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# The Role of ATP in Chronic Cough. Identifying those who may benefit from new anti-cough medications by assessing cough response to ATP and by measuring blood ATP levels

**Submission date**
12/04/2021

**Recruitment status**
Recruiting

**Registration date**
13/04/2021

**Overall study status**
Ongoing

**Last Edited**
15/09/2025

**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
Refractory chronic cough (RCC) is cough that does not respond to treatment. It can have a profound effect on its sufferers' lives, with patients coughing hundreds of times a day without any relief. Previous studies have shown that blocking receptors on airway nerves called P2X3 can dramatically reduce cough. The exact mechanism of this is unknown but these receptors are activated by ATP. This study aims to find out if inhaled hypo-osmolar solutions and ATP shown to promote ATP release in pre clinical studies cause coughing in patients with refractory chronic cough compared to healthy volunteers. It also aims to see if RCC patients have elevated systemic levels of ATP and breakdown products in blood compared to healthy volunteers.

Who can participate?
Samples from people with chronic cough will be compared to samples from health volunteers. Participants can be male or female, and aged 18-80 years. People with no lung disease, except chronic cough in the patient group, and those who have never smoked or ex-smokers who only smoked a little can take part. People on medication which might affect cough such as ACE inhibitors and opiate pain killers, cannot participate, as this may affect the results. People who might have high ATP levels for other reasons, such as people with long-term heart failure or those who exercise and train competitively and those who are pregnant, also cannot take part.

What does the study involve?
The study involves three visits and a telephone follow up.
At visit 1 a researcher will talk through the study again and answer any questions and check that people are eligible to take part in the study. After signing a consent form the researcher will go through the person's past medical history, medication history and measure the person's vital signs (heart rate, blood pressure, saturations, respiratory rate). There will then be a blowing test to make sure the participants lungs work normally.
They will then be asked to indicate the severity of their cough with a line on a 10 point scale known as a visual analogue scale.

The doctor will take a blood sample to measure levels of something called ATP.
The participant will be fitted with a cough monitor to record all sounds (specifically to count coughs) during the cough challenge. This will be removed prior to the end of the visit.
The participant will be asked to wear a nose clip and will be delivered a challenge agent using a nebuliser machine at increasing concentrations. This will be randomised to ATP, hypo-osmolar solution or control (normal saline). The participant will be blinded to the challenge agent used but the researcher will know which agent is being used. The concentration of solution will increase until the participant wants to stop or the maximum concentration is reached. After the challenge the cough monitor will be removed, and the participant will repeat the blowing test. The researcher will then take blood samples from the participant to measure blood ATP and breakdown products at 15 and 30 minutes post-challenge. After this the visit will be over. Visit 2 and visit 3 will follow the same procedures as visit 1 other than no further consent forms need to be completed. They will take place 3-14 days after each other. Each visit will take approximately 1.5 hours.
The final visit can take place on the telephone or in person and is 7-14 days after the end on visit 3. It will take 15-30 minutes and the researcher will ask the participant about any changes in their health since the last visit. After visit 4 the study is over.

What are the possible benefits and risks of participating?
There will be no direct benefit for participants in this study. However, we hope that the results of this study will help us to understand the mechanisms of coughing and improve treatments in the future.
Cough challenge tests which involve inhaling solutions designed to make participants cough. The solutions have been used in research for many years and have been shown to be safe.
The solutions can cause tightening of the airways in some people, although this is rare.
Breathing tests are performed before and after the test to monitor any chest tightening, which is easily treated by inhaling salbutamol (a medication to open up the airways).
A doctor will be present in the department at all times should the participant feel unwell.
Having blood taken can be uncomfortable and may cause a bruise. Participants will be made as comfortable as possible for this procedure and it will be done by somebody who is well skilled in it to minimise any discomfort.

Where is the study run from?
The study is run from the NIHR Clinical Research Facility at Manchester University NHS Foundation Trust (UK)

When is the study starting from and how long is it expecting to run for?
November 2020 to July 2026

Who is funding the study?
The study is funded by a grant from the Wellcome Trust (UK)

Who is the main contact?
Rachel Dockry, cough.research@manchester.ac.uk

# Contact information

### Type(s)
Public, Scientific

### Contact name

Dr Rachel Dockry

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# Additional identifiers

### Clinical Trials Information System (CTIS)
Nil known

### Integrated Research Application System (IRAS)
294664

### ClinicalTrials.gov (NCT)
Nil known

### Protocol serial number
IRAS 294664, WT 207504/B/17/Z

# Study information

### Scientific Title
Effect of inhaled ATP and hypo-osmolar solutions on blood ATP metabolites and cough in refractory chronic cough and healthy volunteers

### Acronym
PHASE

### Study objectives
Current study objectives as of 03/07/2025:
Excessive coughing in refractory chronic cough is due to increased release or reduced breakdown of ATP. By measuring plasma ATP and its breakdown products in a three-way crossover study using inhaled ATP, hypo-osmolar saline and osmolarity-compensated saline, we seek to determine the effects of airway ATP deposition and release on plasma ATP metabolites and cough responses. We hypothesise that these levels will be higher in refractory chronic cough patients than healthy volunteers and that higher levels will be associated with altered airway sensations (“urge-to-cough”), and increased objective cough frequency.

Previous study objectives:
Excessive coughing in refractory chronic cough is due to increased release or reduced breakdown of ATP. By measuring serum ATP and its breakdown products in a three-way crossover study using inhaled ATP, hypo-osmolar saline and osmolarity-compensated saline, we

seek to determine the effects of airway ATP deposition and release on serum ATP metabolites and cough responses. We hypothesise that these levels will be higher in refractory chronic cough patients than healthy volunteers and that higher levels will be associated with altered airway sensations (“urge-to-cough”), and increased objective cough frequency.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
Approved 31/08/2021, North of Scotland Research Ethics Service (Summerfield House, 2 Eday Road, Aberdeen, AB15 6RE, UK; +44 (0)1224 558458; gram.nosres@nhs.scot), ref: 21/NS/0119

## Study design
Single-centre randomized controlled single-blinded three-way crossover study

## Primary study design
Interventional

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
The role of ATP in the mechanism of refractory chronic cough

## Interventions
Subjects with refractory chronic cough and healthy volunteers will be recruited from a single UK centre and undergo inhalational challenges (lasting approximately 40 minutes per challenge) at 2 - 7 day intervals with ATP, hypo-osmolar saline and isotonic saline in a randomised order. Subjects will be randomised to a sequence group defining the order in which cough challenges are to be performed, according to a computer-generated schedule. The randomisation schedule will be produced by a statistician. Patients will be blinded to the nature of each challenge agent but the investigator performing the challenges will not.

## Intervention Type
Other

## Primary outcome(s)
Current primary outcome measures as of 03/07/2025:
1. Cough responses in all subjects measured by Emax and ED50 at each challenge visit
2. Blood ATP levels following inhalational challenges at baseline, 15 minutes, and 30 minutes post-challenge with each challenge agent measured by blood test

Previous primary outcome measures:
1. Cough responses in all subjects measured by Emax and ED50 at each challenge visit
2. Blood ATP levels following inhalational challenges at baseline, 15 minutes, 30 minutes, 45 minutes and 60 minutes with each challenge agent measured by blood test

## Key secondary outcome(s))
Current secondary outcome measures as of 03/07/2025:
1. Blood ATP metabolite levels following inhalational challenges at baseline, 15 minutes, and 30 minutes post-challenge measured by blood test

2. Urge to cough sensations measured by visual analogue scale before and after each inhalational challenge

Previous secondary outcome measures:
1. Blood ATP metabolite levels following inhalational challenges at baseline, 15 minutes, 30 minutes, 45 minutes and 60 minutes measured by blood test
2. Urge to cough sensations measured by visual analogue scale before and after each inhalational challenge

### Completion date
01/07/2026

## Eligibility

### Key inclusion criteria
1. Males and females 18 - 80 years, inclusive
2. Non-smokers; ex-smokers <20 pack years, >6 months abstinence
3. Healthy volunteers:
3.1. No clinically relevant abnormalities based on the medical history, physical examination, vital signs
3.2. No history of current or significant past respiratory disease, specifically a diagnosis of asthma
3.3. Spirometry within normal limits
4. Chronic cough patients:
4.1. Have a refractory chronic cough as defined by BTS/ERS guidelines
4.2. No evidence of asthma during clinical evaluation of chronic cough, e.g. elevated FeNO, bronchodilator reversibility, abnormal methacholine responsiveness

### Participant type(s)
Mixed

### Healthy volunteers allowed
No

### Age group
Adult

### Lower age limit
18 years

### Upper age limit
80 years

### Sex
All

### Key exclusion criteria
1. Any condition that may increase airway/circulating levels of ATP/adenosine, e.g. chronic cardiac failure, chronic hypoxia, and vigorous exercise
2. Pregnancy or breastfeeding
3. Upper or lower respiratory tract infection or significant change in pulmonary status within 4

weeks of enrolment.
4. Any therapy that may modulate cough (e.g. ACE inhibitors, opioids, gabapentin)
5. Patients with asthma

### Date of first enrolment
03/11/2025

### Date of final enrolment
01/06/2026

## Locations

### Countries of recruitment
United Kingdom

England

### Study participating centre
**Manchester University NHS Foundation Trust**
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

## Sponsor information

### Organisation
University of Manchester

### ROR
https://ror.org/027m9bs27

## Funder(s)

### Funder type
Charity

### Funder Name
Wellcome Trust

### Alternative Name(s)

Wellcome, WT

### Funding Body Type
Private sector organisation

### Funding Body Subtype
Trusts, charities, foundations (both public and private)

### Location
United Kingdom

## Results and Publications

### Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be 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 |