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Are ATP levels in the blood and airways higher in people with chronic cough?

Submission date
28/11/2019

Recruitment status
No longer recruiting

Registration date
29/11/2019

Overall study status
Completed

Last Edited
23/01/2026

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
Chronic refractory cough is a cough that does not respond to treatment. This can be extremely disruptive and has a profound effect on sufferers' lives, with patients sometimes coughing hundreds of times a day and unable to get any relief. Previous studies have shown that blocking a certain receptor on the nerves called P2X3 can dramatically reduce the number of times these patients cough. The mechanism behind this is currently unknown. This study aims to investigate whether people with chronic cough have higher levels of ATP, the substance which activates these receptors, in their lungs and their blood.

Who can participate?
Samples from people with chronic cough will be compared to samples from healthy volunteers. Participants can be male or female, with chronic cough patients aged 18-80 years and healthy volunteers aged 45-80 years. People with no lung diseases, except chronic cough in the patient group, and those who have either never smoked or ex-smokers who only smoked a little can take part. People on any medication which might affect cough, such as ACE inhibitors and opiate pain-killers, cannot participate, as this might affect the results. People who might have a high ATP level for other reasons, such as people with long-term heart failure or those who exercise and train competitively, also cannot take part.

What does the study involve?
The study involves three visits. The first visit is a screening visit, to make sure that people are suitable to take part in the study. After signing the consent form, a researcher will ask questions about medical history and any medication which participants may be taking. The participant’s height and weight will be measured, along with their blood pressure, heart-rate and oxygen levels. A doctor will perform a physical examination, which involves them listening to the participant’s chest with a stethoscope. There will be a blowing test to make sure that the participant’s lungs are normal, a blood sample will be taken and some questionnaires about cough to complete. When the research team are happy that the participant is suitable to be included in the study, the participant will be fitted with a cough monitor. This device will record all sounds made by the participant for 24 hours. The recording will then be processed and a researcher will count the number of coughs.
Following the cough recording, the participant will return to the hospital for a second visit to

have a bronchoscopy. This is a test where a long, thin camera is inserted into the nose and down into the lungs. Patients who are already having this procedure done as part of their normal clinical care will be asked to participate in this study. Healthy volunteers would not normally have this test done. While the camera is in the lungs, samples will be taken for the study. These include bronchoalveolar lavage fluid (BALF) (where salt water is squirted into the lungs and sucked back out), brushings (where the airways are brushed to remove some cells) and biopsies (where small pieces of tissue from the airway are taken and pulled out when the camera is removed). Some people prefer to be sedated for this procedure as it can be uncomfortable. If this is the case, a cannula (tube) will be inserted into a vein in the participant's arm for the sedative medication to be given through. Throughout the procedure, heart-rate and oxygen levels will be monitored. After the bronchoscopy, the participant will be monitored in the hospital until the doctor says that they have recovered enough to go home. The day after, a member of the research team will call to make sure that the participant is fully recovered and is well.
One to two weeks after the bronchoscopy, the participant will come back to the hospital for a follow-up visit. Any side effects from the bronchoscopy will be recorded and their blood pressure, heart-rate and oxygen levels measured. They will also be asked to perform another lung function test.

What are the possible benefits and risks of participating?
There are several risks associated with having a bronchoscopy. These include side effects of the sedative, low oxygen and a collapsed lung, although all of these are very rare. There is a risk of fever following a bronchoscopy, which may be increased by taking a BALF sample. This fever usually occurs around 8 hours after the procedure and gets better on its own. There is a slightly increased risk of bleeding in the airway if biopsies are taken. This bleeding is usually mild and does not require any treatment.
Taking part in this study will not benefit any participant directly. However, the researchers hope that the results of this study will help them to understand more about chronic cough and improve treatments in the future.

Where is the study run from?
The North West Lung Research Centre, Wythenshawe Hospital (UK)

When is the study starting and how long is it expected to run for?
October 2017 to January 2026

Who is funding the study?
The Wellcome Trust (UK)

Who is the main contact?
James Wingfield Digby, james.digby@mft.nhs.uk
(updated 14/04/2021, previously: Dr Rachel Dockry, cough.research@manchester.ac.uk)

Contact information

Type(s)
Public

Contact name
Mr James Wingfield Digby

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
260074

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
ANT001, Wellcome Trust grant: 207504

Study information

Scientific Title
ATP in the Airways and Plasma in Chronic Cough

Acronym
ANTHEM

Study objectives
We hypothesise that ATP plays an important role in chronic idiopathic cough, and therefore ATP levels in blood and bronchoscopy samples will be higher in chronic cough patients than healthy volunteers.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 06/12/2021, Dulwich REC (Skipton House, 80 London Road, London, SE1 6LH, United Kingdom; +44 2071048094; dulwich.rec@hra.nhs.uk), ref: 21/PR/1233

Study design
Single-centre observational case-control study

Primary study design

Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Chronic cough

Interventions
Current interventions as of 14/04/2021:

Participants will undergo safety screening, including the recording of medical history; measurement of blood pressure, heart-rate and oxygen saturation; and lung function testing (spirometry). Blood samples will be taken, and the subject will be fitted with a 24-h ambulatory cough monitor. The monitor will record all sounds made by the subject for a full 24-h period. This data will be analysed, and any coughs counted. Following the end of the recording period, the subject will have a bronchoscopy, where research samples (bronchial lavage fluid and biopsies) will be taken. 1-2 weeks following the bronchoscopy, the participant will attend a follow-up visit where their blood pressure, heart-rate and oxygen saturation will be measured, along with their lung function.

Visit 1
Subjects will be invited to attend the screening visit 24-48 hours prior to their bronchoscopy appointment. After consenting to participate, the subject will have their height and weight recorded and BMI calculated. Blood pressure, heart rate, pulse oximetry and respiratory rate will be measured and recorded. The doctor will perform a physical examination. The subject will be asked to perform spirometry. Subject eligibility will be confirmed. 10 participants with chronic cough and 10 healthy volunteers will be asked to do an additional breathing procedure, used a device and a measuring particles in exhaled air (PeXA)

Upon confirmation of eligibility, a blood sample (maximum volume 25 ml) will be taken. Some of this sample will be sent to the local pathology lab to be analysed for safety prior to bronchoscopy (full blood count, urea and electrolytes and clotting time) and some will be processed according to local SOPs so that the blood can be frozen and stored for ATP analysis.

Participants will be fitted with a VitaloJAK ambulatory cough monitor. The device will be worn for 24 h, recording all sound via 2 microphones, one attached to the subject's chest wall and one attached to the subject's clothing. The device will automatically stop recording when the 24 h has passed. Subjects will be made aware that all sound, including speech will be recorded. They will also be informed that the device cannot get wet and therefore they will be unable to shower while wearing it. Participants will also be asked to complete the Leicester Cough Questionnaire. The subject will be provided with a visual analogue score (VAS). This is a 100-mm line on which they can rate the severity of their cough during the day and night while wearing the monitor by placing a vertical mark on the line, where 0 mm is no cough and 100 mm is the most severe cough ever experienced.

Visit 2
This will take place 24-48 h following visit 1. Subjects will be asked to fast for a minimum of 4 h prior to their bronchoscopy visit. They will be informed that if they choose to be sedated they will be unable to drive for 24 h following the procedure, and therefore a taxi can be arranged for them to attend this appointment. The subject will also be informed that they will need to have

someone at home to stay with them overnight following the procedure, which is standard practice following a clinical bronchoscopy. They will also be unable to look after children due to the effects of the sedative for 24 h following the procedure. Upon arrival at the bronchoscopy unit, consent will be reaffirmed by a member of the research team and the study inclusion /exclusion criteria will be checked. The researcher will collect the cough monitors and questionnaires from the chronic cough patients.

The subject will have a cannula put in place in their arm/hand, through which the sedative will be given. This will also be used to draw 20 ml of blood which will be processed and stored for ATP measurements.

The bronchoscopy will be performed by a trained and experienced clinician as described in the British Thoracic Society guidelines. An extra 2 x BALF sample and biopsies will be taken, for research purposes. Upon completion of the bronchoscopy, the subject will be allowed to rest. When they are fully recovered, they will be either picked up by a family member or friend, or accompanied home in a taxi. The research team will ensure that there is someone at home and that the subject will not be alone upon their discharge from the unit.

A follow-up telephone call will be made 24-48 h after the bronchoscopy to record any AEs and to check that the subject has recovered from the procedure.

Visit 3
Subjects will return 1-2 weeks after visit 2 for a follow-up visit. Chronic cough patients may be followed up during outpatient visits if more convenient. At this visit consent will be reaffirmed and the subject will be queried about any AEs following the bronchoscopy which have not already been reported. The subject's blood pressure, heart rate, pulse oximetry and respiratory rate will be recorded. The subject will be asked to perform a repeat spirometry measurement. At the end of this visit the study is complete.

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Previous interventions:

Participants will undergo safety screening, including the recording of medical history; measurement of blood pressure, heart-rate and oxygen saturation; and lung function testing (spirometry). Blood samples will be taken and the subject will be fitted with a 24-h ambulatory cough monitor. The monitor will record all sounds made by the subject for a full 24-h period. This data will be analysed and any coughs counted. Following the end of the recording period, the subject will have a bronchoscopy, where research samples (bronchial lavage fluid, epithelial brushings and biopsies) will be taken. 1-2 weeks following the bronchoscopy, the participant will attend a follow-up visit where their blood pressure, heart-rate and oxygen saturation will be measured, along with their lung function.

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bronchoscopy (full blood count, urea and electrolytes and clotting time) and some will be processed according to local SOPs so that the plasma can be frozen and stored for ATP analysis.

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Visit 2
This will take place 24-48 h following visit 1. Subjects will be asked to fast for a minimum of 4 h prior to their bronchoscopy visit. They will be informed that if they choose to be sedated they will be unable to drive for 24 h following the procedure, and therefore a taxi can be arranged for them to attend this appointment. The subject will also be informed that they will need to have someone at home to stay with them overnight following the procedure, which is standard practice following a clinical bronchoscopy. They will also be unable to look after children due to the effects of the sedative for 24 h following the procedure. Upon arrival at the bronchoscopy unit, consent will be reaffirmed by a member of the research team and the study inclusion /exclusion criteria will be checked. The researcher will collect the cough monitors and questionnaires from the chronic cough patients.

The subject will have a cannula put in place in their arm/hand, through which the sedative will be given. This will also be used to draw 20 ml of blood which will be processed and stored for ATP measurements.

The bronchoscopy will be performed by a trained and experienced clinician as described in the British Thoracic Society guidelines. An extra BALF sample, endothelial brushings and biopsies will be taken, for research purposes. Upon completion of the bronchoscopy, the subject will be allowed to rest. When they are fully recovered, they will be either picked up by a family member or friend, or accompanied home in a taxi. The research team will ensure that there is someone at home and that the subject will not be alone upon their discharge from the unit.

A follow-up telephone call will be made 24-48 h after the bronchoscopy to record any AEs and to check that the subject has recovered from the procedure.

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Subjects will return 1-2 weeks after visit 2 for a follow-up visit. Chronic cough patients may be followed up during outpatient visits if more convenient. At this visit consent will be reaffirmed and the subject will be queried about any AEs following the bronchoscopy which have not already been reported. The subject's blood pressure, heart rate, pulse oximetry and respiratory rate will be recorded. The subject will be asked to perform a repeat spirometry measurement. At the end of this visit the study is complete.

Intervention Type
Mixed

Primary outcome(s)

Level of ATP in bronchial lavage fluid (BALF) measured using validated ATP assays at visit 1 and visit 2

Key secondary outcome(s))
Current secondary outcome measures as of 14/04/2021:

1. Level of adenosine in plasma taken at visit 2
2. Subjective cough severity assessed using cough-related quality of life measured by the Leicester Cough Questionnaire at visit 1
3. Receptors present on airway nerves assessed using staining of nerve cells in bronchial biopsies taken at visit 2
4. Ability of participants with chronic cough to perform PeXA device breathing manoeuvres and if ATP can be measured from exhaled particles
5. To establish if the fungal mycobiome differs between chronic cough patients and healthy volunteers, as a potential source of ATP

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Previous secondary outcome measures as of 14/02/2020:

1. Level of adenosine in plasma taken at visit 2
2. Subjective cough severity assessed using cough-related quality of life measured by the Leicester Cough Questionnaire at visit 1
3. Receptors present on airway nerves assessed using staining of nerve cells in bronchial biopsies taken at visit 2

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Previous secondary outcome measures:

1. Level of adenosine in plasma taken at visit 2
2. Level of inosine in plasma taken at visit 2
3. Level of adenosine in BALF taken at visit 2
4. Level of inosine in BALF taken at visit 2
5. Objective cough frequency measured using an ambulatory cough monitor over a 24-h period
6. Subjective cough severity assessed using cough-related quality of life measured by the Leicester Cough Questionnaire at visit 1
7. Receptors present on airway nerves assessed using staining of nerve cells in bronchial biopsies taken at visit 2

Completion date
31/01/2026

Eligibility

Key inclusion criteria
Chronic cough patients:
1. Aged 18-80 years
2. Have idiopathic chronic cough as defined by BTS guidelines.

3. Non-smokers or ex-smokers with ≤10 pack years of smoking and >6 months abstinence
4. No clinically relevant abnormalities based on the medical history, physical examination, vital signs or significant past respiratory disease, except for chronic cough

Healthy volunteers:
5. Aged 45-80 years
6. Spirometry within normal limits
7. Non-smokers or ex-smokers with ≤10 pack years of smoking and >6 months abstinence
8. No clinically relevant abnormalities based on the medical history, physical examination, vital signs or significant past respiratory disease

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
80 years

Sex
All

Total final enrolment
44

Key exclusion criteria
1. Have received any medications likely to modulate cough within 2 weeks of enrolment. They can be included if willing/able to discontinue these for the duration of the study.
2. Currently taking ACE inhibitors
3. Any condition that may increase circulating levels of ATP/ATP metabolites e.g. chronic cardiac failure, chronic hypoxia, vigorous exercise in the last 48 h, or regular vigorous exercise, such as professional sports or competitive training
4. Pregnant or breastfeeding
5. FEV1/FVC <70%
6. Recent history of upper or lower respiratory tract infection or significant change in pulmonary status within 4 weeks of enrolment
7. Other severe, acute, or chronic medical or psychiatric condition that may increase the risk associated with trial participation or may interfere with the interpretation of trial results

Date of first enrolment
01/10/2021

Date of final enrolment
10/11/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Wythenshawe Hospital
Manchester University NHS Foundation Trust
Southmoor Rd
Wythenshawe
Manchester
England
M23 9LT

Sponsor information

Organisation
Manchester University Foundation Trust

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location

United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary

Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes