Protocol for a double-blind crossover randomised controlled trial to investigate inhalation challenge to assess inducible laryngeal obstruction: CH-ILO

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Shareable abstract (@ERSpublications)
Current ILO diagnosis is dependent on an individual being symptomatic. If results prove citric acid inhalation challenge agent provokes ILO it will provide new insights into neuronal mechanisms and support development of a standardised diagnostic test. https://bit.ly/4hjdsLc

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Abstract

Introduction Inducible laryngeal obstruction (ILO) remains a poorly understood condition in part due to lack of understanding about the underlying neuronal mechanisms. Many suffer delayed confirmed diagnosis as no standardised assessment exists. Based on previous work, we propose citric acid (CA) is the most appropriate inhalation agent for inducing upper airway reflex responses, with a view to developing an inhalation challenge test for ILO.

Methods and analysis This is a single-centre, double-blind crossover study. The primary objective is to identify if CA inhalation challenge provokes laryngeal obstruction in patients with confirmed ILO. We will recruit 10 participants with ILO, 10 with refractory chronic cough (RCC) and 10 healthy controls. Each participant will undergo two inhalation challenges during laryngoscopy, with ascending concentrations of CA or saline control; they will be randomised sequentially by a computer-generated schedule to determine order of delivery. Follow-up is a telephone consultation. Randomisation and preparation of challenge agents will be by an unblinded study team member not involved in data analysis. Challenge agents will only be unblinded on study completion. Log_{10} concentration of CA evoking ILO will be compared between patient groups using a one-way ANOVA, comparing participants with ILO and participants with RCC to healthy controls.

Conclusion This will be the first randomised controlled trial to investigate the role of inhalation challenge as an assessment tool to evoke laryngeal obstruction in patients with confirmed ILO. If results prove CA inhalation challenge agent provokes ILO, it will provide new insights into neuronal mechanisms and support development of a standardised diagnostic test.

Introduction

Rationale

Inducible laryngeal dysfunction (ILO) is a poorly understood condition, despite being associated with high levels of patient morbidity and healthcare use [1]. Individuals typically present with acute breathlessness as the laryngeal aperture inappropriately narrows causing airway obstruction, often in the presence of an "inducer" or triggering factor [2, 3]. Many suffer delayed accurate ILO diagnosis [4], which results in

persistent respiratory symptoms and can lead to inappropriate pharmacological burden from harmful overtreatment, including oral corticosteroid use [5]. A key contributing factor is the lack of a standardised, reproducible, diagnostic ILO assessment tool.

Current diagnostic methods are heterogeneous and include laryngoscopy, dynamic volume computerised tomography and spirometry (with flow volume loops) [6, 7]; laryngoscopy, during a symptomatic ILO episode, is the current clinical gold standard [2]. However, no approach is scientifically proven as an inducer and capture of symptoms, explaining why some individuals can be given a false negative assessment outcome if symptoms were absent during consultation.

In an attempt to unify diagnostic definition and approaches, Leong *et al.* [8] conducted a two-round modified Delphi to obtain consensus on how expert international clinicians recognise and diagnose ILO. The panel identified laryngoscopy with provocation as the gold standard for diagnosis, with the most informative time to perform the test during a clinical attack to support diagnostic yield. However, the experts specifically noted that, "the diagnostic challenge is to confirm abnormal laryngeal movement outside an acute clinical attack" and that "because laryngeal movements may be only transiently abnormal, diagnostic tests may need to be repeated, or provocation employed". Further panel exploration of provocation strategies could not be standardised and the lack of a uniformed approach is likely underpinned by poor understanding of the mechanistic pathways relating to ILO. Therefore, this provides rationale for this study to investigate a standardised, reproducible, assessment to induce ILO.

Hypothesis

Individuals with ILO often describe chemical irritants as the inducer to symptom onset [9]. This is also a typical feature in patients presenting with refractory chronic cough (RCC) and is consistent with the ion channels and receptors expressed by sensory vagal fibres capable of triggering the cough reflex. However, compared with RCC, much less is known about the neuronal mechanisms underlying ILO or why such individuals 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 folds. It is activated by mechanical and chemical stimulation of vagal afferents in the pharyngeal and laryngeal mucosa (*i.e.* at the level above the vocal folds). These vagal afferents synapse in the nucleus tractus solitarius of the brainstem, *via* the nucleus ambiguous and recurrent laryngeal nerves, to produce discrete bilateral contraction of the thyroarytenoid muscles. It is therefore plausible to hypothesise that ILO is a consequence of hyperexcitability of these reflex pathways resulting in inappropriate triggering of the LAR by trivial exposures to mechanical or chemical stimuli.

Clinically the LAR has been assessed using air puffs to the larynx [10]; however, this mechanical stimulus may not optimally assess the chemical sensitivities described by patients with ILO and thus potential underlying neuronal pathology. Data from a pre-clinical model (Professor Belvisi's group, unpublished) suggested that citric acid (CA), which is in use as a cough challenge agent, is the most appropriate agent for investigating and inducing upper airway reflex responses to chemical stimuli. CA is known to activate both chemically and mechanically sensitive vagal afferent nerve fibres innervating the upper and lower airways [11]. This activation is mediated by ion channels and G-protein coupled receptors capable of responding to chemical irritant and thermal stimuli implicated in the triggering of ILO. It is however still possible that different phenotypes of ILO may exist, and only subgroups of patients might be responsive to this challenge.

Methods and analysis

This protocol is written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [12, 13].

Objectives

Primary objectives

The primary objective of this trial is to identify if CA inhalation challenge agent provokes laryngeal obstruction in patients with confirmed ILO. Further, it aims to assess laryngeal obstruction during inhalation of CA compared with osmolarity-compensated solutions (control) in patients with ILO compared with healthy individuals and patients with RCC.

Secondary objectives

Secondary objectives include to assess sensations, coughing and changes in inspiratory and expiratory flow volume loops, evoked by inhaled CA in patients with ILO compared with healthy controls and RCC

patients. Additional objectives include to correlate CA challenge responses to ILO symptoms and compare cough and ILO thresholds in each participant group.

Study design

This is a single-centre, double-blind crossover study (figure 1), sponsored by Manchester University NHS Foundation Trust (Research.Sponsor@mft.nhs.uk).

Recruitment and informed consent

Patient participants will be recruited from the tertiary referral one-stop complex breathlessness clinic and tertiary referral cough clinics held at the North-West Lung Centre, Manchester University NHS Foundation Trust. Potential patient participants will be provided with verbal and written explanation of the study during clinic visits. This will be followed by a telephone conversation, a minimum of 24 h later, to establish interest and answer any questions before booking the first visit.

Healthy volunteers will be approached *via* internal adverts utilising the hospital and University staff bulletins. Healthy volunteers who have previously taken part in research and agreed to be approached about future studies will be contacted by letter. Potential participants who are interested in taking part will be provided with a participant information sheet and given adequate time to consider before being contacted by telephone and booked in for visit 1.

The inclusion and exclusion criteria are listed in table 1. Patient participants with a known overlap of an ILO and RCC diagnosis, or who have symptoms induced primarily by exercise, will be excluded. All potential participants will be provided with a full explanation of the study at the beginning of the first visit and will be given the opportunity to ask questions before providing written consent. Informed consent will be obtained by a trained member of the research team in accordance with good clinical practice criteria.

Study visits

Participants will be asked to attend the Manchester University NHS Foundation Trust clinical research facility ward for two study visits, 4–7 days apart. Study visits one and two will be identical except for which challenge agent is administered. Study visit 3, 7–14 days after study visit 2, will be a telephone consultation. The participant visit schedule is detailed in table 2.

During study visits one and two, participants will inhale either doubling concentrations of CA (0.03–4 M) or osmolarity-compensated solution (isotonic, pH buffered saline) from a dosimeter whilst the laryngeal vestibule is visualised using a laryngoscope, mounted on a headset and video-recorded throughout the procedure (figure 2). A cough monitor (VitaloJAK, Vitalograph, UK) will be attached to the participant throughout for later verification of the number of coughs evoked, and spirometry performed pre and post inhalation challenge to check for bronchoconstriction.

Laryngoscopy will be performed by an expert endoscopist, without the use of topical anaesthesia, to ensure airway sensations are not suppressed during the inhalation challenge. A flexible laryngoscope will be passed transnasally to the hypopharynx to facilitate a view of the laryngeal vestibule. Once a suitable

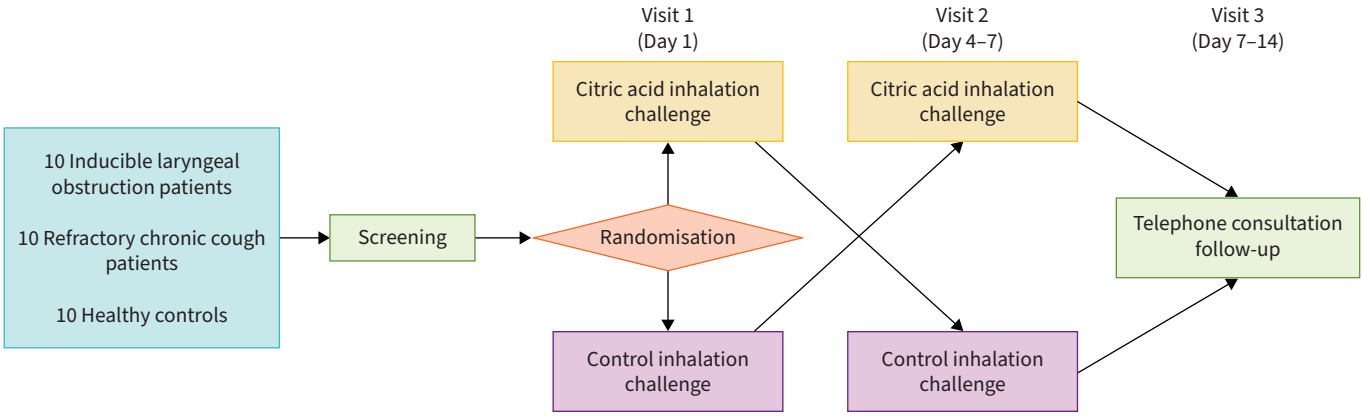

FIGURE 1 Inhalation challenge to assess inducible laryngeal obstruction (CH-ILO) study design.

TABLE 1 Inclusion and exclusion criteria for inhalation challenge to assess inducible laryngeal obstruction (CH-ILO)

Inclusion criteria – patients who meet all the following criteria will be included:
• Male or female >18 years of age
• Nonsmoker for at least 6 months
• No evidence of active asthma airway inflammation or obstruction (defined as fractional exhaled nitric oxide <50 ppb, FEV_1/FVC >70%)
Participants with inducible laryngeal obstruction
• An established diagnosis of ILO based on 1) clinical evaluation AND 2) visualisation of laryngeal obstruction during a symptomatic episode
Participants with refractory chronic cough
• Have RCC as defined by British Thoracic Society guidelines [14] (*i.e.* normal radiology, no airflow obstruction on spirometry and with asthma, gastro-oesophageal reflux disease and nasal disease excluded based on symptoms/investigations and trials of treatment where appropriate)
Healthy volunteers
• Be in good general health with no clinically relevant abnormalities based on medical history, physical examination, vital signs
• >45 years of age to broadly match patient groups
• No history of current or significant past respiratory disease, specifically a previous diagnosis of asthma
Exclusion criteria – patients are NOT eligible for the study if they meet any of the following criteria:
• Current smokers and ex-smokers with cumulative history of >20 pack-years
• FEV_1/FVC <70%
• Fractional exhaled nitric oxide >50 ppb
• Expiratory airflow obstruction on flow volume loop
• Pregnant or breastfeeding
• Upper or lower respiratory chest infection within last 4 weeks or recent significant change in pulmonary status within 4 weeks of study visit
• Have received any medication likely to modulate cough or upper airway symptoms (*e.g.* ACE inhibitors, opioids, gabapentin) within 2 weeks of study visits. Participants can be included if they are wiling/able to discontinue these for the duration of the study
• Have received any non-pharmacological therapy interventions for ILO, RCC or upper airway symptoms (*e.g.* muscle tension dysphonia, globus pharyngeus)
• Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase risk associated with trial participation or may interfere with the interpretation of trial results and, in the judgement of the study team or sponsor, would make the participant inappropriate for entry into this trial

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; RCC: refractory chronic cough; ACE: angiotensin-converting enzyme.

view is obtained, the laryngoscope will be attached to a headset, worn by the participant, to ensure image consistency throughout the inhalation challenge. Prior to the inhalation challenge, a baseline laryngeal assessment will be made, in accordance with local protocol. The images will be video-recorded throughout baseline assessment and inhalation challenge.

Participants will be randomised to receive either a CA or a control inhalation challenge, as described in the randomisation section of this protocol. The inhalation challenge will be performed according to local standard operating procedures using doses of CA from 0.03 M to 4.0 M (made from serial dilution of CA sterile inhalation stock solution 4 M in a 5-mL vial; Stockport Pharmaceuticals Ltd, Stockport, UK) or an identical number of doses of osmolarity-compensated saline solution. Participants will be asked to take single inhalations of doubling concentrations of solution through a flow-regulated air driven nebuliser at 1-min intervals.

Doses of CA/saline will be prepared prior to the start of the study. This includes a total of 10 pots; for the CA challenge eight of them will contain increasing doses of CA. In both cases, one placebo dose of saline at the beginning of the challenge will be given to participants in order for them to practice the test (pot 1). The test will then start with an additional blind placebo pot (pot 2), also containing saline. For the CA challenge, the 4 M stock solution will be serially diluted in physiological saline to produce incremental concentrations of 0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2 and 4 M. Fresh dilutions of stock solution will be made on each day of testing. The number of coughs evoked within 15 s of inhalation will be counted and recorded by the technician administering the cough challenge and later verified using the cough monitor.

TABLE 2 Inhalation challenge to assess inducible laryngeal obstruction (CH-ILO) participant visit schedule

Procedure/assessment	Visit 1 Challenge 1 Day 1	Visit 2 Challenge 2 Day 4–7	Visit 3 Telephone Day 7–14
COVID-19 checks	X	X	
Written informed consent	X		
Demographics; medical and medication history	X		
Inclusion/exclusion criteria (including for participants with ILO, triggers and the diagnostic provocation method used)	X	X	
Vital signs	X		
Height and weight	X		
Body mass index	X		
Brief physical examination	X		
Concomitant medications	X	X	
Spirometry (flow volume loops, inspiratory and expiratory, performed before and after challenge)	X	X	
Laryngoscopy	X	X	
Irritant challenge (citric acid/osmolarity-compensated solution)	X	X	
Cough monitoring throughout irritant challenge	X	X	
ILO questionnaire; VCDQ [3]	X	X	
Cough questionnaire; LCQ [15]	X	X	
Upper airway symptoms rating on a 10-point Likert scale for intensity of: 1) sense of taste; 2) symptoms in throat/upper chest; 3) something in throat unable to clear; 4) breathing difficulty	X	X	
Review of adverse events		X	X

VCDQ: Vocal Cord Dysfunction Questionnaire; LCQ: Leicester Cough Questionnaire.

The following will be recorded after each inhalation on a 10-point Likert scale (by verbally scoring between 1 and 10 with 1 being the lowest):

1) intensity of sense of taste change
2) intensity of symptoms in throat/upper chest
3) intensity of something in throat unable to clear
4) intensity of breathing difficulty

The challenge will be stopped either when the participant reaches their maximum tolerated dose and wishes to stop, or when all concentrations of CA (or control doses) have been inhaled or when consistent laryngeal obstruction is induced. Inhalation challenges stopped due to consistent laryngeal obstruction will be based on operator interpretation (*i.e.* >50% laryngeal closure on inspiration over five respiratory breaths).

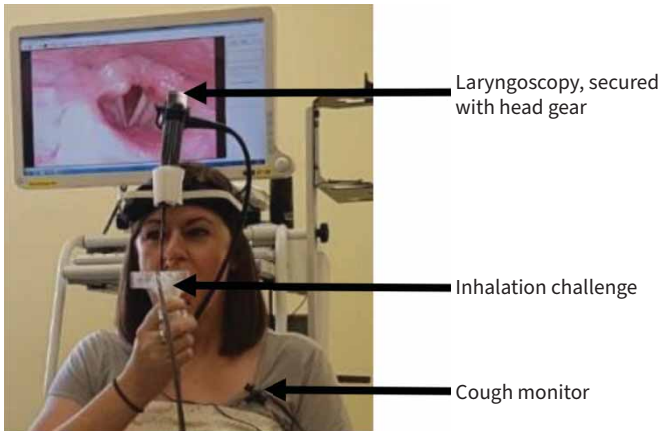

FIGURE 2 Laryngoscopy inhalation challenge.

Laryngeal movement will be rated retrospectively from the video-recorded images by an expert clinician with significant experience in interpreting laryngoscopy examinations. Diagnosis of ILO will be in line with the International Delphi Consensus Study [8] and defined as >50% laryngeal closure on inspiration during laryngoscopy with provocation. To assess inter-rater reliability, a 10% sample of laryngoscopy video-recorded images will be re-rated by a second observer.

Randomisation

Participants will be randomised sequentially to a group to determine the order in which active challenge agent and control challenge agent are given (*i.e.* CA followed by control or control followed by CA), according to a computer-generated schedule. Randomisation and preparation of the challenge agents will be performed by an unblinded member of the study team who will provide a set of blinded challenge agent doses to the remaining study team without disclosing the nature of the challenge to either the study team or study participant. The randomising individual will not perform the laryngoscopy and will not collect or analyse participant data or evaluate study end-points. The challenge agents will only be unblinded once the study is completed including evaluation of the laryngeal video recordings.

Statistical plan

Sample size

We will recruit and analyse complete data sets from 10 participants with ILO, 10 healthy volunteers and 10 RCC patients. There are no data available that describe experimentally induced ILO upon which to base a formal power calculation. Therefore, the sample size is based upon our previous experience of using CA challenge to detect differences in cough threshold between patient groups and healthy controls [16]. With 10 subjects per group, the study will have 80% power to detect differences of ±0.4 log doubling concentration for C5 (*i.e.* concentration evoking at least five coughs) between study groups, assuming a between subject standard deviation of 0.3 for logC5 and the standard level of significance of p=0.05.

Data analysis

Log_{10} concentration of CA evoking ILO will be compared between patient groups using one-way ANOVA, comparing participants with ILO and participants with RCC to healthy controls. The influences of sex and age on the ILO threshold will be assessed as will correlations with sensations evoked by the challenge, ILO symptoms, cough responses and flow volume loop changes. Secondary analysis, using linear mixed effects models, will include comparisons between subject groups for the different sensations experienced during the challenge, the coughing evoked and parameters extracted from the video and acoustic recordings. Correlations between sensations will be analysed using within-subject Bland–Altman analysis.

Patient and public involvement

The development of this work was informed by patient feedback about the need for effective ILO assessment. The study protocol was presented to a patient and carer support forum for feedback on acceptability and patient resources. The group were very supportive of the work; specifically, the proposed study protocol was seen as acceptable with regards to study visits and procedures. On conclusion of the study, findings will be disseminated across existing national patient support group networks.

Timelines and trial status

The study opened to recruitment in July 2019 but was suspended in January 2020 due to the COVID-19 pandemic. A substantial amendment to the original study protocol was submitted to the ethics committee and sponsor in November 2021 to minimise the impact of the pandemic on the study. The amendment requests included changing the study from a multi-site (Royal Brompton Hospital and Manchester University NHS Foundation Trust) to a single site centre (Manchester University NHS Foundation Trust), reducing the target recruitment from 60 participants to 30 (10 participants with ILO, 10 healthy volunteers and 10 participants with RCC) and extending the study end date. Amendments did not significantly alter research design or methodology and were given approval for implementation in January 2022. Subsequent issues with the supply of challenge agents delayed study activity further. The study re-opened to recruitment in August 2023, and the study completion date is expected for January 2025.

Monitoring

The study team is responsible for detecting, documenting and reporting events that meet the definition of an adverse event (AE) or serious adverse event (SAE). Both AEs and SAEs will be collected from the start of visit 1 until follow-up contact in visit 3. Any SAE events will be recorded and reported to the study sponsor, Manchester University NHS Foundation Trust, within 24 h. The study will be subject to the audit and monitoring regime of the study sponsor in line with applicable standing operating procedures and policy.

Data management and confidentiality

All participants enrolled in this study will be allocated a unique pseudonymised identifying code to be used throughout the study on all documentation, audio and video recordings. The results of the cough monitoring and laryngoscopy video files will be stored on a secure electronic database, with limited access and password entry. Paper-based data (case report forms, questionnaires, screening log, enrolment log, participant ID log with pseudonymisation key) will be stored in a locked keypad entry office at Manchester University NHS Foundation Trust, and only the study team will have access to this.

All personal data collected during the study will be handled in accordance with the NHS code of practice for confidential patient information. Objective cough monitoring involves audio recordings to identify coughing. Participants will wear a small recording device (cough monitor) which captures cough sounds through a free-field microphone and records them in a digital format. The monitor will record all conversations during the visit which will be explained to participants at the point of enrolment. Any conversation recorded in this manner will be treated with strict confidentiality, and only the direct study team involved in data analysis will have access to it. The recording is listened to by a trained member of staff to verify the number of coughs recorded during the challenge.

Withdrawal of participants

Participation in the trial is voluntary. Participants may decide to withdraw early from the study, or the research team may feel that it is in the best interests of the participant to terminate their involvement in the study prior to completion for safety reasons. Participants who wish to withdraw their consent do not have to give a reason to do so. Early withdrawal will be clearly documented in the case report form and the hospital case notes in patient participants.

Ethics and dissemination

A favourable ethical opinion for this study has been received from the Northwest Haydock Research Ethics Committee, UK (reference 19/NW/0067, 10 April 2019). The study is registered on the ISRCTN public clinical trial registry (ISRCTN17381278).

A lay summary of study findings will be generated in a study newsletter and disseminated to study participants. Dissemination to the medical and scientific community will be through peer reviewed publications, presentations at national and international conferences and social media. All documentation in relation to the study will be archived in accordance with the most recent version of the Manchester University NHS Foundation Trust standard operating procedure for document storage.

Conclusion

This study is the first to investigate the role of inhalation challenge as a standardised assessment tool for ILO. Results will provide insight into the neuronal mechanisms underlying ILO (and the relationship between overlapping laryngeal dysfunction symptoms such as RCC) and improve understanding about the use of irritant challenge agents to reproduce ILO symptoms. If results demonstrate a positive signal that CA is an effective inhalation challenge agent to provoke laryngeal obstruction in patients with confirmed ILO, it will provide significant scientific advances in the field. This will be beneficial for the research community and have longer-term positive implications for clinical practice.

Provenance: Submitted article, peer reviewed.

Data availability: Data arising from this study will not be shared externally or after the study has ended. This is a novel study, and therefore it is important that the results and primary outcomes are reported in peer reviewed journals and conference papers. The study forms part of doctoral studies so will also be reported in a thesis submission. This reporting is for the benefit of the respiratory research community. All reported data in this sense will be completely anonymous and participants will be made aware of this.

This clinical trial is prospectively registered with ISRCTN Registry (ISRCTN) as ISRCTN 17381278.

Ethics statement: Ethical approval to conduct the study has been granted (UK Northwest Haydock Research Ethics Committee, reference 19/NW/0067). Participation is voluntary and patients can withdraw from the study at any time.

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Conflict of interest: The authors have nothing to disclose.

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