Study protocol

Imbalances of regional pulmonary ventilation in patients with post-acute-COVID-19 symptoms

Prospective observational cohort study

Study Acronym: RegioVentPostCOVID-19

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Summary:

In patients with SARS-CoV-2 infection, symptoms may persist for a long time regardless of the initial severity of the disease. There is no compelling correlation between the subjectively reported symptoms and the diagnostic findings, which in the case of dyspnea include a CT of the thorax and a lung function examination.

With the help of electrical impedance tomography (EIT), the distribution of the respiratory volume in the thorax can be recorded non-invasively and radiation-free at the bedside in a cross-sectional projection, in addition to the established radiological methods. The EIT shows images and associated information depicting the distribution of respiratory volume in a single cross-sectional plane. The EIT data maps two-dimensionally the central region of the thorax based on a three-dimensional morphological structure that is several centimeters thick. While CT provides molecular images of anatomical structures with a high spatial resolution, EIT provides functional images with a rather low spatial but very high temporal resolution. EIT offers the possibility to obtain a bedside overview of the regional distribution of the ventilation situation and to track and verify the effect of therapeutic measures in real time.

While EIT has so far been intended for use in ICU patients whose regional valvular distribution over time is of clinical interest, this technique is not yet established for routine use in the assessment of post-COVID symptoms. Our own data on patients with acute COVID disease show that regional ventilation deficits can be visualized by EIT (Lewejohann et al., submitted for publication).

The aim of this study is to investigate the correspondence of CT-morphologically detectable changes in ventilated lung areas in post-COVID syndrome with changes in regional ventilation that can be visualized by EIT.

Initial situation

Even after several months, a relevant proportion of patients with SARS-CoV-2 infection show persistent symptoms [1,2]. On the one hand, there is a significant fatigue and on the other hand, dyspnea is relevant. [3] Current guidelines recommend the evaluation of respiratory symptoms by pulmonary function testing, pulmonary imaging, and cardiologic evaluation [4], although in a relevant proportion of patients no organic correlate of the symptoms can be verified.

Electrical impedance tomography (EIT), which can be used during spontaneous breathing, mask ventilation, and mechanical ventilation, can be used to supplement established radiological methods by recording the distribution of respiratory volume in the thorax in a cross-sectional projection non-invasively and without radiation at the bedside. The EIT status displays images and related information showing the distribution of respiratory volume in only a single cross-sectional plane. The EIT data thereby maps the central region of the thorax in two dimensions based on a three-dimensional morphological structure that is several centimeters thick. The thickness decreases toward the surface near the electrodes, resulting in a lenticular measurement volume. While CT provides snapshots of morphological structures with a high spatial resolution, EIT provides functional images with a rather low spatial but very high temporal resolution. The spatial distribution of pulmonary ventilation determined by EIT showed a good correlation with the results obtained by CT examinations in animal experiments and a good correlation between EIT and CT images in patients in critical condition could also be demonstrated.

In the EIT image, ventilated and non-ventilated areas of the lung and their changes as a function of time can be seen. Real-time impedance curves show respiration over time. Changes in the entire cross-section are reflected by a global impedance curve that correlates with the total volume inhaled. A contour plot allows delineation of ventilated regions per breath and identification of lung regions with restricted ventilation or delayed inspiratory events in a dynamic image as well as in an end-inspiratory trend. In the end-inspiratory trend, this contour marks the maximally ventilated lung regions in a selected observation period from 1 min to 120 min. Negative impedance changes represent inverted curve appearances that can occur physiologically as a result of cardiac activity, diaphragmatic movements, or as artifacts (e.g., during body movements or belt repositioning), but also in the presence of fluid accumulation such as a pleural effusion or deeper expiration than inspiration, as well as pendulum air.

EIT thus offers the possibility of obtaining a bedside overview of the regional distribution of the ventilation situation and of tracking and verifying the effect of therapeutic measures in real time.

While EIT has so far been intended for use in ICU patients whose regional ventilation distribution over time is of clinical interest, this method has not yet been validated for other patients. However, our own initial data indicate that even in acute COVID patients there are recognizable regional reduced ventilations (Lewejohann et al., submitted for publication) and EIT may thus represent a useful alternative or supplement for patients with post-COVID syndrome.

The present study aims to answer the following question

Is there a correspondence between CT morphologically detectable changes in ventilated lung areas in post-COVID patients and changes that can be visualized by elec¬t-roimpedance tomography?

Justification of the treatment and examination procedures

CT thorax is currently performed as a standard part of the diagnostic work-up when the presence of post-COVID syndrome is suspected. In intensive care medicine, the EIT examination is already an established non-invasive examination method that provides regional information on ventilation-related changes in the air content of the lungs. In cases of post-COVID syndrome, changes in regional ventilation distribution are of clinical interest. Potentially valuable clinical information can be derived non-invasively from the EIT data

Study objectives

Primary study objective and primary endpoint

The primary study objective is to match CT morphological changes in regional ventilation in post-COVID patients and/or changes in lung function examination with changes that can be visualized by electroimpedance tomography.

EIT is used to measure regional variation in the form of changes in thoracic impedance within a single breath.

Secondary study objectives and secondary endpoints

Correlation of EIT findings with pulmonary function testing.

Patient recruitment

Accessibility of the intended number of patients: given due to COVID-19 pandemic

- Number of study participants that can be recruited: > 50

- Patient recruitment procedure: patients are screened and informed/included during presentation at the post-COVID outpatient clinic. Currently, approximately 150 patients are screened here per month.

- In this study, 50 patients are to be included and examined. It is planned to recruit this number of patients in one center.

Schedule

The expected total study duration is 6 months.

- Recruitment phase: 2 months

- Duration of the study in the individual patient: approx. 10 min EIT examination.

- End of study: after examination of n = 50 patients

participating study center

Central Emergency Department of the University Hospital Jena and

Department of Internal Medicine IV - post-COVID outpatient clinic

University Hospital Jena

At the hospital 1

07749 Jena

Inclusion criteria

1) All patients presenting to the post-COVID outpatient clinic with an indication for CT thorax as part of the diagnostic workup.

2) Age over 18 years

3) Presence of written informed consent.

Exclusion criteria

1) Patients in whom the application of the electrode belt could pose a risk for, e.g. patients with unstable spinal injuries or fractures.

2) Patients with a BMI over 50, in these patients the PulmoVista® 500 system should not be used according to the manufacturer.

3) Patients with uncontrolled body movements.

4) Patients with a pacemaker.

Study procedure

Patients undergoing a chest CT as part of the diagnostic work-up for the presence of post-COVID syndrome will undergo an EIT examination lasting 10 min after the CT.

Information and consent

Patient education about the study will be provided prior to each scheduled CT thoracic examination.

Each patient will be informed about the nature, significance, objectives, potential risks, anticipated benefits, implications, and other aspects of the clinical trial through a discussion between the investigator and the patient. The patient receives the written patient information. The investigator verifies that the patient has understood the information. After the information session, each patient is given enough time and opportunity to clarify any unanswered questions and to decide whether to participate.

Each patient signs and dates his or her consent to participate in the study in writing on the informed consent form. The patient's consent must also explicitly refer to the collection and processing of personal data. Therefore, patients are explicitly informed about the purpose and scope of the collection and the use of these data, especially health data.

If a patient is unable to sign the consent form personally, a witness must be present during the information process who can confirm the patient's verbal information and consent by signing it. In the case of patients who are incapable of giving consent, the consent is given by court-appointed guardians or other procedures established at the respective testing center.

One copy of the signed consent form (copy or 2nd original) is given to the patient, the other remains at the trial center.

The patient may withdraw consent at any time and without giving any reason and may discontinue treatment or discontinue the study. In such cases, the patient will be asked to state the reason for discontinuation (of treatment or participation) but will be advised that he/she does not have to do so. The time of withdrawal of consent to treatment or study must be documented.

Randomization: no

Description of the individual visits

If a suitable patient presents at the outpatient clinic, he/she will be informed about the study when the CT is indicated, and the corresponding information will be provided as described as before. If consent is given, the EIT is performed for 10 min immediately after the CT. In addition, symptoms, concomitant diseases and medication, further examination findings, of the physical examination, the CT thorax and, if necessary, further equipment procedures such as lung function examination and blood sampling findings are recorded. After completion of the EIT, any adverse events are recorded by the measurement and the studies are terminated for the patient.

Premature withdrawal of a patient from the study (Discontinuation criteria)

Participation in the clinical study is voluntary. Each participant has the right to withdraw from the study at any time at his own request and without giving reasons (consent is withdrawn) or to decide to discontinue treatment (no further treatment) without any disadvantages for his further (medical) treatment.

If a patient withdraws his consent and drops out of the study, this constitutes a discontinuation of participation. If it is possible and the patient is willing to give information, an attempt should be made to find out the reason for the premature termination of the study. The participant is asked to state the reason for discontinuation but is advised that he/she does not have to do so. It is documented that, when and, if applicable, why he/she withdrew his/her consent.

Regular end of study:

The study participation ends regularly for each study participant after completion of the EIT study.

Premature end of study/termination of the entire study

Reasons for premature termination of the entire study may include:

- Inadequate recruitment rate.
- Decision of the study director if new scientific evidence is available.

The decision to discontinue the study will be made by the decision panel.

Recording and documentation of adverse events

No adverse events or procedure-dependent complications are expected. If procedure-related adverse events occur, they will be documented and, if requested by the local ethics committee, collected and submitted for information after the end of the study.7

Biometry

Planning of the study size (sample size planning)

In view of the initial investigation of agreement, a general case number estimation according to Bland/Altman will be used (Bland, J. M., & Altman, D. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. The Lancet, 327(8476), 307-310). To obtain a 95% confidence interval for the limits of agreement of 1 standard deviation of the differences, 50 patients are to be included in the study. It is assumed that breath volume data can be collected from all patients (no dropouts).

Statistical analysis

The agreement between CT and EIT variables (regional tidal variation in terms of change in thoracic impedance within one breath) will be investigated using Bland-Altman method. The mean difference of the two methods (CT and EIT) and the limits of agreement are given, furthermore 95% confidence intervals for the mean difference as well as the upper and lower limits are calculated. The agreement is graphically represented by a Bland-Altman plot.

Data management

Patient identification list

All patient-related data is recorded in pseudonymized form. For this purpose, a non-speaking pseudonym is used, from which alone the identity of the patient cannot be deduced. In order to obtain unique patient identification numbers, a combination of a defined test center number and a consecutive center-specific patient number is selected. The patient identification number is centrally assigned during the internet-based randomization.

The trial center maintains a patient identification list in which the patient identification numbers are linked to the full patient names of the participants, patient identification number and, if applicable, date of birth. This list is used for the possibility of later identification of participating persons. It is to be treated confidentially and may not leave the test center. It must be archived for at least ten years after the end of the study.

In addition, the participation of the persons concerned in the study is noted in the respective patient file.

List of responsibilities

At the study site, a signature list with, among other things, the name, function in the study, study-related activity and abbreviation of the responsible persons is filed in the study site folder.

Data collection/documentation forms

In order to achieve the study objective, it is necessary to collect and process medical data of individual patients. Data collection will take place in the trial centers participating in the study. Data will be collected using paper-based documentation forms (p-CRF). The corresponding staff members in the study centers will receive instructions on how to fill in the paper-based documents.

Data processing

Data processing of the pseudonymized data will be performed in SPSS.

Data management

The collection and management of the pseudonymized data will be done by Ms. Ilona Timmler (Coordinator Central Emergency Department) and Ms. Isabelle Utech (Research Assistant post-COVID Outpatient Clinic).

Study documents and their retention (archiving)

The originals of all essential study documents are kept by the study director for at least ten years after preparation of the final report.

At each study site, accrued administrative documents (e.g., correspondence with ethics committee(s), study director), patient identification list, signed informed consent forms, and general study documentation (study protocol, amendments) are retained for the period. All documentation must be kept in a safe place and treated confidentially. The patient identification list should be kept separate from the documentation records.

Original study patient data (e.g., medical records) or essential study documents must be retained in accordance with the archiving period applicable to the trial sites, but not less than ten years). The trial site or the investigator-in-charge must take precautions to prevent the accidental or premature destruction of these documents.

Data Protection

Within the scope of the study, the EIT data, diagnoses, data regarding the treatment and the course of the disease (e.g. medical findings) are recorded, electronically stored, processed and evaluated in pseudonymized form (i.e. without direct reference to the patient's name).

In the event of revocation of consent to the study by the patient, including further data collection, no further data will be collected from the time of revocation. The data collected so far will continue to be used and evaluated within the study. If a patient only discontinues the study treatment, the data required for the study can continue to be collected and used.

quality assurance

Create chapter in cooperation with quality management, e.g. with the following structure

Standardization

The investigations evaluated in this observational study are subject to guidelines and standard operating procedures (SOP). These defined investigation schemes standardize the decision paths and thus ensure the quality of the triage and the respective investigation procedures.

Audits

In the event of an audit or inspection, auditors and inspectors have a right to inspect the data and personal medical records due to legal regulations. These persons are also bound to secrecy. Inspection and disclosure will only take place within the scope of the legally regulated tasks of the inspectors, namely for the purpose of verifying the data.

Ethical concerns, legal and administrative regulations

Declaration of Helsinki and Good Clinical Practice

The study will be conducted in accordance with the ethical principles originating in the Declaration of Helsinki. The latest version of the Declaration will be observed.

The recommendations of the Good Clinical Practice, valid since 17.1.1997, will be considered, if applicable.

Ethics Committees

The study protocol is submitted with the required additional documents to the responsible lead ethics committee of the study director with a request for evaluation. The study can only begin after the ethics committee has given its approval.

The ethics committees of the participating study centers will receive a copy of the approving evaluation of the first ethics committee and the documents required for granting the "second vote" in each case. Each participating trial site will receive copies of the positive evaluation of the first ethics committee and its responsible ethics committee for the trial site file.

Subsequent Changes

The study protocol must be followed. Any deviation from the planned examination and treatment measures or times for which the investigator is responsible must be documented and justified (e.g. emergency measures).

Changes or additions to the study protocol can only be initiated and authorized by the study management. The lead ethics committee and the ethics committees of the participating study centers are informed about changes to the study protocol. If necessary, the approval of the ethics committee will be obtained again. Changes requiring evaluation may not be implemented prior to the decision of the Ethics Committee.

Changes to the study evaluated by the ethics committee with approval that are likely to
affect the safety of the persons concerned,
additional data collection or analysis that require a change in patient information and/or consent,
the interpretation of the scientific documents on which the study is based, or to affect the scientific validity of the study results,
substantially change the manner in which the study is conducted or performed,
may only be made if these changes have been approved by the Ethics Committee.

Legal regulations
This study is an observational study according to professional regulations. The legal regulations of the Thuringian Hospital Act (ThürKHG) § 27 para. 4 apply.

Registration
The study shall be registered in the following public register: www.clinicaltrial.gov.
Mrs. Yvonne Gremme and Mrs. Ilona Timmler are responsible for the registration in the register and the maintenance of the register data.

Funding
The study will be funded by budgetary resources.

Final report and publication
The publication of the study results will take place regardless of the outcome of the study

Note: We plan to extend the study with a lung-healthy comparison group, which does not require an additional ethics vote (stand: 8.02.2022).

Literature:

[1] Taboada M, Cariñena A, Moreno E, et al. Post-COVID-19 functional status six-months after hospitalization. J Infect 2021; 82: e31–e33. doi:10.1016/j.jinf.2020.12.022

[2] Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. Nat Med 2021; doi:10.1038/s41591-021-01292-y

[3] Augustin M, Schommers P, Stecher M, et al. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. The Lancet Regional Health - Europe 2021; 6: 100122. doi:10.1016/j.lanepe.2021.100122

[4] NICE Guideline No 188. COVID-19 rapid guideline: managing the long-term effects of COVID-19. London: National Institute for Health and Care Excellence (UK); 2020