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An investigation of cough responses to a variety of inhaled irritants in order to compare the mechanisms underlying cough in health and disease

Submission date
14/09/2015

Recruitment status
No longer recruiting

Registration date
08/01/2016

Overall study status
Completed

Last Edited
27/01/2025

Condition category
Respiratory

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

Plain English summary of protocol

Background and study aims
The autonomic nervous system (ANS) is the part of the nervous system which controls automatic bodily functions. One of these is the cough reflex, a protective response which is used to clear the airways of irritating material or phlegm. Long-term persistent cough (chronic cough) is one of the most common health complaints for which people seek medical advice. Chronic cough is a common feature of a range of different conditions that affect the lungs and airways (respiratory disease). There are a number of different cough medicines on the market, but they do not always work. A possible explanation for this is that the reason that chronic cough develops is only partially understood. It is thought that in many causes, a cough is caused by irritants (substances which irritate the airways), triggering the reflex to expel them from the lungs. This study will look at a range of common respiratory diseases, as well as healthy people, in order to investigate the triggers of coughing. The study will look at the long-term respiratory diseases chronic obstructive pulmonary disease (a condition where the airways become narrowed or blocked), idiopathic pulmonary fibrosis (a condition where scar tissue grows inside the lungs, preventing them from expanding fully) and asthma (where the airways are particularly sensitive and become narrowed or swollen).

Who can participate?
Adults who are either healthy or suffer from respiratory disease (asthma, chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF)).

What does the study involve?
Participants are split into groups based on their condition, and are asked to attend 6 study visits. In the first visit, participants have their general health and breathing (lung function) is measured, as well as completing a number of questionnaires to find out how serious their cough is. The participants are then asked to breathe in an irritant (substances intended to irritate the airways, making them cough) and their response is recorded (cough challenge). At the second study visit, the participants have a brief physical examination and then repeat the cough challenge with a

different irritant. The cough challenge is then repeated on visits 3, 4 and 5. In the sixth study visit, participants are interviewed in order to find out if there has been any change to their health since the previous study visit. If participants are unable to attend this visit, then they can be interviewed over the telephone.

What are the possible benefits and risks of participating?
There are no direct benefits of taking part in the study, although the results could help to improve treatment for future people suffering from chronic cough. There are no significant risks of taking part, however the irritants used in the cough challenge may cause temporary discomfort in participants.

Where is the study run from?
University Hospital of South Manchester (UK)

When is the study starting and how long is it expected to run for?
September 2015 to January 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
1. Dr Jenny King (Public)
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2. Professor Jacky Smith (Scientific)
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Nil known

Study information

Scientific Title
The Role of Transient Receptor Potential (TRP) Channels in the Mechanisms Underlying Cough in Health and Disease

Acronym
oRChiD

Study objectives
Excessive coughing in respiratory diseases occurs as a consequence of differing patterns of airway neuronal dysfunction mediated by altered TRP channel function. Cough responses to inhaled irritants known to activate TRP channels will be differentially modulated in respiratory conditions.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West - Liverpool East Research Ethics Committee, 15/02/2017, ref: 15/NW/0726

Study design
Single-centre cross-sectional study

Primary study design
Interventional

Secondary study design
Cross-sectional study

Study setting(s)
Hospital

Study type(s)
Not Specified

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet.

Health condition(s) or problem(s) studied
Asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) or chronic cough

Interventions
100 participants will be recruited, incuding 20 healthy controls, 20 asthma patients, 20 chronic obstructive pulmonary disease (COPD) patients, 20 idiopathic pulmonary fibrosis (IPF) patients and 20 chronic cough patients.

Each group will be split into 10 males and 10 females. Each participant will visit the department on 5 or 6 occasions (1 visit can be performed over the telephone if the patient prefers). During visit 1, informed consent will be taken, medical history will be noted and study eligibility will be checked. Vital signs and a brief physical examination will be undertaken, and baseline spirometry will be performed. Each participant will be asked to complete a Leicester Cough Questionnaire (LCQ) and visual analogue scale (VAS) to record severity of cough. A cough challenge will then be performed. A different agent at each study visit will be used, in a random order. Increasing concentrations of challenge agent are inhaled through a nebuliser up to the maximum tolerated dose. Four breaths of each concentration are inhaled 30 seconds apart and after each inhalation, the number of coughs provoked is recorded. When the participant can not tolerate the challenge any longer or the maximum concentration is reached, the test is stopped. Spirometry will be performed before and after the cough challenge test as a safety measure for bronchoconstriction, in which case bronchodilator therapy will be administered.

After at least 2 days (but no more than 7 days), visit 2 will take place. A review of medications and changes in medical status will be undertaken. Vital signs and a brief physical examination will be undertaken and each participant will be asked to complete a visual analogue scale (VAS). A cough challenge will then be performed using a different agent to the previous visit.

Visits 3, 4 and 5 occur between 27 days of the previous visit and are identical to visit 2.

Visit 6 will take place at least 2 days but no more than 7 days after visit 5. Patients will be asked to report any changes in health status since their last visit. If the patient prefers, this visit can be carried out over the telephone.

Intervention Type
Not Specified

Primary outcome measure
Maximal cough response (Emax) is measured through inhalation tests at study visits 1, 2, 3, 4 and 5.

Secondary outcome measures
1. Irritant concentration evoking 50% of maximum cough response (ED50) is measured through inhalation tests at study visits 1, 2, 3, 4 and 5
2. Cough severity is measured using visual analogue scale (VAS) at study visits 1, 2, 3, 4 and 5
3. Cough specific quality of life is measured using the Leicester Cough Questionnaire at the first study visit

Overall study start date
01/09/2015

Completion date
07/01/2025

Eligibility

Key inclusion criteria
All participants:
1. Aged 18 years and over

Healthy volunteers:
1. Normal spirometry
2. No current or past history of chronic cough or respiratory disease
3. Non-smokers or ex-smokers (>6months abstinence) with smoking history of ≤ 10 pack years

Asthma:
1. Physician diagnosis of asthma
2. Evidence of airways hyper-responsiveness to methacholine (PC20<16mg/ml) or significant bronchodilator reversibility (>12% FEV1) within the last 2 years.
3. Non-smokers or ex-smoker (>6months abstinence) with a smoking history of ≤ 20 pack years
4. The subjects treated with:
4.1. Short acting Beta 2 Agonist PRN
4.2. AND/OR inhaled corticosteroid (≤250mcg fluticasone propionate daily or equivalent)

COPD
1. Physician diagnosis of COPD
2. Ex-smokers (> 6 months abstinence) with smoking history of ≥ 20 pack years
3. Spirometry demonstrating airflow obstruction i.e. FEV1/FVC ratio <70%

Idiopathic Pulmonary Fibrosis
1. Diagnosis of idiopathic pulmonary fibrosis following review by a Multi-Disciplinary Team (MDT).
2. Non-smokers or ex-smoker (>6months abstinence) with a smoking history of ≤20 pack years
Refractory Chronic Cough
3. History of a dry/minimally productive cough for 12 months
4. Normal spirometry
5. No clinically significant findings to explain chronic cough on CXR or CT scan of thorax
6. Completed appropriate investigation and/or trials of treatment for common causes of chronic cough
7. Non-smokers or ex-smoker (>6months abstinence) with a smoking history of ≤20 pack years

Participant type(s)
All

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
100 (20 in each group)

Total final enrolment
101

Key exclusion criteria
All participants:
1. Ex-smokers with <6 months abstinence
2. Upper respiratory tract infection within last 4 weeks
3. Exacerbation of respiratory disease in the last 4 weeks requiring additional medication.
4. A change in regular medication within the past 4 weeks prior to screening
5. Patients with severe respiratory disease e.g. FEV1 <1 litre, requirement of oxygen therapy
6. Use of ACE inhibitors
7. Use of centrally acting medications that may alter the cough reflex e.g. opiates, gabapentin, pregabalin, amitriptyline (unless they are willing and medically able to withdraw from such medication for the duration of the study and sought advice from their GP or clinician)
8. History of drug or alcohol abuse
9. Pregnancy or breastfeeding
10. Concomitant conditions which may alter cough responses e.g. diabetes mellitus with autonomic neuropathy, Parkinson's disease, stroke.
11. Concomitant conditions which affect the subjects' ability to participate in the study.
12. Uncontrolled hypertension (i.e., >165/95 mmHg despite adequate medical therapy).
13. Allergy or intolerance of salbutamol

Asthma:
1. Subjects treated with high dose inhaled corticosteroid (>250mcg fluticasone propionate daily or equivalent)

Idiopathic Pulmonary Fibrosis
1. High dose systemic steroids i.e. prednisolone >20mg daily or equivalent. Those patients on lower doses of steroids for >1 month may be included
2. Resting blood oxygen saturation of <90 %
3. Concurrent use of pirfenidone, unless receiving a stable dose for at least 4 weeks prior to screening
4. A history of concomitant asthma or obstructive airway disease, or those with an FEV1/FVC ratio at screening of <70%

Date of first enrolment
01/01/2018

Date of final enrolment
07/01/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Respiratory and Allergy Clinical Research Facility
University Hospital of South Manchester
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Sponsor information

Organisation
University Hospital of South Manchester

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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The results will be reported in peer reviewed journals, at conferences and as part of a MSc thesis.

Intention to publish date
06/06/2025

Individual participant data (IPD) sharing plan
Will be available to share following full analysis and publication. Data sharing statement to 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?
HRA research summary			28/06/2023	No	No