Exploring Novel Biomarkers for Emphysema Detection: the ENBED study

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The goal of the present study is to evaluate whether voice or capnometry, alone or in combination with other (non-invasive) biomarkers, can be used to detect emphysema predominant COPD phenotype (>=25% emphysematous lung tissue).

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational invasive

Summary

ID

NL-OMON53600

Source
ToetsingOnline

Brief title
ENBED

Condition

- Bronchial disorders (excl neoplasms)

Synonym
COPD, emphysema

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Roche

Intervention

Keyword: capnography, COPD, emphysema, Voice

Outcome measures

Primary outcome

To evaluate whether voice or capnometry, alone or in combination with other (non-invasive) biomarkers, can be used to classify emphysema predominant COPD phenotype (>=25% emphysematous lung tissue). Study endpoints are: Emphysema quantification (25% of voxels below *950HU on a HRCT scan), Voice characteristics (see table 1), Capnometry (end-tidal CO2, Slp2 and Slp3) and Emphysema Severity Index (FEF25, FEF25, FEF75)

Secondary outcome

- To evaluate if adding a blood biomarkers for emphysema (sRAGE) increases the diagnostic accuracy of the classification model (< 25% or >= 25% emphysema)for detecting emphysema phenotype COPD (>= 25% emphysema). Study endpoints are: Emphysema quantification (25% of voxels below *950HU on a HRCT scan), Voice characteristics (see table 1), Capnometry (end-tidal CO2, Slp2 and Slp3) and Emphysema Severity Index (FEF25, FEF25, FEF75) , blood (sRAGE)

- To evaluate which lung function parameters increase the accuracy of the classification model (< 25% or >= 25% emphysema). Outcomes: Emphysema quantification: 25% percentage of voxels below *950HU on a HRCT scan. Study endpoints are: Emphysema quantification (25% of voxels below *950HU on a HRCT scan), Voice characteristics (see table 1), Capnometry (end-tidal CO2, Slp2 and Slp3) and Emphysema Severity Index (FEF25, FEF25, FEF75) , blood (sRAGE),

lung function: FEV1, FVC, FEV/FVC, TLC, FRC, RV, FRC/TLC, RV/TLC, TLCO,

- To evaluate if specific features extracted from speech are associated with

the percentage of emphysema on a chest CT scan from patients with COPD.

Endpoints are: Emphysema quantification (Percentage of voxels below *950HU on a

HRCT scan (range 0-100%)), voice features (see table 1)

- To evaluate if specific features extracted from the capnogram are associated

with the percentage of emphysema on a chest CT scan from patients with COPD.

Endpoints are: Emphysema quantification (Percentage of voxels below *950HU on a

HRCT scan (range 0-100%)),

Capnometry (End-tidal CO2, Slp2 and Slp3).

Study description

Background summary

Chronic obstructive pulmonary disease (COPD) consists of two main phenotypes; airway predominant COPD and emphysema predominant COPD There are novel drugs in the therapeutic pipeline that specifically target one of these two specific phenotypes of COPD. To assist in drug development targeting specific COPD phenotypes it is necessary to reliably distinguish between these two COPD phenotypes.

The reference standard for diagnosing emphysema is the high-resolution computed tomography (HRCT) scan. Emphysema is characterized by permanently enlarged air spaces with destruction of alveolar walls that can be visualized as focal areas of low attenuation on the HR-CT scan, often without visible walls. Though many studies nowadays include CT scanning for emphysema screening, such screening exposes participants to radiation. Alternatives to HRCT scanning are pulmonary function testing, of which body plethysmography is most suitable for detecting emphysema.. Static hyperinflation (high total lung capacity and residual volume) are markers for emphysema but not sensitive enough to predict

emphysema. Moreover, the technique of performing body plethysmography requires an experienced pulmonary function laboratory and the device itself is not portable, which hampers scalability of these screening methods. Third, specific blood biomarkers , such as sRAGE have been linked to emphysema, but their diagnostic accuracy has not yet been tested and this would still require the sampling of venous blood. Novel, easy-to-use and preferably non-invasive ways are necessary to detect emphysema in patients with COPD.

Speech analysis might be a first of such novel diagnostics. Dyspnea and cough are common symptoms in COPD patients, and are likely to affect the vocal features of the individuals. Studies have shown that voice biomarkers can be used to differentiate COPD from healthy controls, and changes in voice are associated with changes in symptoms in COPD. Also emphysema has a specific speech characteristics when patient breath at a certain pace, putatively reflecting dynamic hyperinflation. Though certain speech characteristics are associated with COPD, particularly with emphysema, it is not yet known whether speech can be used to distinguish between the two COPD phenotypes.

Besides speech, time-based capnometry might be another non-invasive, breathing-based, diagnostic method for the detection of emphysema. Capnometry analyzes the pattern of carbon dioxide (CO_2) eliminated from the lungs as a function of time. It produces a curve, the capnogram, which represents the total amount of CO_2 eliminated by the lungs during each breath. Features extracted from the capnogram, such as the Slope of phase 2 (Slp2) and Slope of phase 3 (Slp3) have been demonstrated to relate to airway obstruction and may provide useful information about the heterogeneous involvement of lung structures in COPD.(9) Slp2 represents the rapid increase in CO_2 coming from short paths to alveoli; it comes immediately after the elimination of the air from the dead space. Slp3 is an important feature of gas washout curves and contains information about gas transport in the alveolated airways of the lung periphery. In volumetric capnography, emphysema patients reportedly have lower $ETCO_2$, Slp2, and Slp3 compared to COPD patients with predominantly airway disease, and might thus be useful biomarkers to distinguish the two phenotypes in time capnography.

Study objective

The goal of the present study is to evaluate whether voice or capnometry, alone or in combination with other (non-invasive) biomarkers, can be used to detect emphysema predominant COPD phenotype (>=25% emphysematous lung tissue).

Study design

The present study will be a cross-sectional, single-center observational study at the Department of Respiratory Medicine at Maastricht UMC+.

Study burden and risks

The present study will only include adult and capacitated patients with COPD who are able to understand, read and write Dutch language. Risk and inconveniences associated with this study are minimal and are limited to the time investment associated with the non-invasive study measurements. The study participants will undergo one venipuncture that poses a small risk of a local hematoma, but is considered to be a very low risk procedure. The 5-STS is a safe and low risk procedure for COPD patients to induce exercise(17) and might be associated with feelings of dyspnea in those patients but this is generally not considered as unpleasant (e.g. low BORG scores, < 4 on average).(18) The NTC device that will be used in this study is a portable, handheld capnometer (N-Tidal C Handset) through which patients can breathe freely without any resistance, and will not be of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health in this study. The device used in this study will not otherwise present a potential for serious risk to the health, safety, or welfare of a subject. We will only include adult patients with stable disease and incapacitated patients will not be able to participate.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Adults aged over 18 years
- current respiratory symptoms (any dyspnea, cough, or sputum)
- Spirometry-confirmed diagnosis of a non-fully reversible airflow obstruction (defined as postbronchodilator FEV1/FVC < 0.7) and/or emphysema on imaging
- Presence of risk factors or causes associated with COPD
- chest CT scan performed in the past 12 months before the start of the study
- able to understand, read and write Dutch language.

Exclusion criteria

- acute exacerbation of COPD within 8 weeks of start of the study
- comorbidities affecting speech or breathing coordination (neuromuscular disease, CVA)
- comorbidities affecting speech characteristics of dyspnea (severe heart failure, interstitial lung disease)
- comorbidities affecting respiratory system including but not exclusive to asthma or cystic fibrosis
- Comorbidities that significantly interfere with interpretation of speech (audio signals), such as Parkinson*s disease, bulbar palsy, or vocal cord paralysis.
- inability to carry out a capnography recording.
- Investigator*s uncertainty about the willingness or ability of the patients to comply with the protocol requirements.
- Participation in another study involving investigational products. Participation in observational studies is allowed.
- Medical history of lobectomy or Endoscopic Long Volume Redcution (ELVR)
- BMI > 40

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-09-2023
Enrollment:	200
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	12-06-2023
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-10-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-05-2025
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL83173.068.22