defined as a temporary obstruction of the voice box (larynx) associated with breathlessness that typically develops in the presence of an 'inducer' or triggering factor. Patients with ILO often describe chemical irritants (e.g. strong scents) as the inducer to symptom onset. This is also a typical feature in patients presenting with idiopathic chronic cough (ICC) and is consistent with the ion channels and receptors expressed by sensory vagal fibres capable of triggering the cough reflex. However, compared with cough, much less is known about the neuronal mechanisms underlying ILO or why such patients respond to similar irritant exposures with inappropriate laryngeal obstruction as opposed to coughing.
The laryngeal adductor reflex (LAR) is a protective airway vagal reflex which produces brief closure of the vocal cords in response to stimulation of the pharyngeal and laryngeal mucosa (above the vocal cords). It is therefore possible to hypothesise that ILO represents an inappropriate triggering of the LAR by chemical stimuli. Clinically the LAR is most frequently assessed using air puffs to the larynx, however this mechanical stimulus may not optimally assess the chemical sensitivities described by patients and thus the potential underlying neuronal pathology.
The current gold standard diagnosis of ILO depends upon direct visualisation of the laryngeal vestibule, reporting the location of obstruction (i.e. supraglottic, glottic or both), the phase of the respiratory cycle during which the obstruction is present, the onset and resolution. Laryngeal obstruction can occur spontaneously or in response to exposuresreported by patients that induce symptoms.
No standard challenge test has been established to assess ILO, and very little is known about which irritant challenge agents are most likely to reproduce symptoms. Based upon our knowledge of cough challenge methodology, airway innervation and protective airway reflexes we aim to investigate inhalational challenges in ILO, with a view todeveloping a standard challenge test.
In a novel model of upper airway innervation (ex-vivo, guinea pig) it has been demonstrated that the sensory innervation of the upper airway (pharynx/larynx above the vocal cords) differs from that of the lower airway, exhibiting the greatest responses to transient receptor potential ankyrin 1 (TRPA1) agonists acrolein (a simple aldehyde found in cigarette smoke) and citric acid (CA).
The TRPA1 receptor is likely responsible for mediating responses to the aldehydes found in scents and other chemical irritants described by ILO patients. In contrast, the lower airways show the greatest sensitivity to the TRPV1 (vanilloid 1) agonist capsaicin, the pungent extract of chilli peppers, used for evoking cough. Acrolein is carcinogenic, and therefore cannot be used as a clinical challenge agent, but CA is in use as a cough challenge agent and therefore we hypothesise the most appropriate agent for investigating upper airway reflex responses to chemical stimuli.

Based on our hypothesis we make the following predictions:
Compared with control agent, CA will evoke inducible laryngeal obstruction in ILO patients and evoke upper airway sensations in ILO and ICC patients but not in healthy volunteers.

Ethics approval required
Ethics approval required

Ethics approval(s)

approved 10/04/2019, North West - Haydock Research Ethics Committee (4 Minshull Street, Manchester, M1 3DZ, United Kingdom; +44 (0)2071048012; nrescommittee.northwest-haydock@nhs.net), ref: 19/NW/0067

We plan to submit the study for ethical approval via the IRAS system in July 2018

Study design
Double-blind randomised crossover interventional study

Primary study design
Interventional

Study type(s)
Screening

Health condition(s) or problem(s) studied
Chronic idiopathic cough and inducible laryngeal obstruction (ILO)

Interventions
On the first two visits, participants will be asked to complete a standard cough challenge (where an increasing amount of challenge solution is inhaled through a mouth piece) at the same time as having a laryngoscopy (a small flexible tube passed through a nostril to rest just above the voice box). Participants will wear two bands around their chest to monitor breathing movements and a microphone to record sounds. The challenge agent given on each visit will be determined by randomisation and the person doing the test and the participant will not know which is being administered. Before and after the challenge simple breathing tests and questionnaires will be completed. After each dose challenge questions will be asked about throat and breathing symptoms. On the final visit some questionnaires and a simple breathing test will be performed. This is a crossover study, so the participants will be randomised to either a citric acid cough challenge or placebo challenge and will then have the other intervention on the next visit.

The influences of gender and age on the ILO threshold will be assessed as will correlations with sensations evoked by the challenge, ILO symptoms (VCDQ), cough responses and flow volume loop changes. Comparisons will also be made between the subject groups for the different sensations experienced during the challenge, the coughing evoked and parameters extracted from the video and acoustic recordings using Linear Mixed Effects models. Correlations between the sensations will be analysed using within-subject Bland Altman analyses.

The level of citric acid evoking laryngeal obstruction in the ILO subjects is determined by the speech and language therapist who is viewing the larynx via the laryngoscope throughout testing. Laryngeal narrowing measures will be calculated at the glottic and supraglottic aperture. Image stills will be taken from the continuous recording, at end inspiration and end expiration. Breathing cycle will be verified by corresponding pneumotachograph flow data. An expiratory narrowing ratio will be calculated for the glottic (distance between vocal folds at the midpoint of their length, the glottic narrowing ratio) and supraglottic apertures (distance between the medial margin of the arytaenoid cartilage, supraglottic narrowing ratio) as equal to 1-aperture measurements at end expiration divided by the width at end inspiration; whereby a narrowing ratio of 1=complete narrowing and 0=no change. This ratio provides a measure of the narrowing of the laryngeal structures in relative terms during one breathing cycle, which is independent of the distance between the laryngoscope and the glottis. Images will be taken

from a 10 second breath sequence considered representative of the last inhalation dose and free of artefact (e.g., coughing). Narrowing scores will be determined as the mean of scores reported independently by two observers, blinded to subject characteristics.

Intervention Type
Other

Primary outcome(s)
The level of citric acid evoking laryngeal obstruction in the ILO subjects, as determined by the speech and language therapist who is viewing the larynx via the laryngoscope throughout testing

Key secondary outcome(s))
1. Spirometry performed pre and post inhalation and flow volume loops
2. Sensation: the following will be recorded on a 100 mm visual analogue scale after each inhalation challenge:
2.1. Intensity of sense of taste
2.2. Intensity of symptoms in throat/upper chest
2.3. Intensity of something in throat unable to clear
2.4. Intensity of breathing difficulty
3. Objective cough monitoring measured throughout the inhalation challenge. Measurements will be recorded specifically 10 seconds after each incremental dose
4. The VCDQ (acute) questionnaire and the Leicester Cough Questionnaire (acute) will be administered post inhalation challenge

Completion date
01/05/2025

Eligibility

Key inclusion criteria
All participants:
1. Aged >18 years
2. Non-smoker for at least 6 months
3. No evidence of active asthma

Healthy volunteers:
4. In good general health with no clinically relevant abnormalities based on the medical history, physical examination, vital signs
5. Aged >45 years to broadly age-match to patient groups
6. No history of current or significant past respiratory disease, specifically a previous diagnosis of asthma

ILO patients:
7. An established diagnosis of ILO based on clinical evaluation AND visualisation of laryngeal obstruction during a symptomatic episode

Chronic cough patients:
8. Refractory/idiopathic chronic cough as defined by BTS guidelines (i.e. normal radiology, no airflow obstruction on spirometry and have asthma, gastro-oesophageal reflux disease and nasal disease excluded based on symptoms/investigations and trials of treatment where appropriate)

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Current and ex-smokers with cumulative history of >20 pack years
2. FEV1/FVC <70%
3. Fractional exhaled nitric oxide >50 ppb
4. Eosinophilia blood count >0.45
5. Expiratory airflow obstruction on flow volume loop
6. Pregnant or breastfeeding
7. Upper or lower respiratory tract infection within last 4 weeks or recent significant change in pulmonary status within 4 weeks of study visit
8. Have received any medications likely to modulate cough or upper airway symptoms (e.g. ACE inhibitors, opioids, gabapentin etc.) within 2 weeks of study visit. Patients can be included if they are willing/able to discontinue these for the duration of the study
9. Have received any non-pharmacological therapy interventions for ILO, ICC or upper airway symptoms (e.g. muscle tension dysphonia, globus pharyngeus)
10. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or may interfere with the interpretation of trial results and, in the judgement of the Investigator or Sponsor, would make the subject inappropriate for entry into this trial.

Date of first enrolment
01/09/2018

Date of final enrolment
31/10/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

Manchester Clinical Research Facility
Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

Sponsor information

Organisation
Manchester NHS Foundation Trust, Wythenshawe Hospital

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
North West Lung Research Centre

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	22/01/2019	23/11/2020	Yes	No