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Increase in the effectiveness of inhaled salbutamol by supportive use of electrical impedance tomography in ventilated ICU patients: study protocol for a randomized controlled clinical trial

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Running head: EIT-guided ventilator optimization for salbutamol inhalation

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Abstract

Introduction: The inhalative administration of drugs is a non-invasive application form that is regularly used in the treatment of ventilated patients in critical care setting. However, assessment of effectiveness or distribution of nebulized drugs is one of the lacking cornerstones of modern intensive care monitoring. Electrical impedance tomography (EIT) may provide a promising new monitoring and guiding tool for an adequate optimization of mechanical ventilation in critically ill patients. EIT may assist in defining mechanical ventilation settings, assess distribution of tidal volume and evaluation of associated pathologies at bedside. This study wants to elucidate the extent to which the effectiveness of inhaled salbutamol can be increased by the additional use of EIT for optimization of respirator settings.

Methods and analysis: This study is a randomized, open-label superiority trial, conducted on an intensive care unit of a German university hospital, comparing two groups of mechanically ventilated patients with an acute or chronic bronchial airway obstruction according the effectiveness of inhaled salbutamol with (intervention) or without (control) additional use of EIT for optimizing the ventilator settings. Primary outcome is change in airway resistance 30 minutes after salbutamol inhalation.

Ethics and dissemination: The study has received the following approvals: Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306). Results will be made available to critical care survivors, their caregivers, the funders, the critical care societies and other researchers by publication in a peer-reviewed journal.

Trial registration: German trial register (DRKS.de); ID: DRKS00014706; registered on 14th May 2018

Article Summary

Strengths and limitations of this study

- This is the first interventional trial assessing, whether the additional usage of EIT can improve the effectiveness of inhalative drug administration in critical ill and ventilated patients.
- EIT could help to visualize and verify an effective nebulization that could provide a safe, efficient and individualized way of inhalative drug application, e.g. by increasing the effective dose for reaching the distal airway.
- Despite few possible limitations of EIT, this device can provide a remarkable advance in the field of individualized and guided mechanical ventilation adjustments at bedside.
- The secondary outcomes of this study will possibly offer a opportunity to recommend standard respirator settings for inhalative drug application.
- The lack of blinding of the assessors collecting data on EIT usage is a limitation to the study design.

Introduction

Electrical impedance tomography (EIT) is an imaging method that is already used in clinical setting. For several years it has been mainly used for monitoring of lung function [1]. With regard to lung monitoring, EIT makes use of changes in thoracic impedance, which in turn result in different concentrations of free ions due to changes in air content of the lung tissue [2]. In brief, the principle of EIT is based on the application of very small alternating electrical currents, which are applied and measured via alternating pairs of electrodes. With a scan rate of 50 images per second, voltage profiles from 16 electrode positions are continuously combined to a cross-sectional image [2]. With these cross-sectional images, the EIT enables a continuous real-time monitoring of lung function at bedside [3]. With its high resolution, EIT enables reliably the immediate and non-invasive assessment of changes in regional lung tissue [4 5]. It can also help to optimize ventilation settings to prevent regional overinflating of the lungs and atelectasis [6]. Prior studies demonstrated that equivalent diagnostic findings between EIT and thoracic computed tomography could be achieved in critically ill patients in terms of regional ventilation in different thoracic regions, and also offered a valid examiner-independent test reproducibility of the results [5 7-9]. In addition, the bedside applicability of EIT can eliminate the logistical burden of diagnostic transports with several associated risk factors and could even reduce treatment costs [1 10].

There are only a few contraindications for EIT, like the usage in active implants (e.g. pacemaker or implantable cardioverter-defibrillator) due to the lack of experience of interactions with the generated alternating electric field of EIT [11]. Furthermore, a certain amount of expertise and a sufficient level of experience of the nursing and medical staff is needed to ensure the correct interpretation of EIT values and avoidance of technical errors [5 12].

The inhalative administration of drugs is an established, non-invasive and painless application form, which is used in treatment of obstructive airways diseases. An important advantage is that significant higher local concentrations of the drug at the site of action are achieved without significant systemic exposure [13 14]. Several studies could not show a benefit of inhaled medication [15-17]. Unfortunately, all these studies could not address the crucial issue whether the medication itself or its distribution was less effective. To the present day, there is no established non-invasive real-time monitoring to measure or visualize the effectiveness or distribution of nebulized drugs in ventilated patients at bedside [14].

Based on this issue, our study wants to elucidate the extent to which the effectiveness of inhaled drugs, e.g. β2 sympathomimetics, can be optimized by the additional use of EIT for adjusting ventilator settings. Accordingly, we want to test the hypothesis whether EIT can increase the effectiveness of inhaled salbutamol.

Methods and analysis

This study is a randomized, open-label superiority trial comparing an interventional group with optimization of respirator settings under use of EIT and a control group without optimization of respirator settings. Ventilation distribution images will be obtained with a commercially available EIT system (PulmoVista™ , Dräger Medical, Lübeck, Germany).

Study population and general data acquisition

This study was reviewed and approved by the Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306) and registered in the German Clinical Trial Register (DRKS00014706). It will be conducted in accordance with the Declaration of Helsinki and German laws and regulations. All patients will be admitted to the intensive care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum and will be recruited from June 2018 to June 2019. We will perform EIT measurements with PulmoVista™ (Dräger Medical, Lübeck, Germany) and a size adjusted chest belt with 16 electrodes. The diagnosis of acute or chronic airway obstruction will include clinical examination and expiration-flow analyzation. Patients at the age of 18 years or more, diagnosed with an acute airway obstruction or known chronic obstructive pulmonary disease under mechanical ventilation and providing written informed consent or a positive vote of an independent consultant are eligible for inclusion. Exclusion criteria are: pregnancy or lactation, severe obesity (body mass index > 35), missing medical indication and/or contraindication for inhaled salbutamol administration, Horowitz index ≥ 400, long-term ventilation > 14 days, a study-independent medical indication for salbutamol nebulization in obstructive pulmonary disease and/or an acute obstructive condition and procedure of withdrawing life-sustaining therapy. Furthermore, patients with the following pre-existing conditions and operations will be excluded: patients with

chest trauma or surgery (e.g. pneumectomy), pneumonia, ARDS with or without ECMO therapy, neuromuscular diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic events, active implants (e.g. pacemakers, ICD) or thoracic skin lesions and wound dressings.

Patients will be treated generally with a multimodal concept, which includes analgesia and sedation, fluid administration, lung-protective mechanical ventilation, anticoagulation, as well as hemodynamic, antibiotic and diagnostic management as recommended by guidelines, standard operating procedures or evidence based best practice. Additionally, after pseudonymization a large body of clinical and demographic data will be entered into a database for later analysis, including pre-existing morbidities, Simplified Acute Physiology Score II (SAPSII), Sepsis-related Organ Failure Assessment Score (SOFA), body mass index (BMI), necessity for renal replacement therapy, ventilator settings, PaO2/FiO2 ratio (Horowitz index), vital parameters, medications and dosage of vasoactive drugs and blood chemistry values.

Sample size calculation

A total of 80 mechanically ventilated patients will be included in the study, with 40 patients in the intervention group and 40 patients in the control group. With a total cohort size of n=80, a power of > 95% (alpha error p = 0.05, beta error < 0.05) will be reached, referring to the data from a reference work (table 1) by Malliotakis et al. [18]. Calculations from these values indicate that 76 participants (38 per group) are required to achieve a power of 95% with an alpha error of 5%.

Table 1: Baseline characteristics of sample size calculation

Variable	R_{int}	R_{rs}
$n_{Baseline}$	10	10
n_{30min}	10	10
$Mean_{Baseline}$ ± SD	18.4±4.0 [cmH2O/l/sec]	15.5±3.6 [cmH2O/l/sec]
$Mean_{30min}$ ± SD	26.5±4.1 [cmH2O/l/sec]	23.1±3.6 [cmH2O/l/sec]
Effect-size	0.762	0.881
n_{total} Power 80%	44	34
n_{total} Power 90%	62	46
n_{total} Power 95%	76	58

Airway resistance and related sample size (n) before and 30 min after salbutamol administration in ventilated patients of reference work [18]; R_{int}, R_{rs}: minimum and maximum inspiratory resistance (cm H2O/l/s), respectively

Study design

The total study duration is planned for 18 months. It will take 12 months for recruitment of patients and collection of data, last 6 months are scheduled for analyzation. For each patient an individual study duration is assigned of one day. In the control group, 1.75 hours are scheduled per patient. These include study education and randomization (30 mins), data collection before inhalation (30 mins), drug nebulization and inhalation (15 mins) and measurements after inhalation (30 mins; figure 1). In the interventional group, study explanation and randomization (30 mins), data collection before inhalation (30 mins), the installation and adjustment of EIT (30 mins), the optimization of ventilator settings (15 mins), drug nebulization and inhalation (15 mins), resetting ventilator settings to baseline and measurements 30 minutes after inhalation add up to a total duration of 2.5 hours (figure 1).

Randomization

Block-balanced randomization, in a 1:1 ratio, will be computer-generated by StatsDirect (StatsDirect Ltd., Cambridge, United Kingdom) with random block sizes between n = 10 and n = 20, additionally using random permutations of treatments within each block. Investigators will be blinded to the allocation according to the randomization list until the study patient has been included.

Interventional procedure

EIT and control group undergo an arterial blood gas analysis and corresponding airway measurements to determine baseline parameters before salbutamol inhalation (figure 1; Supplemental material 1+2). Therefore, 1.25 mg / 2.5 mL salbutamol (Sultanol®, Glaxo Smith Kline plc., Brentford, United Kingdom) is applied with a vibrating mesh nebulizer (Solo®, Aerogen, Galway, Ireland).

In the control group, baseline measurement is followed by ultrasound nebulization and inhalation with salbutamol for 15 minutes, following measurements and arterial blood gas analysis 30 minutes after inhalation (figure 1). In addition, all study-relevant data are documented pseudonymised in the case report form (CRF) to ensure a standardized operating (Supplemental material 2). This CRF will be handed over to the principal investigator immediately after collection of data. The principal investigator keeps the study documents in a study folder not accessible to third parties.

In the intervention group, baseline measurements are followed by the standardized setup and adjustment of EIT, where a belt with 16 integrated electrodes is attached circularly to the thorax (Supplemental material 3). This is followed by the optimization of the respirator settings by means of EIT using a defined algorithm (Supplemental

material 3), according the recommendations of the Translational EIT Development Study Group (TREND) [5]. The next step is nebulization and inhalation of salbutamol for 15 minutes. Subsequently, ventilator settings are reset to baseline as before EIT adjustment. After a period of 30 minutes, a new data collection after salbutamol administration including EIT measurement is done and an arterial blood gas analysis is performed (figure 1). Data is documented in the CRF (Supplemental material 1).

Objectives

The primary objective is to assess if additional use of EIT can increase the effectiveness of inhaled salbutamol, and therefore decrease the airway resistance 30 minutes after salbutamol inhalation more effective than without usage of EIT. The secondary objectives will be to compare the EIT-intervention group and the control group regarding:

- Before and 30 minutes after salbutamol inhalation:
  - Changes made in ventilator settings under EIT,
  - tidal volume, compliance, resistance, arterial oxygen partial pressure (p_aO2), Horowitz index, arterial carbon dioxide partial pressure (p_aCO_2), peripheral and arterial oxygen saturation,
  - upper and lower inflection point of the pressure-volume curve,
  - EIT parameters: Region of Interest (ROI), changes of end expiratory lung volume (Delta-EELV) and changes of end expiratory lung impedance (Delta-EELI),
  - heart rate, blood pressure
- duration of mechanical ventilation,
- length of stay on ICU and hospital, readmission rate on ICU.
- 30-days mortality

Data collection

The documentation of the data will be pseudonymized and computer-assisted from our patient data management system (PDMS) (Dräger ICM, Dräger Medical, Lübeck, Germany) in a central offline database. Therefore, all collected data will solely be provided in pseudonymized form for further study analyzation. Access to the pseudonymization key, which is password protected, is only available to the principal investigator of this study. All above mentioned parameters will be collected during the patients stay in hospital until discharge, death or 30th day of stay on ICU. In case of discharge from ICU, follow-up to evaluate 30-days survival will be performed by visit on normal ward or a phone call by one of the investigators. Data entered in the central offline database will be monitored by an independent clinical research associate and checked for consistency and missing values. All records, subjects' identities and data management will remain confidential with the General Data Protection Regulation (GDPR) of the European Parliament and the Council of the European Union. Furthermore, this protocol was designed following the recommendations for interventional trials (SPIRIT; Figure 2).

Statistical analysis

Since this is a study designed to demonstrate superiority of the composite endpoint, whether an additional use of EIT increases the effectiveness of inhaled salbutamol, we will perform an intention-to-treat and additionally a per-protocol analysis as recommended by the CONSORT guidelines [19]. The per-protocol population will be defined as randomized patients without major protocol deviations, such as non-considerations of exclusion criteria or missing data for the primary endpoint. Baseline characteristics of all patients will be described per group. Qualitative data will be described as frequencies and percentages. Continuous variables are presented as

means ± standard deviation in case of normal distribution and as median and interquartile range (25th; 75th percentile) in case of non-normally distributed variables. Continuous variables will be compared using parametric Student's t-test or non-parametric Mann-Whitney-U-Test. Categorical variables will be characterized by numbers with percentages and will be compared using the Chi-square test or a Fisher's exact test.

The graphical processing of variables will be performed depending on the measurement level of the variables as histograms, mean value curves with corresponding standard deviations or box whisker plots.

Ethics and dissemination

A manuscript with the results of the study will be published in a peer-reviewed journal. The study has received the following approvals: Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306). On completion of the trial, and after publication of the primary manuscript, data will be made availabele in a free accessable online repository.

Discussion

This study, to our knowledge, is the first interventional trial assessing, whether the additional usage of EIT can improve the effectiveness of inhalative drug administration in critical ill and ventilated patients.

The administration of inhaled drugs is routinely used in intensive care units, due to the advantage of delivering high drug concentrations to the airway, along with rapid onset of action and fewer systemic side effects. However, it is believed that the beneficial effects of inhaled drugs are smaller in patients on mechanical ventilation than in those breathing spontaneously. In this regard, a previous study could demonstrate that only 2.9% of the administered drug dose reached the distal airway in ventilated patients, compared to 11.9% in patients without artificial airway [16]. A recently published review, regarding inhalative drug therapy in mechanical ventilation, stated that ventilator settings play an crucial role in inhaled drug delivery [14]. A tidal volume of at least 500 mL, increased inspiratory time and a low inspiratory flow are general recommendations in order to optimize drug distribution in the lungs [14 20 21]. Nevertheless, attention should be paid to serious adverse effects of high (> 500 mL) tidal volumes, especially in patients with acute or chronic airway obstructions. In these patients high tidal volumes can lead to dynamic hyperinflation or can cause a severe barotrauma [14]. Furthermore, no clinical studies exist showing the beneficial effects of any particular ventilation mode on inhaled drug delivery [20 21]. Therefore, a new diagnostic and guiding tool for adequate optimization of ventilator settings prior to nebulization of inhalative drugs would be desirable. Hence, fast, non-invasive and reliable assessment at bedside in critical ill and ventilated patients is one of the cornerstones for modern intensive care monitoring. EIT, although with some constrains, may be a promising solution. EIT images are valid measurements of the regional distribution of ventilation and changes in lung volume in real-time. This dynamic evaluation makes EIT a promising tool for guided optimization

of ventilator parameters on an individualized base. Several studies in the last years have already demonstrated that EIT-guided respirator optimization results in significant improved respiratory mechanics and improved gas exchange [1 4 7 22]. However, a global standard based on a broad base of evidence was one of the most discussed topics in Respiratory Medicine over the last years. Therefore, the plausibility of EIT measurements highly depends on the correct belt position, proper impedance visualization, correct analysis and data interpretation [23].

The crucial step forward was the publication of recommendations of the TREND (Translational EIT Development Study) group [5]. These recommendations highlight the need for a consensus about examinations, consistent terminology and generally accepted approaches to EIT images and analysis. Based on this highly appreciated consensus statement we are now able to compare, understand and reproduce study findings from among different research groups and provide a standardized use in clinical routine.

A further limitation is that EIT captures only ventral-to-dorsal ventilation distribution. However, Bikker et al. also reported different ventilation distribution between cranial and caudal lung levels during decremental PEEP trials [24], concluding that existing EIT systems will not be able to cover the optimal PEEP titration for the whole lung.

Despite the possible limitations of EIT, this device can provide a remarkable advance in the field of individualized and guided mechanical ventilation adjustments. Therefore, this study can shed light on the extent to which the additional use of EIT for optimizing the ventilator settings can increase the effectiveness of inhaled salbutamol.

Outlook

EIT could help to visualize and verify an effective nebulization that could provide a safe, efficient and individualized way of inhalative drug application, e.g. by increasing the effective dose reaching distal airway.

Trial status

The first patients were randomized in June 2018. The inclusion of participants is ongoing and is expected to continue until June 2019.

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List of abbreviations

ARDS	Acute respiratory distress syndrome
BMI	Body mass index
CRF	Case report form
delta-EELI	Change of end expiratory lung impedance
delta-EELV	Change of end expiratory lung volume
DRKS	Deutsches Register für klinische Studien
ECMO	Extracorporeal membrane oxygenation
EIT	Electrical impedance tomography
GDPR	General data protection regulation
ICD	Implantable cardioverter defibrillator
ICU	Intensive care unit
NYHA	New York Heart Association
p_aCO_2	Partial pressure of arterial carbon dioxide
p_aO_2	Partial pressure of arterial oxygen
PDMS	Patient data management systems
PEEP	Positive end-expiratory pressure
R	Resistance
ROI	Region of interest
SAPSII	Simplified acute physiology score II
SD	Standard deviation
SOFA score	Sepsis-related organ failure assessment score
Spirit	Standard Protocol Items - Recommendations for Interventional
TREND group	Translational EIT Development Study group

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of the Medical Faculty of the Ruhr-Universität Bochum (no. 17-6306) and written informed consent or a positive vote of an independent consultant are eligible for inclusion.

Consent for publication

Not applicable

Availability of data and material

The data of the described study will be available from the Dryad repository after publication.

Conflict of interests

None to declare

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Author Statement

Dr. med. Tim Rahmel: Main author of this manuscript, written and revising the manuscript

Alexandra Koniusch: Supporting methodical description and participated in the design of this study

Dr. med. Günther Oprea: Supporting data collection, participated in the design of this study, and revising the manuscript

Martin Schwertner: Supporting data collection, participated in the design of this study, and revising the manuscript

Prof. Dr. med. Michael Adamzik: Supporting data collection, participated in the design of this study and revising the manuscript

Dr. med. Hartmuth Nowak: Supporting data collection, participated in the design of this study, written and revising the manuscript

All authors read and approved the final manuscript.

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Legends

Figure 1: Flowchart of interventional procedures on intervention and control group with duration of each step and performed measurements (EIT = electrical impedance tomography, ICU = intensive care unit)

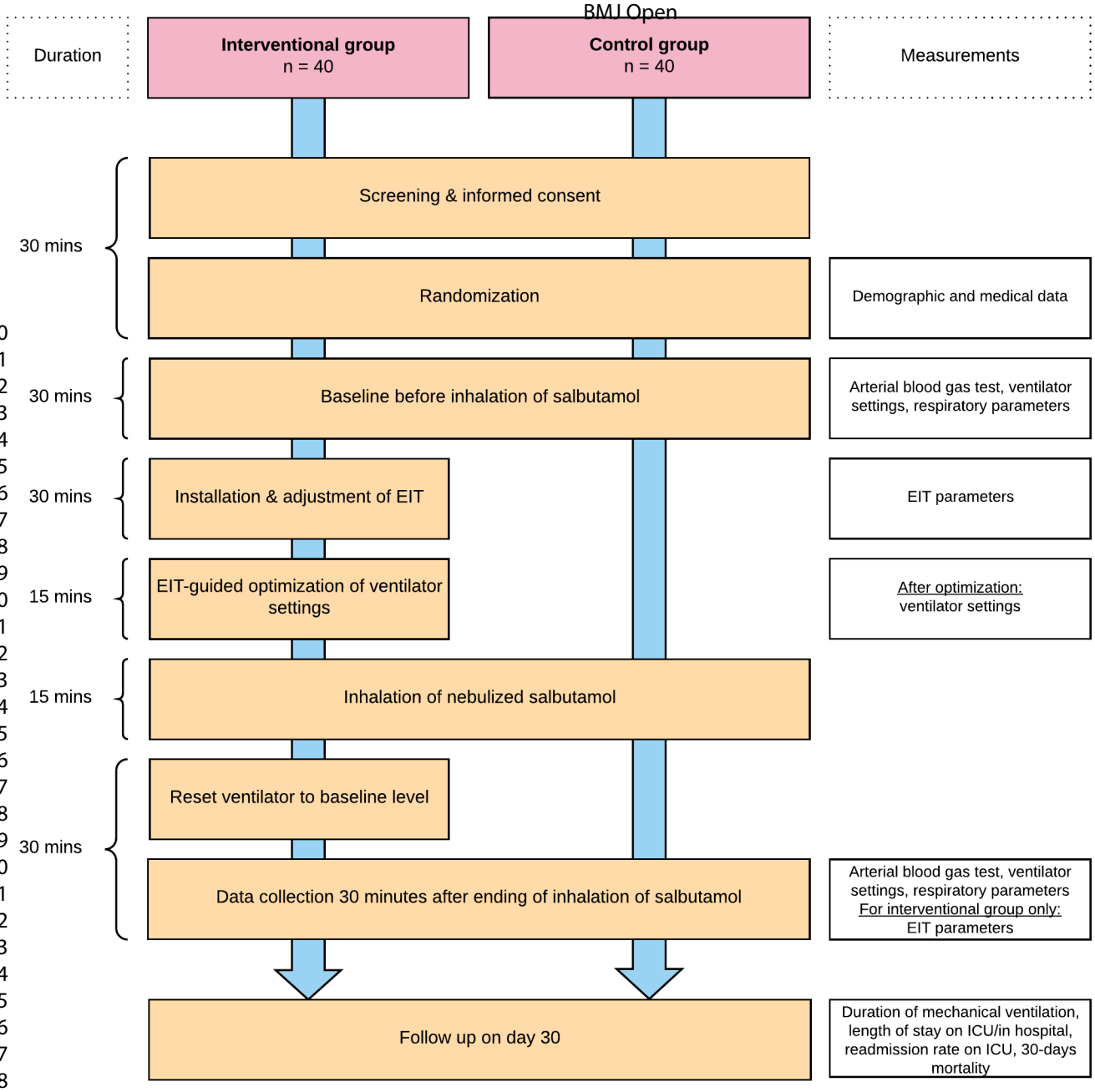
Figure 2: Schedule of enrolment, interventions and assessments – SPIRIT Figure (SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials, EIT = electrical impedance tomography, ICU = intensive care unit)

Supplemental material

Supplemental material 1: Case report form of intervention group

Supplemental material 2: Case report form of control group

Supplemental material 3: EIT algorithm for standardized EIT application and assessment


Duration
Interventional group
n = 40
Control group
n = 40
Measurements
Screening & informed consent
30 mins
Randomization
Demographic and medical data
30 mins
Baseline before inhalation of salbutamol
Arterial blood gas test, ventilator settings, respiratory parameters
30 mins
Installation & adjustment of EIT
EIT parameters
15 mins
EIT-guided optimization of ventilator settings
After optimization:
ventilator settings
15 mins
Inhalation of nebulized salbutamol
Reset ventilator to baseline level
30 mins
Data collection 30 minutes after ending of inhalation of salbutamol
Arterial blood gas test, ventilator settings, respiratory parameters
For interventional group only:
EIT parameters
Follow up on day 30
Duration of mechanical ventilation, length of stay on ICU/in hospital, readmission rate on ICU, 30-days mortality

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
TIMEPOINT	Prior randomization	0	Baseline	After Baseline	After intervention	30 days
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
INTERVENTIONS:						
EIT-guided optimization of ventilation, inhalation of nebulized salbutamol afterwards				X		
Inhalation of nebulized salbutamol				X		
ASSESSMENTS:						
Demographic & medical data			X			
Ventilator settings			X		X	
Respiratory parameters			X		X	
Arterial blood gas test			X		X	
EIT parameters (*for EIT group only*)			X		X	
Duration of mechanical ventilation, length of stay on ICU/in hospital, readmission rate on ICU						X
30-days mortality						X

Randomization |__|__|.|__|__|.201__

No. |__|__| ***CRF EIT-Trial (intervention group)*** VU

Patient

Inclusion criteria	Yes	No
• Age ≥ 18 years	☐	☐
• Known obstructive airway disease or acute airway obstruction ***and*** • Medical indication for salbutamol inhalation	☐	☐
• Mechanical ventilated patient and Horowitz index (p_aO_2/F_iO_2) < 400	☐	☐
• Written informed consent or positive vote of an independent consultant	☐	☐

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	☐	☐
• Lack of medical indication and/or contraindications to administration of salbutamol	☐	☐
• Age < 18 years	☐	☐
• Pre-existing conditions or operations: Patients with chest trauma or chest surgery; thoracic skin lesions and wound dressings; ARDS and/or ECMO therapy; neuromuscular diseases; severe cardiac diseases (e.g. NYHA III-IV); acute ischemic events; active implants (e.g. pacemakers, ICDs)	☐	☐
• Severe obesity (BMI > 35)	☐	☐
• Long-term ventilation > 14 days	☐	☐
• Do-not-resuscitate order	☐	☐
• Pregnancy or lactation	☐	☐

- Copy patient file/printout! (Anamnesis, concomitant medications, concomitant diseases, physical examination, ECG, vital parameters ☐ carried out

  ☐ male ☐ female

  Height |__|__|__| cm **weight** |__|__|__|.|__| kg **BMI** |__|__|.|__| kg/m^2

- **Blood pressure** |__|__|__| / |__|__| **heart rate** |__|__|__| bpm

  body temperature |__|__|.|__| °C

- Pregnancy excluded ☐

- Note participation in the medical record! ☐ carried out

- **Procedure in the intervention group**
  - Study education including randomization (30 min) ☐
    - Measurement of SOFA-Score (_____), PCT (_____), CRP (_____), antibiotics (_____), vital parameters (_____), catecholamines (_____), sedation (_____) ☐
  - Data collection before inhalation (30 min)
    - Measurement of airway resistance before salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
  - Installation and adjustment of the EIT (30 min) ☐
    - Measurement of Region of Interest (ROI) (_____), changes of end-exspiratory lung volume (Delta-EELV) (_____) and changes of end-exspiratory lung impedance (Delta-EELI) (_____) ☐
  - Optimization of ventilator settings (15 min) ☐
    - Measurement of ventilator settings after EIT-guided optimization (P_{insp} (_____), PEEP (_____), I:E (_____), T_{insp} (_____), RR (_____), ventilation mode (_____)) ☐
  - Salbutamol nebulization and inhalation (15 min) ☐
  - Reset ventilator to baseline level ☐
  - Data collection after inhalation (30 min)
    - Measurement of airway resistance after salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
    - Measurement of Region of Interest (ROI) (_____), changes of end-exspiratory lung volume (Delta-EELV) (_____) and changes of end-exspiratory lung impedance (Delta-EELI) (_____) ☐

Date |__|__|.|__|__| 201__ Signature of the examiner _____

Randomization |__|__|.|__|__|.201__

No. |__|__| ***CRF EIT-Trial (control group)*** VU

Patient

Inclusion criteria	Yes	No
• Age ≥ 18 years	☐	☐
• Known obstructive airway disease or acute airway obstruction ***and*** • Medical indication for salbutamol inhalation	☐	☐
• Mechanical ventilated patient and Horowitz index (p_aO_2/F_iO_2) < 400	☐	☐
• Written informed consent or positive vote of an independent consultant	☐	☐

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	☐	☐
• Lack of medical indication and/or contraindications to administration of salbutamol	☐	☐
• Age < 18 years	☐	☐
• Pre-existing conditions or operations: Patients with chest trauma or chest surgery; thoracic skin lesions and wound dressings; ARDS and/or ECMO therapy; neuromuscular diseases; severe cardiac diseases (e.g. NYHA III-IV); acute ischemic events; active implants (e.g. pacemakers, ICDs)	☐	☐
• Severe obesity (BMI > 35)	☐	☐
• Long-term ventilation > 14 days	☐	☐
• Do-not-resuscitate order	☐	☐
• Pregnancy or lactation	☐	☐

- Copy patient file/printout! (Anamnesis, concomitant medications, concomitant diseases, physical examination, ECG, vital parameters ☐ carried out

  ☐ male ☐ female

  Height |__|__|__| cm **weight** |__|__|__|.|__| kg **BMI** |__|__|.|__| kg/m^2

- **Blood pressure** |__|__|__| / |__|__| **heart rate** |__|__|__| bpm

  body temperature |__|__|.|__| °C

- Pregnancy excluded ☐

- Note participation in the medical record! ☐ carried out

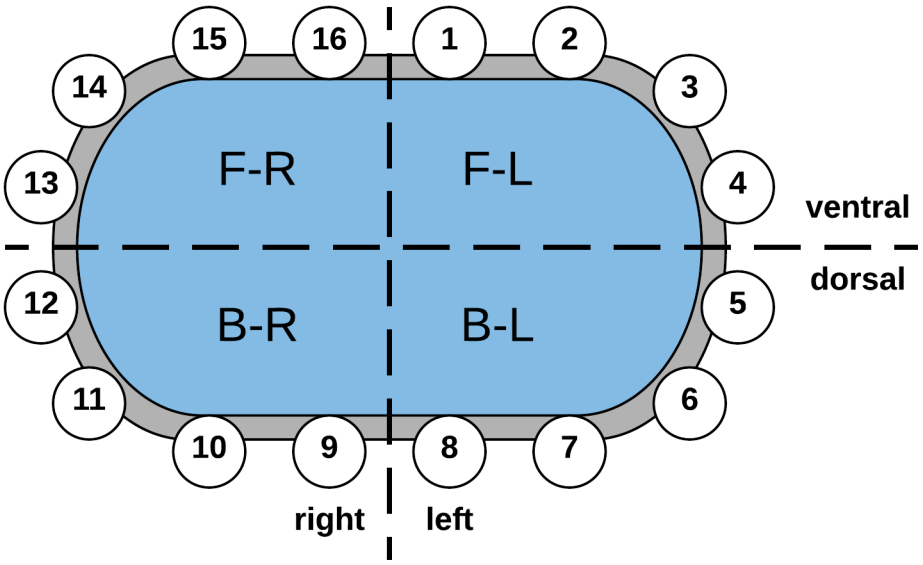
- **Procedure in the control group**
  - Study education including randomization (30 min) ☐
    - Measurement of SOFA-Score (_____), PCT (_____), CRP (_____), antibiotics (_____), vital parameters (_____),catecholamines (_____), sedation (_____) ☐
  - Data collection before inhalation (30 min)
    - Measurement of airway resistance before salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
  - Salbutamol nebulization and inhalation (15 min) ☐
  - Data collection after inhalation (30 min)
    - Measurement of airway resistance after salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐

Date |__|__|.|__|__| 201__ Signature of the examiner _____

EIT algorithm

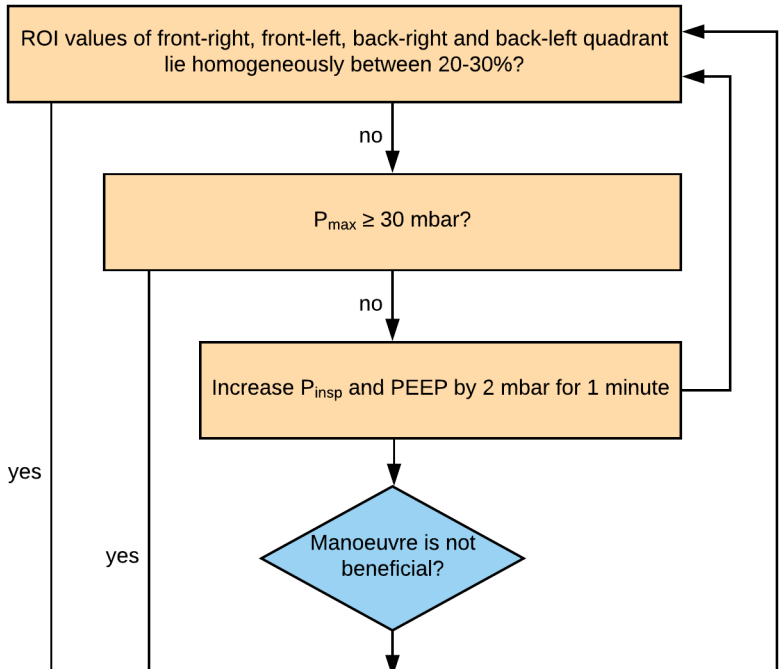
Installation procedure for EIT (PulmoVista 500, Dräger Medical, Lübeck, Germany)		
1.	To turn on the EIT system press the green “Power on”-button in the left, lower corner of the screen (it will light up after switching on). Afterwards, the system will be in “Standby”-mode.	☐
2.	Connect the main plug of the trunk cable to the upper connection socket. Connect the color-coded plugs to the corresponding test socket (green = right/R), red = left/L).	☐
3.	Choose “System Test” on the touch screen. Press “Start” and confirm this selection by pressing the control knob in the right, lower corner of the screen. The EIT system will perform a self-check to ensure proper functioning of all components and the trunk cable.	☐
4.	Choose a belt according to the patient’s circumference of chest (S = 70-85 cm, M = 80-96 cm, L = 92-110 cm, XL = 106-127 cm, XXL = 124-150 cm). Connect electrodes of the corresponding connection cable with the belt (number 1 to 1, number 2 to 2, …, number 16 to 16).	☐
5.	Placement of EIT belt: Between 8th and 9th electrode is a perceptible silicone mark, place this mark centrally over the spine between 4th and 6th intercostal space. Both lateral ends are folded forward towards the chest and connected in front of the sternum, so that electrode number 1 is placed left and number 16 right to the sternum (figure 1). Connect the “C”-electrode of the connection cable with the seal of the EIT belt. Place an ECG-electrode on the skin of the abdomen and connect it with the “REF”-electrode of the connection cable.	☐
6.	Plug the green and red color-coded plugs of the trunk cable out of the test socket and connect them to the connection cable of the EIT belt (ensure the correct connection: green to green and red to red).	☐
7.	Select the option “New Patient” on the touch screen in the Start/Standby menu. By choosing “Signal Check” skin resistance of each electrode is shown, a blue bar appears for all electrodes. If skin resistance is insufficiently high (> 300 ohms), the corresponding electrode is marked in red. In that case, prove the correct positioning of that electrode, moisturize the electrode with water or electrode gel where applicable. Move on to step 8 when all bars appear blue.	☐
8.	Register patient data by selecting “New Patient”. Afterwards, press “Start” to start EIT measurements. A short calibration is performed (approximately 30 seconds), afterwards the system is ready for measuring.	☐

Figure 1: schematic cross-section image of thorax with positions of 16 EIT electrodes at the level of 4th to 6th intercostal space *(F-R = front-right quadrant, F-L = front-left quadrant, B-R = back-right quadrant, B-L = back-left quadrant)*



Measurement of EIT parameters (ROI, Delta-EELV and Delta-EELI)		
1.	ROI (Region of interest): Choose "Views" in right upper corner of the screen and tap on "Full Screen". Values for each quadrant (F-R, F-L, B-R, B-L) are displayed.	☐
2.	Delta-EELV (changes of end exspiratory lung volume): Choose "Views" in right upper corner of the screen and tap on "End exspiratory trend".	☐
3.	Delta-EELI (changes of end exspiratory lung impedance): Choose "Views" in right upper corner of the screen and tap on "Delta-EELI".	☐

Figure 2: flowchart of EIT-guided optimization of ventilator settings *(ROI = region of interest, P_{max} = maximum airway pressure, P_{insp} = inspiratory pressure, PEEP = positive end expiratory pressure)*



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Evaluation of inhaled salbutamol effectiveness under supportive use of electrical impedance tomography in ventilated ICU patients: study protocol for a randomized controlled clinical trial

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Evaluation of inhaled salbutamol effectiveness under supportive use of electrical impedance tomography in ventilated ICU patients: study protocol for a randomized controlled clinical trial

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Running head: EIT-guided ventilator optimization for salbutamol inhalation

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Abstract

Introduction: The inhalative administration of drugs is a non-invasive application form that is regularly used in the treatment of ventilated patients in critical care setting. However, assessment of effectiveness or distribution of nebulized drugs is one of the lacking cornerstones of modern intensive care monitoring. Electrical impedance tomography (EIT) may provide a promising new monitoring and guiding tool for an adequate optimization of mechanical ventilation in critically ill patients. EIT may assist in defining mechanical ventilation settings, assess distribution of tidal volume and evaluation of associated pathologies at bedside. This study wants to elucidate the extent to which the effectiveness of inhaled salbutamol can be increased by the additional use of EIT for optimization of respirator settings.

Methods and analysis: This study is a randomized, open-label superiority trial, conducted on an intensive care unit of a German university hospital, comparing two groups of mechanically ventilated patients with an acute or chronic bronchial airway obstruction according the effectiveness of inhaled salbutamol with (intervention) or without (control) additional use of EIT for optimizing the ventilator settings. Primary outcome is change in airway resistance 30 minutes after salbutamol inhalation.

Ethics and dissemination: The study has received the following approvals: Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306). Results will be made available to critical care survivors, their caregivers, the funders, the critical care societies and other researchers by publication in a peer-reviewed journal.

Trial registration: German trial register (DRKS.de); ID: DRKS00014706; registered on 14th May 2018

Article Summary

Strengths and limitations of this study

- This is the first interventional trial assessing, whether the additional usage of EIT can improve the effectiveness of inhalative drug administration in critical ill and ventilated patients.
- EIT could help to visualize and verify an effective nebulization that could provide a safe, efficient and individualized way of inhalative drug application, e.g. by increasing the effective dose for reaching the distal airway.
- Despite few possible limitations of EIT, this device can provide a remarkable advance in the field of individualized and guided mechanical ventilation adjustments at bedside.
- The secondary outcomes of this study will possibly offer a opportunity to recommend standard respirator settings for inhalative drug application.
- The lack of blinding of the assessors collecting data on EIT usage is a limitation to the study design.

Keywords: EIT, optimization of ventilation, inhalation, nebulization, region of interest, end expiratory lung volume, end expiratory lung impedance

Introduction

Electrical impedance tomography (EIT) is an imaging method that is already used in clinical setting. For several years it has been mainly used for monitoring of lung function [1]. With regard to lung monitoring, EIT makes use of changes in thoracic impedance, which in turn result in different concentrations of free ions due to changes in air content of the lung tissue [2]. In brief, the principle of EIT is based on the application of very small alternating electrical currents, which are applied and measured via alternating pairs of electrodes. With a scan rate of 50 images per second, voltage profiles from 16 electrode positions are continuously combined to a cross-sectional image [2]. With these cross-sectional images, the EIT enables a continuous real-time monitoring of lung function at bedside [3]. With its high resolution, EIT enables reliably the immediate and non-invasive assessment of changes in regional lung tissue [4 5]. It can also help to optimize ventilation settings to prevent regional overinflating of the lungs and atelectasis [6]. Prior studies demonstrated that equivalent diagnostic findings between EIT and thoracic computed tomography could be achieved in critically ill patients in terms of regional ventilation in different thoracic regions, and also offered a valid examiner-independent test reproducibility of the results [5 7-9]. In addition, the bedside

applicability of EIT can eliminate the logistical burden of diagnostic transports with several associated risk factors and could even reduce treatment costs [1 10].

There are only a few contraindications for EIT, like the usage in active implants (e.g. pacemaker or implantable cardioverter-defibrillator) due to the lack of experience of interactions with the generated alternating electric field of EIT [11]. Furthermore, a certain amount of expertise and a sufficient level of experience of the nursing and medical staff is needed to ensure the correct interpretation of EIT values and avoidance of technical errors [5 12].

The inhalative administration of drugs is an established, non-invasive and painless application form, which is used in treatment of obstructive airways diseases. An important advantage is that significant higher local concentrations of the drug at the site of action are achieved without significant systemic exposure [13 14]. Several studies could not show a benefit of inhaled medication [15-17]. Unfortunately, these studies could not address the crucial issue whether the medication was distributed effectively in critical ill ventilated patients. To the present day, there is no established non-invasive real-time monitoring to measure or visualize the effectiveness or distribution of nebulized drugs in ventilated patients at bedside [14].

Based on this issue, our study wants to elucidate the extent to which the effectiveness of inhaled drugs, e.g. β2 sympathomimetics, can be optimized by the additional use of EIT for adjusting ventilator settings. Accordingly, we want to test the hypothesis whether EIT can increase the effectiveness of inhaled salbutamol.

Methods and analysis

This study is a randomized, open-label superiority trial comparing an interventional group with optimization of respirator settings under use of EIT and a control group without optimization of respirator settings. Ventilation distribution images will be obtained with a commercially available EIT system (PulmoVista™, Dräger Medical, Lübeck, Germany).

Study population and general data acquisition

This study was reviewed and approved by the Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306) and registered in the German Clinical Trial Register (DRKS00014706). It will be conducted in accordance with the Declaration of Helsinki and German laws and regulations. All patients will be admitted to the intensive care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum and will be recruited from June 2018 to June 2019. We will perform EIT measurements with PulmoVista™ (Dräger Medical,

Lübeck, Germany) and a size adjusted chest belt with 16 electrodes. The diagnosis of acute or chronic airway obstruction will include clinical examination and expiration-flow analyzation. Patients at the age of 18 years or more, diagnosed with an acute airway obstruction or known chronic obstructive pulmonary disease under mechanical ventilation for less than 48 hours and providing written informed consent or a positive vote of an independent consultant are eligible for inclusion. Exclusion criteria are: pregnancy or lactation, severe obesity (body mass index > 35), missing medical indication and/or contraindication for inhaled salbutamol administration, Horowitz index ≥ 400, prior phase of long-term ventilation > 14 days, a study-independent medical indication for salbutamol nebulization in obstructive pulmonary disease and/or an acute obstructive condition and procedure of withdrawing life-sustaining therapy. Furthermore, patients with the following pre-existing conditions and operations will be excluded: patients with chest trauma or surgery (e.g. pneumectomy), pneumonia, ARDS with or without ECMO therapy, neuromuscular diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic events, active implants (e.g. pacemakers, ICD) or thoracic skin lesions and wound dressings.

Patients will be treated generally with a multimodal concept, which includes analgesia and sedation, fluid administration, lung-protective mechanical ventilation, anticoagulation, as well as hemodynamic, antibiotic and diagnostic management as recommended by guidelines, standard operating procedures or evidence based best practice. Additionally, after pseudonymization a large body of clinical and demographic data will be entered into a database for later analysis, including pre-existing morbidities, Simplified Acute Physiology Score II (SAPSII), Sepsis-related Organ Failure Assessment Score (SOFA), body mass index (BMI), necessity for renal replacement therapy, ventilator settings, PaO2/FiO2 ratio

(Horowitz index), vital parameters, medications and dosage of vasoactive drugs and blood chemistry values.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measures or study design.

Sample size calculation

A total of 80 mechanically ventilated patients will be included in the study, with 40 patients in the intervention group and 40 patients in the control group. With a total cohort size of n=80, a power of > 95% (alpha error p = 0.05, beta error < 0.05) will be reached, referring to the data from a reference work (table 1) by Malliotakis et al. [18]. Calculations from these values indicate that 76 participants (38 per group) are required to achieve a power of 95% with an alpha error of 5%.

Table 1: Baseline characteristics of sample size calculation

Variable	R_{int}	R_{rs}
$n_{Baseline}$	10	10
n_{30min}	10	10
$Mean_{Baseline} \pm SD$	18.4±4.0 [cmH2O/l/sec]	26.5±4.1 [cmH2O/l/sec]
$Mean_{30min} \pm SD$	15.5±3.6 [cmH2O/l/sec]	23.1±3.6 [cmH2O/l/sec]
Effect-size	0.762	0.881
n_{total} Power 80%	44	34
n_{total} Power 90%	62	46
n_{total} Power 95%	76	58

Airway resistance and related sample size (n) before and 30 min after salbutamol administration in ventilated patients of reference work [18]; R_{int}, R_{rs}: minimum and maximum inspiratory resistance (cm H2O/l/s), respectively

Study design

The total study duration is planned for 18 months. It will take 12 months for recruitment of patients and collection of data, last 6 months are scheduled for analyzation. For each patient an individual study duration is assigned of one day. In the control group, 1.75 hours are scheduled per patient. These include study education and randomization (30 mins), data collection before inhalation (30 mins), drug nebulization and inhalation (15 mins) and measurements after inhalation (30 mins; figure 1). In the interventional group, study explanation and randomization (30 mins), data collection before inhalation (30 mins), the installation and adjustment of EIT (30 mins), the optimization of ventilator settings (15 mins), drug nebulization and inhalation (15 mins), resetting ventilator settings to baseline and measurements 30 minutes after inhalation add up to a total duration of 2.5 hours (figure 1).

Randomization

Block-balanced randomization, in a 1:1 ratio, will be computer-generated by StatsDirect (StatsDirect Ltd., Cambridge, United Kingdom) with random block sizes between n = 10 and n = 20, additionally using random permutations of treatments within each block. Investigators will be blinded to the allocation according to the randomization list until the study patient has been included.

Interventional procedure

EIT and control group undergo an arterial blood gas analysis and corresponding airway measurements to determine baseline parameters before salbutamol inhalation (figure 1; Supplemental material 1+2). Therefore, 1.25 mg / 2.5 mL salbutamol (Sultanol®, Glaxo Smith Kline plc., Brentford, United Kingdom) is applied with a vibrating mesh nebulizer (Solo®, Aerogen, Galway, Ireland).

In the control group, baseline measurement is followed by ultrasound nebulization and inhalation with salbutamol for 15 minutes, following measurements and arterial blood gas analysis 30 minutes after inhalation (figure 1). In addition, all study-relevant data are documented pseudonymised in the case report form (CRF) to ensure a standardized operating (Supplemental material 2). This CRF will be handed over to the principal investigator immediately after collection of data. The principal investigator keeps the study documents in a study folder not accessible to third parties.

In the intervention group, baseline measurements are followed by the standardized setup and adjustment of EIT, where a belt with 16 integrated electrodes is attached circularly to the thorax (Supplemental material 3). This is followed by the optimization of the respirator settings by means of EIT using a defined algorithm (figure 2), according the recommendations of the Translational EIT Development Study Group (TREND) [5]. The EIT algorithm focuses on homogenisation of lung ventilation described by the fast-response parameter ROI (region of interest) to titrate protective PEEP and tidal volume combinations (figure 2). The next step is nebulization and inhalation of salbutamol for 15 minutes. Subsequently, ventilator settings are reset to baseline as before EIT adjustment. After a period of 30 minutes, a new data collection after salbutamol administration including EIT

measurement is done and an arterial blood gas analysis is performed (figure 1). Data is documented in the CRF (Supplemental material 1).

Objectives

The primary objective is to assess if additional use of EIT can increase the effectiveness of inhaled salbutamol, and therefore decrease the airway resistance 30 minutes after salbutamol inhalation more effective than without usage of EIT. The secondary objectives will be to compare the EIT-intervention group and the control group regarding:

- Before and 30 minutes after salbutamol inhalation:
  - Changes made in ventilator settings under EIT,
  - tidal volume, compliance, resistance, arterial oxygen partial pressure (p_aO2), Horowitz index, arterial carbon dioxide partial pressure (p_aCO_2), peripheral and arterial oxygen saturation,
  - upper and lower inflection point of the pressure-volume curve,
  - EIT parameters: Region of Interest (ROI), changes of end expiratory lung volume (Delta-EELV) and changes of end expiratory lung impedance (Delta-EELI),
  - heart rate, blood pressure
- duration of mechanical ventilation,
- length of stay on ICU and hospital, readmission rate on ICU.
- 30-days mortality

Data collection

The documentation of the data will be pseudonymized and computer-assisted from our patient data management system (PDMS) (Dräger ICM, Dräger Medical, Lübeck, Germany) in a central offline database. Therefore, all collected data will solely be provided in pseudonymized form for further study analyzation. Access to the pseudonymization key, which is password protected, is only available to the principal investigator of this study. All above mentioned parameters will be collected during the patients stay in hospital until discharge, death or 30th day of stay on ICU. In case of discharge from ICU, follow-up to evaluate 30-days survival will be performed by visit on normal ward or a phone call by one of the investigators. Data entered in the central offline database will be monitored by an independent clinical research associate and checked for consistency and missing values. All records, subjects' identities and data management will remain confidential with the General Data Protection Regulation (GDPR) of the European Parliament and the Council of the European Union. Furthermore, this protocol was designed following the recommendations for interventional trials (SPIRIT; figure 3; Supplemental material 4).

Statistical analysis

Since this is a study designed to demonstrate superiority of the primary endpoint (change in airway resistance 30 minutes after salbutamol inhalation), whether an additional use of EIT increases the effectiveness of inhaled salbutamol, we will perform an intention-to-treat and additionally a per-protocol analysis as recommended by the CONSORT guidelines [19]. The per-protocol population will be defined as randomized patients without major protocol deviations, such as non-considerations of exclusion criteria or missing data for the primary endpoint. Baseline characteristics of all patients will be described per group. Qualitative data will be described as frequencies and percentages. Continuous variables are presented as

means ± standard deviation in case of normal distribution and as median and interquartile range (25th; 75th percentile) in case of non-normally distributed variables. Continuous variables will be compared using parametric Student's t-test or non-parametric Mann-Whitney-U-Test. Categorical variables will be characterized by numbers with percentages and will be compared using the Chi-square test or a Fisher's exact test. Superiority will be assumed, if the 95% confidence interval for the difference between the means excludes zero or p-values are statistically significantly different at an a priori alpha error of less than 0.05. The graphical processing of variables will be performed depending on the measurement level of the variables as histograms, mean value curves with corresponding standard deviations or box whisker plots.

Ethics and dissemination

A manuscript with the results of the study will be published in a peer-reviewed journal. The study has received the following approvals: Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306). On completion of the trial, and after publication of the primary manuscript, data will be made availabele in a free accessable online repository.

Discussion

This study, to our knowledge, is the first interventional trial assessing, whether the additional usage of EIT can improve the effectiveness of inhalative drug administration in critical ill and ventilated patients.

The administration of inhaled drugs is routinely used in intensive care units, due to the advantage of delivering high drug concentrations to the airway, along with rapid onset of action and fewer systemic side effects. However, it is believed that the beneficial effects of inhaled drugs are smaller in patients on mechanical ventilation than in those breathing spontaneously. In this regard, a previous study could demonstrate that only 2.9% of the administered drug dose reached the distal airway in ventilated patients, compared to 11.9% in patients without artificial airway [16]. A recently published review, regarding inhalative drug therapy in mechanical ventilation, stated that ventilator settings play an crucial role in inhaled drug delivery [14]. A tidal volume of at least 500 mL, increased inspiratory time and a low inspiratory flow are general recommendations in order to optimize drug distribution in the lungs [14 20 21]. Nevertheless, attention should be paid to serious adverse effects of high (> 500 mL) tidal volumes, especially in patients with acute or chronic airway obstructions. In these patients high tidal volumes can lead to dynamic hyperinflation or can cause a severe barotrauma [14]. Furthermore, no clinical studies exist showing the beneficial effects of any particular ventilation mode on inhaled drug delivery [20 21]. Therefore, a new diagnostic and guiding tool for adequate optimization of ventilator settings prior to nebulization of inhalative drugs would be desirable. Hence, fast, non-invasive and reliable assessment at bedside in critical ill and ventilated patients is one of the cornerstones for modern intensive care monitoring. EIT, although with some constrains, may be a promising solution. EIT images are valid measurements of the regional distribution of ventilation and changes in lung volume in real-time. This dynamic evaluation makes EIT a promising tool for guided optimization of

ventilator parameters on an individualized base. Several studies in the last years have already demonstrated that EIT-guided respirator optimization results in significant improved respiratory mechanics and improved gas exchange [1 4 7 22]. However, a global standard based on a broad base of evidence was one of the most discussed topics in Respiratory Medicine over the last years. Therefore, the plausibility of EIT measurements highly depends on the correct belt position, proper impedance visualization, correct analysis and data interpretation [23].

The crucial step forward was the publication of recommendations of the TREND (Translational EIT Development Study) group [5]. These recommendations highlight the need for a consensus about examinations, consistent terminology and generally accepted approaches to EIT images and analysis. Based on this highly appreciated consensus statement we are now able to compare, understand and reproduce study findings from among different research groups and provide a standardized use in clinical routine.

A further limitation is that EIT captures only ventral-to-dorsal ventilation distribution. However, Bikker et al. also reported different ventilation distribution between cranial and caudal lung levels during decremental PEEP trials [24], concluding that existing EIT systems will not be able to cover the optimal PEEP titration for the whole lung.

Despite the possible limitations of EIT, this device can provide a remarkable advance in the field of individualized and guided mechanical ventilation adjustments. Therefore, this study can shed light on the extent to which the additional use of EIT for optimizing the ventilator settings can increase the effectiveness of inhaled salbutamol.

Outlook

EIT could help to visualize and verify an effective nebulization that could provide a safe, efficient and individualized way of inhalative drug application, e.g. by increasing the effective dose reaching distal airway. Therefore, these results are also of great interest beyond salbutamol nebulization, e.g. for safe usage of inhalative antibiotics in critical ill and ventilated patients.

Trial status

The first patients were randomized in June 2018. The inclusion of participants is ongoing and is expected to continue until June 2019.

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List of abbreviations

ARDS	Acute respiratory distress syndrome
BMI	Body mass index
CRF	Case report form
delta-EELI	Change of end expiratory lung impedance
delta-EELV	Change of end expiratory lung volume
DRKS	Deutsches Register für klinische Studien
ECMO	Extracorporeal membrane oxygenation
EIT	Electrical impedance tomography
GDPR	General data protection regulation
ICD	Implantable cardioverter defibrillator
ICU	Intensive care unit
NYHA	New York Heart Association
p_aCO_2	Partial pressure of arterial carbon dioxide
p_aO_2	Partial pressure of arterial oxygen
PDMS	Patient data management systems
PEEP	Positive end-expiratory pressure
R	Resistance

ROI	Region of interest
SAPSII	Simplified acute physiology score II
SD	Standard deviation
SOFA score	Sepsis-related organ failure assessment score
Spirit	Standard Protocol Items - Recommendations for Interventional
TREND group	Translational EIT Development Study group

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of the Medical Faculty of the Ruhr-Universität Bochum (no. 17-6306) and written informed consent or a positive vote of an independent consultant are eligible for inclusion.

Consent for publication

Not applicable

Availability of data and material

The data of the described study will be available from the Dryad repository after publication.

Conflict of interests

None to declare

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Author Statement

Dr. med. Tim Rahmel: Main author of this manuscript, written and revising the manuscript

Alexandra Koniusch: Supporting methodical description and participated in the design of this study

Dr. med. Günther Oprea: Supporting data collection, participated in the design of this study, and revising the manuscript

Martin Schwertner: Supporting data collection, participated in the design of this study, and revising the manuscript

Prof. Dr. med. Michael Adamzik: Supporting data collection, participated in the design of this study and revising the manuscript

Dr. med. Hartmuth Nowak: Supporting data collection, participated in the design of this study, written and revising the manuscript

All authors read and approved the final manuscript.

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Legends

Figure 1: Flowchart of interventional procedures on intervention and control group with duration of each step and performed measurements (EIT = electrical impedance tomography, ICU = intensive care unit)

Figure 2: Flowchart of EIT-guided optimization of ventilator settings (ROI = region of interest, Pmax = maximum airway pressure, Pinsp = inspiratory pressure, PEEP = positive end expiratory pressure)

Figure 3: Schedule of enrolment, interventions and assessments – SPIRIT Figure (SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials, EIT = electrical impedance tomography, ICU = intensive care unit)

Supplemental material

Supplemental material 1: Case report form of intervention group

Supplemental material 2: Case report form of control group

Supplemantal material 3: Additional information - EIT algorithm

Supplemental material 4: Spirit checklist

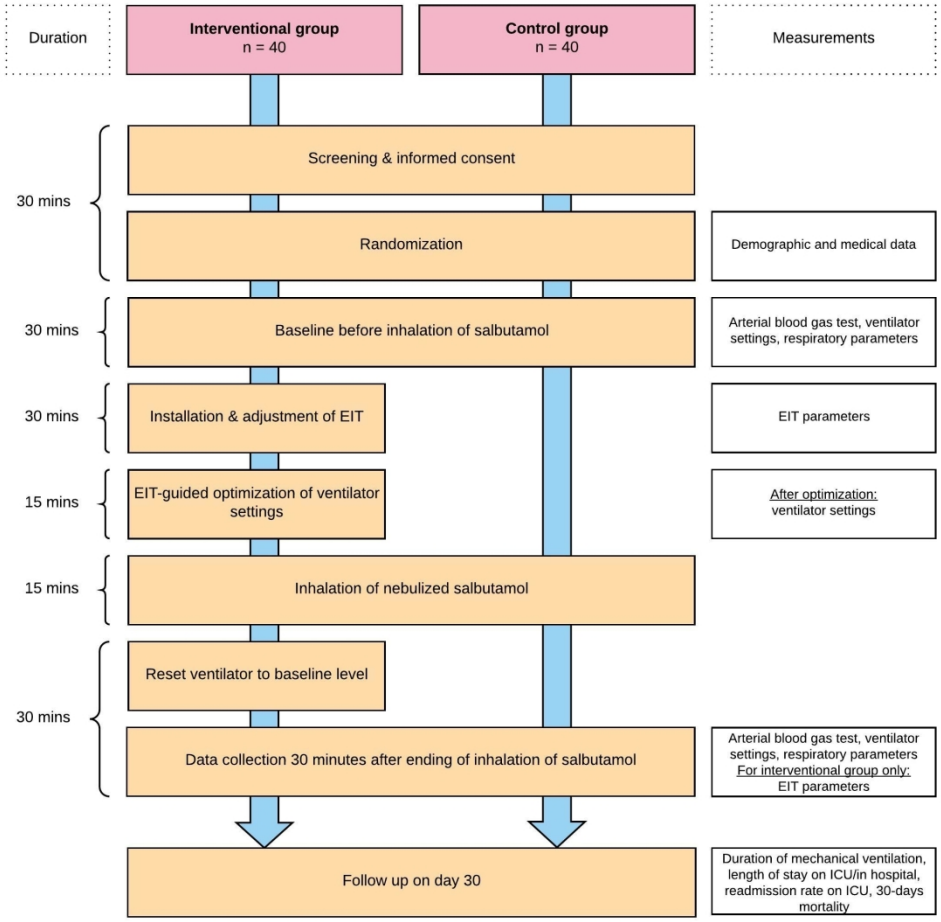


Figure 1: Flowchart of interventional procedures on intervention and control group with duration of each step and performed measurements (EIT = electrical impedance tomography, ICU = intensive care unit)

184x181mm (300 x 300 DPI)

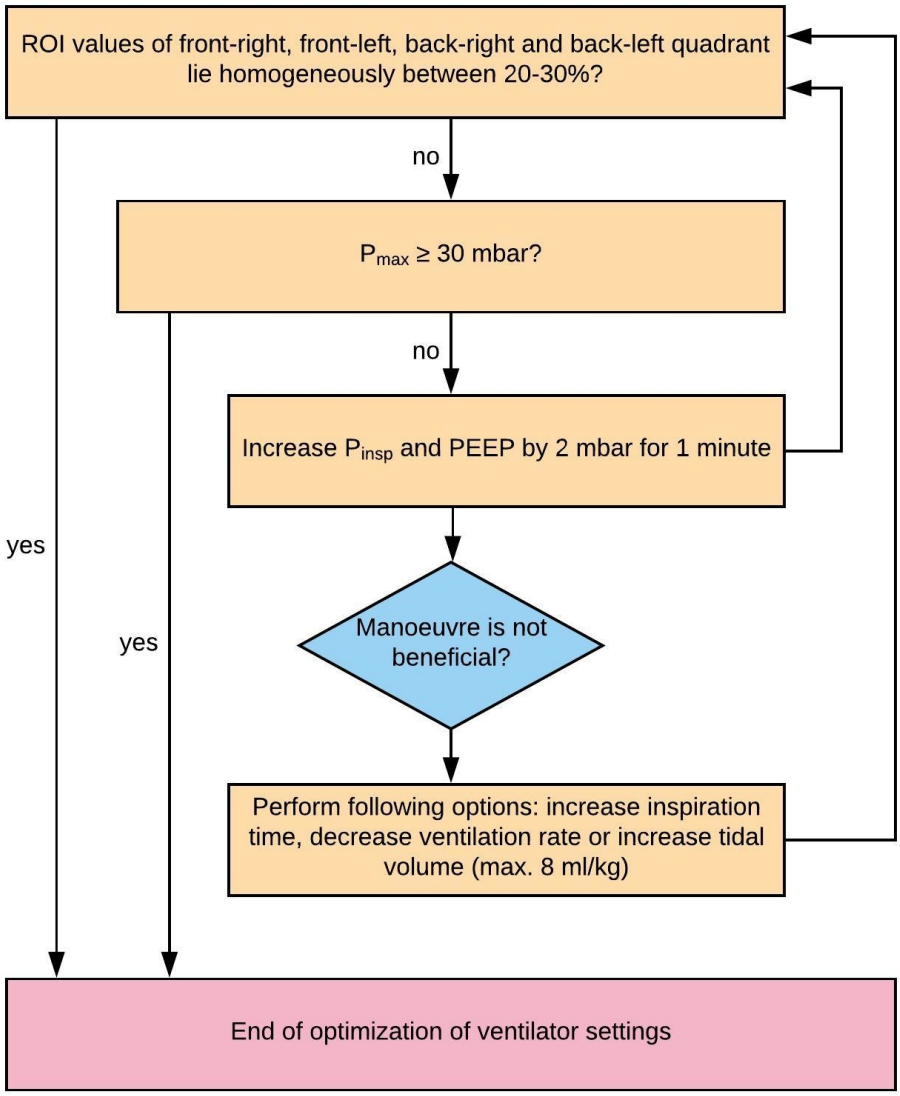


Figure 2: Flowchart of EIT-guided optimization of ventilator settings (ROI = region of interest, Pmax = maximum airway pressure, Pinsp = inspiratory pressure, PEEP = positive end expiratory pressure)

114x136mm (300 x 300 DPI)

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
TIMEPOINT	Prior randomization	0	Baseline	After Baseline	After intervention	30 days
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
INTERVENTIONS:						
EIT-guided optimization of ventilation, inhalation of nebulized salbutamol afterwards				X		
Inhalation of nebulized salbutamol				X		
ASSESSMENTS:						
Demographic & medical data			X			
Ventilator settings			X		X	
Respiratory parameters			X		X	
Arterial blood gas test			X		X	
EIT parameters (*for EIT group only*)			X		X	
Duration of mechanical ventilation, length of stay on ICU/in hospital, readmission rate on ICU						X
30-days mortality						X

Figure 3: Schedule of enrolment, interventions and assessments – SPIRIT Figure (SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials, EIT = electrical impedance tomography, ICU = intensive care unit)

139x224mm (300 x 300 DPI)

Randomization |__|__|.|__|__|.201__

No. |__|__| ***CRF EIT-Trial (intervention group)*** VU

Patient

	Inclusion criteria	Yes	No
•	Age ≥ 18 years	☐	☐
•	Known obstructive airway disease or acute airway obstruction ***and*** • Medical indication for salbutamol inhalation	☐	☐
•	Mechanical ventilated patient (<48h) and Horowitz index (p_aO_2/F_iO_2) < 400	☐	☐
•	Written informed consent or positive vote of an independent consultant	☐	☐

	Exclusion criteria	Yes	No
•	Refusal of the patient or lack of consent	☐	☐
•	Lack of medical indication and/or contraindications to administration of salbutamol	☐	☐
•	Age < 18 years	☐	☐
•	Pre-existing conditions or operations: Patients with chest trauma or chest surgery; thoracic skin lesions and wound dressings; ARDS and/or ECMO therapy; neuromuscular diseases; severe cardiac diseases (e.g. NYHA III-IV); acute ischemic events; active implants (e.g. pacemakers, ICDs)	☐	☐
•	Severe obesity (BMI > 35)	☐	☐
•	Prior phase of long-term ventilation > 14 days	☐	☐
•	Do-not-resuscitate order	☐	☐
•	Pregnancy or lactation	☐	☐

- Copy patient file/printout! (Anamnesis, concomitant medications, concomitant diseases, physical examination, ECG, vital parameters ☐ carried out

  ☐ male ☐ female

  Height |__|__|__| cm **weight** |__|__|__|.|__| kg **BMI** |__|__|.|__| kg/m^2

- **Blood pressure** |__|__|__| / |__|__| **heart rate** |__|__|__| bpm

  body temperature |__|__|.|__| °C

- Pregnancy excluded ☐

- Note participation in the medical record! ☐ carried out

- **Procedure in the intervention group**
  - Study education including randomization (30 min) ☐
    - Measurement of SOFA-Score (_____), PCT (_____), CRP (_____), antibiotics (_____), vital parameters (_____), catecholamines (_____), sedation (_____) ☐
  - Data collection before inhalation (30 min)
    - Measurement of airway resistance before salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
  - Installation and adjustment of the EIT (30 min) ☐
    - Measurement of Region of Interest (ROI) (_____), changes of end-exspiratory lung volume (Delta-EELV) (_____) and changes of end-exspiratory lung impedance (Delta-EELI) (_____) ☐
  - Optimization of ventilator settings (15 min) ☐
    - Measurement of ventilator settings after EIT-guided optimization (P_{insp} (_____), PEEP (_____), I:E (_____), T_{insp} (_____), RR (_____), ventilation mode (_____)) ☐
  - Salbutamol nebulization and inhalation (15 min) ☐
  - Reset ventilator to baseline level ☐
  - Data collection after inhalation (30 min)
    - Measurement of airway resistance after salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
    - Measurement of Region of Interest (ROI) (_____), changes of end-exspiratory lung volume (Delta-EELV) (_____) and changes of end-exspiratory lung impedance (Delta-EELI) (_____) ☐

Date |__|__|.|__|__| 201__ Signature of the examiner _____

Randomization |__|__|.|__|__|.201__

No. |__|__| ***CRF EIT-Trial (control group)*** VU

Patient

Inclusion criteria	Yes	No
• Age ≥ 18 years	☐	☐
• Known obstructive airway disease or acute airway obstruction ***and*** • Medical indication for salbutamol inhalation	☐	☐
• Mechanical ventilated patient (<48h) and Horowitz index (p_aO_2/F_iO_2) < 400	☐	☐
• Written informed consent or positive vote of an independent consultant	☐	☐

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	☐	☐
• Lack of medical indication and/or contraindications to administration of salbutamol	☐	☐
• Age < 18 years	☐	☐
• Pre-existing conditions or operations: Patients with chest trauma or chest surgery; thoracic skin lesions and wound dressings; ARDS and/or ECMO therapy; neuromuscular diseases; severe cardiac diseases (e.g. NYHA III-IV); acute ischemic events; active implants (e.g. pacemakers, ICDs)	☐	☐
• Severe obesity (BMI > 35)	☐	☐
• Prior phase of long-term ventilation > 14 days	☐	☐
• Do-not-resuscitate order	☐	☐
• Pregnancy or lactation	☐	☐

- Copy patient file/printout! (Anamnesis, concomitant medications, concomitant diseases, physical examination, ECG, vital parameters ☐ carried out

  ☐ male ☐ female

  Height |__|__|__| cm **weight** |__|__|__|.|__| kg **BMI** |__|__|.|__| kg/m^2

- **Blood pressure** |__|__|__| / |__|__| **heart rate** |__|__|__| bpm

  body temperature |__|__|.|__| °C

- Pregnancy excluded ☐

- Note participation in the medical record! ☐ carried out

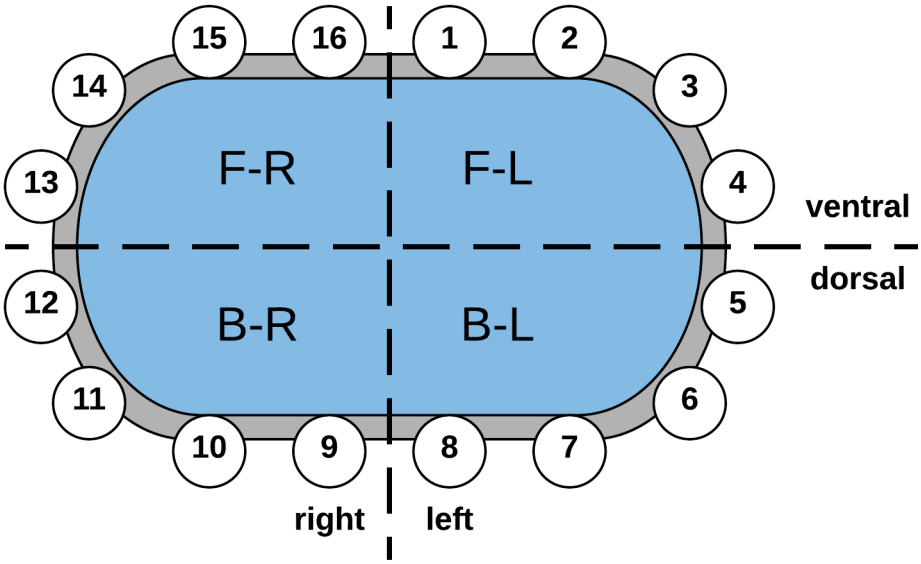
- **Procedure in the control group**
  - Study education including randomization (30 min) ☐
    - Measurement of SOFA-Score (_____), PCT (_____), CRP (_____), antibiotics (_____), vital parameters (_____),catecholamines (_____), sedation (_____) ☐
  - Data collection before inhalation (30 min)
    - Measurement of airway resistance before salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
  - Salbutamol nebulization and inhalation (15 min) ☐
  - Data collection after inhalation (30 min)
    - Measurement of airway resistance after salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐

Date |__|__|.|__|__| 201__ Signature of the examiner _____

Additional information - EIT algorithm

Installation procedure for EIT (PulmoVista 500, Dräger Medical, Lübeck, Germany)		
1.	To turn on the EIT system press the green “Power on”-button in the left, lower corner of the screen (it will light up after switching on). Afterwards, the system will be in “Standby”-mode.	☐
2.	Connect the main plug of the trunk cable to the upper connection socket. Connect the color-coded plugs to the corresponding test socket (green = right/R), red = left/L).	☐
3.	Choose “System Test” on the touch screen. Press “Start” and confirm this selection by pressing the control knob in the right, lower corner of the screen. The EIT system will perform a self-check to ensure proper functioning of all components and the trunk cable.	☐
4.	Choose a belt according to the patient’s circumference of chest (S = 70-85 cm, M = 80-96 cm, L = 92-110 cm, XL = 106-127 cm, XXL = 124-150 cm). Connect electrodes of the corresponding connection cable with the belt (number 1 to 1, number 2 to 2, …, number 16 to 16).	☐
5.	Placement of EIT belt: Between 8th and 9th electrode is a perceptible silicone mark, place this mark centrally over the spine between 4th and 6th intercostal space. Both lateral ends are folded forward towards the chest and connected in front of the sternum, so that electrode number 1 is placed left and number 16 right to the sternum (figure 1). Connect the “C”-electrode of the connection cable with the seal of the EIT belt. Place an ECG-electrode on the skin of the abdomen and connect it with the “REF”-electrode of the connection cable.	☐
6.	Plug the green and red color-coded plugs of the trunk cable out of the test socket and connect them to the connection cable of the EIT belt (ensure the correct connection: green to green and red to red).	☐
7.	Select the option “New Patient” on the touch screen in the Start/Standby menu. By choosing “Signal Check” skin resistance of each electrode is shown, a blue bar appears for all electrodes. If skin resistance is insufficiently high (> 300 ohms), the corresponding electrode is marked in red. In that case, prove the correct positioning of that electrode, moisturize the electrode with water or electrode gel where applicable. Move on to step 8 when all bars appear blue.	☐
8.	Register patient data by selecting “New Patient”. Afterwards, press “Start” to start EIT measurements. A short calibration is performed (approximately 30 seconds), afterwards the system is ready for measuring.	☐

Figure 1: schematic cross-section image of thorax with positions of 16 EIT electrodes at the level of 4th to 6th intercostal space *(F-R = front-right quadrant, F-L = front-left quadrant, B-R = back-right quadrant, B-L = back-left quadrant)*



Measurement of EIT parameters (ROI, Delta-EELV and Delta-EELI)		
1.	ROI (Region of interest): Choose "Views" in right upper corner of the screen and tap on "Full Screen". Values for each quadrant (F-R, F-L, B-R, B-L) are displayed.	☐
2.	Delta-EELV (changes of end exspiratory lung volume): Choose "Views" in right upper corner of the screen and tap on "End exspiratory trend".	☐
3.	Delta-EELI (changes of end exspiratory lung impedance): Choose "Views" in right upper corner of the screen and tap on "Delta-EELI".	☐

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Evaluation of inhaled salbutamol effectiveness under supportive use of electrical impedance tomography in ventilated ICU patients: study protocol for a randomized controlled clinical trial ***(page 1)***
Trial registration	2	German trial register (DRKS.de); ID: DRKS00014706; registered on 14th May 2018 ***(page 6)***
Protocol version	3	10th March 2018, version 1.0
Funding	4	We acknowledge support by the DFG Open Access Publication Funds of the Ruhr-University Bochum (Ref. No. IN-1214264), just for financial support for publication costs. This will have no impact on our study design or collection, analysis and interpretation of our data. ***(page 19)***

Roles and responsibilities	5a	Dr. med. Tim Rahmel, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Principal investigator, main author of this manuscript, written and revising the manuscript Alexandra Koniusch, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting methodical description and participated in the design of this study Dr. med. Günther Oprea, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting data collection, participated in the design of this study, and revising the manuscript Martin Schwertner, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting data collection, participated in the design of this study, and revising the manuscript Prof. Dr. med. Michael Adamzik, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting data collection, participated in the design of this study and revising the manuscript Dr. med. Hartmuth Nowak, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Co-Principal investigator, supporting data collection, participated in the design of this study, written and revising the manuscript ***(pages 19-20)***
	5b	NA
	5c	Support is granted by the DFG Open Access Publication Funds of the Ruhr-University Bochum (Ref. No. IN-1214264), just for financial support for publication costs. This will have no impact on our study design or collection, analysis and interpretation of our data. ***(page 19)***
	5d	NA

Introduction

Background and rationale	6a	The inhalative administration of drugs is a non-invasive application form that is regularly used in the treatment of ventilated patients in critical care setting. However, assessment of effectiveness or distribution of nebulized drugs is one of the lacking cornerstones of modern intensive care monitoring as several studies could not show a benefit of inhaled medication. Unfortunately, these studies could not address the crucial issue whether the medication was distributed effectively in critical ill ventilated patients. To the present day, there is no established non-invasive real-time monitoring to measure or visualize the effectiveness or distribution of nebulized drugs in ventilated patients at bedside. Electrical impedance tomography (EIT) may provide a promising new monitoring and guiding tool for an adequate optimization of mechanical ventilation in critically ill patients. EIT makes use of changes in thoracic impedance, which in turn result in different concentrations of free ions due to changes in air content of the lung tissue. Therefore, EIT may assist in defining mechanical ventilation settings, assess distribution of tidal volume and evaluation of associated pathologies at bedside. Prior studies demonstrated that equivalent diagnostic findings between EIT and thoracic computed tomography could be achieved in critically ill patients in terms of regional ventilation in different thoracic regions, and also offered a valid examiner-independent test reproducibility of the results. ***(pages 4-5)***
	6b	As no non-invasive real-time monitoring for visualization of nebulized drugs in ventilated patients at bedside is established to the present day, comparator will be standard of care with no EIT-optimized application of salbutamol. ***(pages 4-5)***
Objectives	7	Our study wants to elucidate the extent to which the effectiveness of inhaled drugs, e.g. β2 sympathomimetics, can be optimized by the additional use of EIT for adjusting ventilator settings. Accordingly, we want to test the hypothesis whether EIT can increase the effectiveness of inhaled salbutamol. ***(page 5)***
Trial design	8	This study is a randomized, open-label superiority trial, comparing two groups of mechanically ventilated patients with an acute or chronic bronchial airway obstruction according the effectiveness of inhaled salbutamol with (intervention) or without (control) additional use of EIT for optimizing the ventilator settings. ***(page 6)***

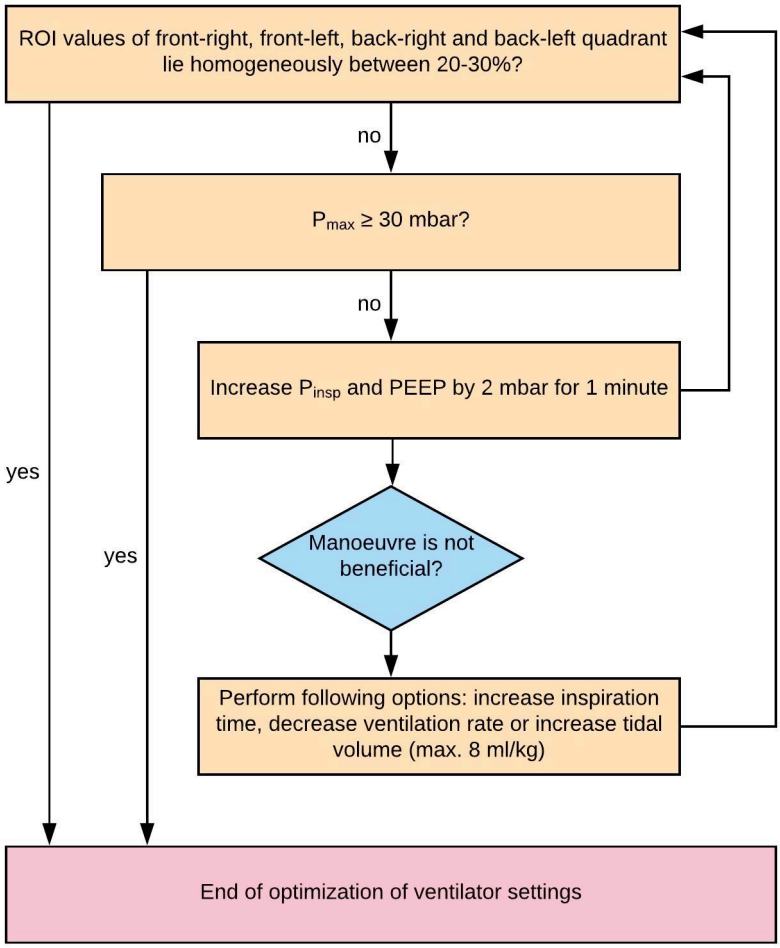
Methods: Participants, interventions, and outcomes

Study setting	9	This study will be conducted at the interdisciplinary, operative intensive care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum, a university hospital of Ruhr-University Bochum in Bochum, Germany. ***(page 6)***

Eligibility criteria	10	Patients at the age of 18 years or more, diagnosed with an acute airway obstruction or known chronic obstructive pulmonary disease under mechanical ventilation for less than 48 hours and providing written informed consent or a positive vote of an independent consultant are eligible for inclusion. ***(page 6)***
		Exclusion criteria are: pregnancy or lactation, severe obesity (body mass index > 35), missing medical indication and/or contraindication for inhaled salbutamol administration, Horowitz index ≥ 400, prior phase of long-term ventilation > 14 days, a study-independent medical indication for salbutamol nebulization in obstructive pulmonary disease and/or an acute obstructive condition and procedure of withdrawing life-sustaining therapy. Furthermore, patients with the following pre-existing conditions and operations will be excluded: patients with chest trauma or surgery (e.g. pneumectomy), pneumonia, ARDS with or without ECMO therapy, neuromuscular diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic events, active implants (e.g. pacemakers, ICD) or thoracic skin lesions and wound dressings. ***(page 6-7)***

Interventions	11a	EIT and control group undergo an arterial blood gas analysis and corresponding airway measurements to determine baseline parameters before salbutamol inhalation. Therefore, 1.25 mg / 2.5 mL salbutamol (Sultanol®, Glaxo Smith Kline plc., Brentford, United Kingdom) is applied with a vibrating mesh nebulizer (Solo®, Aerogen, Galway, Ireland). ***(page 9)***
		In the control group, baseline measurement is followed by ultrasound nebulization and inhalation with salbutamol for 15 minutes, following measurements and arterial blood gas analysis 30 minutes after inhalation. In addition, all study-relevant data are documented pseudonymised in the case report form (CRF) to ensure a standardized operating. This CRF will be handed over to the principal investigator immediately after collection of data. The principal investigator keeps the study documents in a study folder not accessible to third parties. ***(page 9)***
		In the intervention group, baseline measurements are followed by the standardized setup and adjustment of EIT, where a belt with 16 integrated electrodes is attached circularly to the thorax. This is followed by the optimization of the respirator settings by means of EIT using a defined algorithm, according the recommendations of the Translational EIT Development Study Group (TREND) (see below, figure 2). The EIT algorithm focuses on homogenisation of lung ventilation described by the fast-response parameter ROI (region of interest) to titrate protective PEEP and tidal volume combinations. The next step is nebulization and inhalation of salbutamol for 15 minutes. Subsequently, ventilator settings are reset to baseline as before EIT adjustment. After a period of 30 minutes, a new data collection after salbutamol administration including EIT measurement is done and an arterial blood gas analysis is performed (figure 1). Data is documented in the CRF. ***(page 9-10)***

EIT algorithm for optimization of respirator settings (figure 2):



11b As study procedure is only done once, no specific criteria for discontinuing or modifying allocated interventions is needed.

11c NA

11d NA

Outcomes	12	The primary objective is to assess if additional use of EIT can increase the effectiveness of inhaled salbutamol, and therefore decrease the airway resistance 30 minutes after salbutamol inhalation more effective than without usage of EIT. ***(page 10)***
		The secondary objectives will be to compare the EIT-intervention group and the control group regarding: Before and 30 minutes after salbutamol inhalation [Changes made in ventilator settings under EIT, tidal volume, compliance, resistance, arterial oxygen partial pressure (paO2), Horowitz index, arterial carbon dioxide partial pressure (paCO2), peripheral and arterial oxygen saturation, upper and lower inflection point of the pressure-volume curve, EIT parameters: Region of Interest (ROI), changes of end expiratory lung volume (Delta-EELV) and changes of end expiratory lung impedance (Delta-EELI), heart rate, blood pressure]; duration of mechanical ventilation; length of stay on ICU and hospital, readmission rate on ICU; 30-days mortality. ***(pages 10-11)***
		Additionally, after pseudonymization a large body of clinical and demographic data will be entered into a database for later analysis, including pre-existing morbidities, Simplified Acute Physiology Score II (SAPSII), Sepsis-related Organ Failure Assessment Score (SOFA), body mass index (BMI), necessity for renal replacement therapy, ventilator settings, PaO2/FiO2 ratio (Horowitz index), vital parameters, medications and dosage of vasoactive drugs and blood chemistry values. ***(page 7)***

Participant timeline

13 Study schedule is presented in the following table (figure 3):

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
TIMEPOINT	Prior randomization	0	Baseline	After Baseline	After intervention	30 days
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
INTERVENTIONS:						
EIT-guided optimization of ventilation, inhalation of nebulized salbutamol afterwards				X		
Inhalation of nebulized salbutamol				X		
ASSESSMENTS:						
Demographic & medical data			X			
Ventilator settings			X		X	
Respiratory parameters			X		X	
Arterial blood gas test			X		X	
EIT parameters (*for EIT group only*)			X		X	
Duration of mechanical ventilation, length of stay on ICU/in hospital, readmission rate on ICU						X
30-days mortality						X

Sample size	14	A total of 80 mechanically ventilated patients will be included in the study, with 40 patients in the intervention group and 40 patients in the control group. With a total cohort size of n=80, a power of > 95% (alpha error p = 0.05, beta error < 0.05) will be reached, referring to the data from a reference work (table 1) by Malliotakis et al. Calculations from these values indicate that 76 participants (38 per group) are required to achieve a power of 95% with an alpha error of 5%. ***(pages 7-8)***

Variable	**R_{int}**	**R_{rs}**
$n_{Baseline}$	10	10
n_{30min}	10	10
$Mean_{Baseline}$ ± SD	18.4±4.0 [cmH2O/l/sec]	26.5±4.1 [cmH2O/l/sec]
$Mean_{30min}$ ± SD	15.5±3.6 [cmH2O/l/sec]	23.1±3.6 [cmH2O/l/sec]
Effect-size	0.762	0.881
n_{total} Power 80%	44	34
n_{total} Power 90%	62	46
n_{total} Power 95%	76	58

Airway resistance and related sample size (n) before and 30 min after salbutamol administration in ventilated patients of reference work 18; Ri_{nt}, R_{rs}: minimum and maximum inspiratory resistance (cm H2O/l/s), respectively

Recruitment	15	We will ensure patient recruitment by screening patients on ICU daily. Eligible patients will be approached by the principal inverstigator and/or one of the eligible physicians.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Block-balanced randomization, in a 1:1 ratio, will be computer-generated by StatsDirect (StatsDirect Ltd., Cambridge, United Kingdom) with random block sizes between n = 10 and n = 20, additionally using random permutations of treatments within each block. Investigators will be blinded to the allocation according to the randomization list until the study patient has been included. ***(page 9)***
Allocation concealment mechanism	16b	Concealment of allocation mechanism will be performed by using sealed envelopes. For each patient included, a sealed envelope will be drawn and opened.

Implementation	16c	A physician who is independent to this trial will generate allocation sequence. Enrolment and assignment will be done by the principal investigator and/or eligible physicians.
Blinding (masking)	17a	No blinding will be performed.
	17b	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	The documentation of the data will be pseudonymized and computer-assisted from our patient data management system (PDMS) (Dräger ICM, Dräger Medical, Lübeck, Germany) in a central offline database. ***(page 11)***
	18b	All above mentioned parameters will be collected during the patients stay in hospital until discharge, death or 30th day of stay on ICU. In case of discharge from ICU, follow-up to evaluate 30-days survival will be performed by visit on normal ward or a phone call by one of the investigators. ***(page 11)***
Data management	19	All collected data will solely be provided in pseudonymized form for further study analyzation. Access to the pseudonymization key, which is password protected, is only available to the principal investigator of this study. ***(page 11)***

Statistical methods	20a	Since this is a study designed to demonstrate superiority of the primary endpoint (change in airway resistance 30 minutes after salbutamol inhalation), whether an additional use of EIT increases the effectiveness of inhaled salbutamol, we will perform an intention-to-treat and additionally a per-protocol analysis as recommended by the CONSORT guidelines. The per-protocol population will be defined as randomized patients without major protocol deviations, such as non-considerations of exclusion criteria or missing data for the primary endpoint. Baseline characteristics of all patients will be described per group. Qualitative data will be described as frequencies and percentages. Continuous variables are presented as means ± standard deviation in case of normal distribution and as median and interquartile range (25th; 75th percentile) in case of non-normally distributed variables. Continuous variables will be compared using parametric Student's t-test or non-parametric Mann-Whitney-U-Test. Categorical variables will be characterized by numbers with percentages and will be compared using the Chi-square test or a Fisher's exact test. Superiority will be assumed, if the 95% confidence interval for the difference between the means excludes zero or p-values are statistically significantly different at an a priori alpha error of less than 0.05. The graphical processing of variables will be performed depending on the measurement level of the variables as histograms, mean value curves with corresponding standard deviations or box whisker plots. ***(pages 11-12)***
	20b	NA
	20c	We will perform an intention-to-treat and additionally a per-protocol analysis as recommended by the CONSORT guidelines. ***(page 11)***
Methods: Monitoring		
Data monitoring	21a	Data entered in the central offline database will be monitored by an independent clinical research associate and checked for consistency and missing values. ***(page 11)***
	21b	No interim analyses are planned.
Harms	22	During study conduct and follow-up patients will be continuously monitored for possible adverse events. Those will be recorded in the database.
Auditing	23	NA
Ethics and dissemination		
Research ethics approval	24	This study was reviewed and approved by the Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306). ***(page 6)***

Protocol amendments	25	Prinicipal investigator will communicate all important modifications to study personnel.
Consent or assent	26a	Informed consent will be obtained by principal investigator and/or eligible physicians.
	26b	NA
Confidentiality	27	All records, subjects' identities and data management will remain confidential with the General Data Protection Regulation (GDPR) of the European Parliament and the Council of the European Union. ***(page 11)***
Declaration of interests	28	None to declare ***(page 19)***
Access to data	29	The data of the described study will be available from the Dryad repository after publication. ***(page 19)***
Ancillary and post-trial care	30	No arrangements have been made for compensation to those who suffer harm from trial participation. This has been stated in the informed consent.
Dissemination policy	31a	A manuscript with the results of the study will be published in a peer-reviewed journal. ***(page 12)***
	31b	NA
	31c	A publication of this study protocol in BMJ Open is submitted.
Appendices		
Informed consent materials	32	An informed consent form is available in German language can be obtained from the authors.
Biological specimens	33	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Evaluation of inhaled salbutamol effectiveness under supportive use of electrical impedance tomography in ventilated ICU patients: study protocol for a randomized controlled clinical trial

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Keywords:	optimization of ventilation, inhalation, nebulization, region of interest, end expiratory lung volume, end expiratory lung impedance

Evaluation of inhaled salbutamol effectiveness under supportive use of electrical impedance tomography in ventilated ICU patients: study protocol for a randomized controlled clinical trial

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Running head: EIT-guided ventilator optimization for salbutamol inhalation

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Abstract

Introduction: The inhalative administration of drugs is a non-invasive application form that is regularly used in the treatment of ventilated patients in critical care setting. However, assessment of effectiveness or distribution of nebulized drugs is one of the lacking cornerstones of modern intensive care monitoring. Electrical impedance tomography (EIT) may provide a promising new monitoring and guiding tool for an adequate optimization of mechanical ventilation in critically ill patients. EIT may assist in defining mechanical ventilation settings, assess distribution of tidal volume and evaluation of associated pathologies at bedside. This study wants to elucidate the extent to which the effectiveness of inhaled salbutamol can be increased by the additional use of EIT for optimization of respirator settings.

Methods and analysis: This study is a randomized, open-label superiority trial, conducted on an intensive care unit of a German university hospital, comparing two groups of mechanically ventilated patients with an acute or chronic bronchial airway obstruction according the effectiveness of inhaled salbutamol with (intervention) or without (control) additional use of EIT for optimizing the ventilator settings. Primary outcome is change in airway resistance 30 minutes after salbutamol inhalation.

Ethics and dissemination: The study has received the following approvals: Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306). Results will be made available to critical care survivors, their caregivers, the funders, the critical care societies and other researchers by publication in a peer-reviewed journal.

Trial registration: German trial register (DRKS.de); ID: DRKS00014706; registered on 14th May 2018

Article Summary

Strengths and limitations of this study

- This is the first interventional trial assessing, whether the additional usage of EIT can improve the effectiveness of inhalative drug administration in critical ill and ventilated patients.
- EIT could help to visualize and verify an effective nebulization that could provide a safe, efficient and individualized way of inhalative drug application, e.g. by increasing the effective dose for reaching the distal airway.
- Despite few possible limitations of EIT, this device can provide a remarkable advance in the field of individualized and guided mechanical ventilation adjustments at bedside.
- The secondary outcomes of this study will possibly offer a opportunity to recommend standard respirator settings for inhalative drug application.
- The lack of blinding of the assessors collecting data on EIT usage is a limitation to the study design.

Keywords: EIT, optimization of ventilation, inhalation, nebulization, region of interest, end expiratory lung volume, end expiratory lung impedance

Introduction

Electrical impedance tomography (EIT) is an imaging method that is already used in clinical setting. For several years it has been mainly used for monitoring of lung function [1]. With regard to lung monitoring, EIT makes use of changes in thoracic impedance, which in turn result in different concentrations of free ions due to changes in air content of the lung tissue [2]. In brief, the principle of EIT is based on the application of very small alternating electrical currents, which are applied and measured via alternating pairs of electrodes. With a scan rate of 50 images per second, voltage profiles from 16 electrode positions are continuously combined to a cross-sectional image [2]. With these cross-sectional images, the EIT enables a continuous real-time monitoring of lung function at bedside [3]. With its high resolution, EIT enables reliably the immediate and non-invasive assessment of changes in regional lung tissue [4 5]. It can also help to optimize ventilation settings to prevent regional overinflating of the lungs and atelectasis [6]. Prior studies demonstrated that equivalent diagnostic findings between EIT and thoracic computed tomography could be achieved in critically ill patients in terms of regional ventilation in different thoracic regions, and also offered a valid examiner-independent test reproducibility of the results [5 7-9]. In addition, the bedside applicability of EIT can eliminate the logistical burden of diagnostic transports with several associated risk factors and could even reduce treatment costs [1 10].

There are only a few contraindications for EIT, like the usage in active implants (e.g. pacemaker or implantable cardioverter-defibrillator) due to the lack of experience of interactions with the generated alternating electric field of EIT [11]. Furthermore, a certain amount of expertise and a sufficient level of experience of the nursing and medical staff is needed to ensure the correct interpretation of EIT values and avoidance of technical errors [5 12].

The inhalative administration of drugs is an established, non-invasive and painless application form, which is used in treatment of obstructive airways diseases. An important advantage is that significant higher local concentrations of the drug at the site of action are achieved without significant systemic exposure [13 14]. Several studies could not show a benefit of inhaled medication [15-17]. Unfortunately, these studies could not address the crucial issue whether the medication was distributed effectively in critical ill ventilated patients. To the present day, there is no established non-invasive real-time monitoring to measure or visualize the effectiveness or distribution of nebulized drugs in ventilated patients at bedside [14].

Based on this issue, our study wants to elucidate the extent to which the effectiveness of inhaled drugs, e.g. β2 sympathomimetics, can be optimized by the additional use of EIT for adjusting ventilator settings. Accordingly, we want to test the hypothesis whether EIT can increase the effectiveness of inhaled salbutamol.

Methods and analysis

This study is a randomized, open-label superiority trial comparing an interventional group with optimization of respirator settings under use of EIT and a control group without optimization of respirator settings. Ventilation distribution images will be obtained with a commercially available EIT system (PulmoVista™ , Dräger Medical, Lübeck, Germany).

Study population and general data acquisition

This study was reviewed and approved by the Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306) and registered in the German Clinical Trial Register (DRKS00014706). It will be conducted in accordance with the Declaration of Helsinki and German laws and regulations. All patients will be admitted to the intensive care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum and will be recruited from June 2018 to June 2019. We will perform EIT measurements with PulmoVista™ (Dräger Medical, Lübeck, Germany) and a size adjusted chest belt with 16 electrodes. The diagnosis of acute or chronic airway obstruction will include clinical examination and expiration-flow analyzation. Patients at the age of 18 years or more, diagnosed with an acute airway obstruction or known chronic obstructive pulmonary disease under mechanical ventilation for less than 48 hours and providing written informed consent or a positive vote of an independent consultant are eligible for inclusion. Exclusion criteria are: pregnancy or lactation, severe obesity (body mass index > 35), missing medical indication and/or contraindication for inhaled salbutamol administration, Horowitz index ≥ 400, prior phase of long-term ventilation > 14 days, a study-independent medical indication for salbutamol nebulization in obstructive pulmonary disease and/or an acute obstructive condition and procedure of withdrawing life-sustaining therapy. Furthermore, patients with the following pre-existing conditions

and operations will be excluded: patients with chest trauma or surgery (e.g. pneumectomy), pneumonia, ARDS with or without ECMO therapy, neuromuscular diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic events, active implants (e.g. pacemakers, ICD) or thoracic skin lesions and wound dressings.

Patients will be treated generally with a multimodal concept, which includes analgesia and sedation, fluid administration, lung-protective mechanical ventilation, anticoagulation, as well as hemodynamic, antibiotic and diagnostic management as recommended by guidelines, standard operating procedures or evidence based best practice. Additionally, after pseudonymization a large body of clinical and demographic data will be entered into a database for later analysis, including pre-existing morbidities, Simplified Acute Physiology Score II (SAPSII), Sepsis-related Organ Failure Assessment Score (SOFA), body mass index (BMI), necessity for renal replacement therapy, ventilator settings, PaO2/FiO2 ratio (Horowitz index), vital parameters, medications and dosage of vasoactive drugs and blood chemistry values.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measures or study design.

Sample size calculation

A total of 80 mechanically ventilated patients will be included in the study, with 40 patients in the intervention group and 40 patients in the control group. With a total cohort size of n=80, a power of > 95% (alpha error p = 0.05, beta error < 0.05) will be reached, referring to the data from a reference work (table 1) by Malliotakis et al. [18]. Calculations from these values indicate that 76 participants (38 per group) are required to achieve a power of 95% with an alpha error of 5%. To compensate a potential

insufficiency of our a-priori sample size calculation, due to the lack of comparable studies, we will also perform a post-hoc power analysis to evaluate our beta-error. Additionally, all results will be presented with an effect size estimation described as standardized mean difference.

Table 1: Baseline characteristics of sample size calculation

Variable	R_{int}	R_{rs}
$n_{Baseline}$	10	10
n_{30min}	10	10
$Mean_{Baseline}$ ± SD	18.4±4.0 [cmH2O/l/sec]	26.5±4.1 [cmH2O/l/sec]
$Mean_{30min}$ ± SD	15.5±3.6 [cmH2O/l/sec]	23.1±3.6 [cmH2O/l/sec]
Effect-size	0.762	0.881
n_{total} Power 80%	44	34
n_{total} Power 90%	62	46
n_{total} Power 95%	76	58

Airway resistance and related sample size (n) before and 30 min after salbutamol administration in ventilated patients of reference work [18]; R_{int}, R_{rs}: minimum and maximum inspiratory resistance (cm H2O/l/s), respectively

Study design

The total study duration is planned for 18 months. It will take 12 months for recruitment of patients and collection of data, last 6 months are scheduled for analyzation. For each patient an individual study duration is assigned of one day. In the control group, 1.75 hours are scheduled per patient. These include study education and randomization (30 mins), data collection before inhalation (30 mins), drug nebulization and inhalation (15 mins) and measurements after inhalation (30 mins; figure 1). In the interventional group, study explanation and randomization (30 mins), data collection before inhalation (30 mins), the installation and adjustment of EIT (30 mins), the optimization of ventilator

settings (15 mins), drug nebulization and inhalation (15 mins), resetting ventilator settings to baseline and measurements 30 minutes after inhalation add up to a total duration of 2.5 hours (figure 1).

Randomization

Block-balanced randomization, in a 1:1 ratio, will be computer-generated by StatsDirect (StatsDirect Ltd., Cambridge, United Kingdom) with random block sizes between n = 10 and n = 20, additionally using random permutations of treatments within each block. Investigators will be blinded to the allocation according to the randomization list until the study patient has been included.

Interventional procedure

EIT and control group undergo an arterial blood gas analysis and corresponding airway measurements to determine baseline parameters before salbutamol inhalation (figure 1; Supplemental material 1+2). Therefore, 1.25 mg / 2.5 mL salbutamol (Sultanol®, Glaxo Smith Kline plc., Brentford, United Kingdom) is applied with a vibrating mesh nebulizer (Solo®, Aerogen, Galway, Ireland).

In the control group, baseline measurement is followed by ultrasound nebulization and inhalation with salbutamol for 15 minutes, following measurements and arterial blood gas analysis 30 minutes after inhalation (figure 1). In addition, all study-relevant data are documented pseudonymised in the case report form (CRF) to ensure a standardized operating (Supplemental material 2). This CRF will be handed over to the principal investigator immediately after collection of data. The principal investigator keeps the study documents in a study folder not accessible to third parties.

In the intervention group, baseline measurements are followed by the standardized setup and adjustment of EIT, where a belt with 16 integrated electrodes is attached circularly to the thorax (Supplemental material 3). This is followed by the optimization of the respirator settings by means of EIT using a defined algorithm (figure 2), according the recommendations of the Translational EIT Development Study Group (TREND) [5]. The EIT algorithm focuses on homogenisation of lung ventilation described by the fast-response parameter ROI (region of interest) to titrate protective PEEP and tidal volume combinations (figure 2). The next step is nebulization and inhalation of salbutamol for 15 minutes. Subsequently, ventilator settings are reset to baseline as before EIT adjustment. After a period of 30 minutes, a new data collection after salbutamol administration including EIT measurement is done and an arterial blood gas analysis is performed (figure 1). Data is documented in the CRF (Supplemental material 1).

Objectives

The primary objective is to assess if additional use of EIT can increase the effectiveness of inhaled salbutamol, and therefore decrease the airway resistance 30 minutes after salbutamol inhalation more effective than without usage of EIT. The secondary objectives will be to compare the EIT-intervention group and the control group regarding:

- Before and 30 minutes after salbutamol inhalation:
  - Changes made in ventilator settings under EIT,
  - tidal volume, compliance, resistance, arterial oxygen partial pressure (p_aO2), Horowitz index, arterial carbon dioxide partial pressure (p_aCO_2), peripheral and arterial oxygen saturation,
  - upper and lower inflection point of the pressure-volume curve,

- EIT parameters: Region of Interest (ROI), changes of end expiratory lung volume (Delta-EELV) and changes of end expiratory lung impedance (Delta-EELI),
- heart rate, blood pressure

- duration of mechanical ventilation,
- length of stay on ICU and hospital, readmission rate on ICU.
- 30-days mortality

Data collection

The documentation of the data will be pseudonymized and computer-assisted from our patient data management system (PDMS) (Dräger ICM, Dräger Medical, Lübeck, Germany) in a central offline database. Therefore, all collected data will solely be provided in pseudonymized form for further study analyzation. Access to the pseudonymization key, which is password protected, is only available to the principal investigator of this study. All above mentioned parameters will be collected during the patients stay in hospital until discharge, death or 30th day of stay on ICU. In case of discharge from ICU, follow-up to evaluate 30-days survival will be performed by visit on normal ward or a phone call by one of the investigators. Data entered in the central offline database will be monitored by an independent clinical research associate and checked for consistency and missing values. All records, subjects' identities and data management will remain confidential with the General Data Protection Regulation (GDPR) of the European Parliament and the Council of the European Union. Furthermore, this protocol was designed following the recommendations for interventional trials (SPIRIT; figure 3; Supplemental material 4).

Statistical analysis

Since this is a study designed to demonstrate superiority of the primary endpoint (change in airway resistance 30 minutes after salbutamol inhalation), whether an additional use of EIT increases the effectiveness of inhaled salbutamol, we will perform an intention-to-treat and additionally a per-protocol analysis as recommended by the CONSORT guidelines [19]. The per-protocol population will be defined as randomized patients without major protocol deviations, such as non-considerations of exclusion criteria or missing data for the primary endpoint. Baseline characteristics of all patients will be described per group. Qualitative data will be described as frequencies and percentages. Continuous variables are presented as means ± standard deviation in case of normal distribution and as median and interquartile range (25th; 75th percentile) in case of non-normally distributed variables. Continuous variables will be compared using parametric Student's t-test or non-parametric Mann-Whitney-U-Test. Categorical variables will be characterized by numbers with percentages and will be compared using the Chi-square test or a Fisher's exact test. Superiority will be assumed, if the 95% confidence interval for the difference between the means excludes zero or p-values are statistically significantly different at an a priori alpha error of less than 0.05.

The graphical processing of variables will be performed depending on the measurement level of the variables as histograms, mean value curves with corresponding standard deviations or box whisker plots.

Ethics and dissemination

A manuscript with the results of the study will be published in a peer-reviewed journal. The study has received the following approvals: Ethics Committee of the Medical

Faculty of Ruhr-University Bochum (17-6306). On completion of the trial, and after publication of the primary manuscript, data will be made availabele in a free accessable online repository.

Discussion

This study, to our knowledge, is the first interventional trial assessing, whether the additional usage of EIT can improve the effectiveness of inhalative drug administration in critical ill and ventilated patients.

The administration of inhaled drugs is routinely used in intensive care units, due to the advantage of delivering high drug concentrations to the airway, along with rapid onset of action and fewer systemic side effects. However, it is believed that the beneficial effects of inhaled drugs are smaller in patients on mechanical ventilation than in those breathing spontaneously. In this regard, a previous study could demonstrate that only 2.9% of the administered drug dose reached the distal airway in ventilated patients, compared to 11.9% in patients without artificial airway [16]. A recently published review, regarding inhalative drug therapy in mechanical ventilation, stated that ventilator settings play an crucial role in inhaled drug delivery [14]. A tidal volume of at least 500 mL, increased inspiratory time and a low inspiratory flow are general recommendations in order to optimize drug distribution in the lungs [14 20 21]. Nevertheless, attention should be paid to serious adverse effects of high (> 500 mL) tidal volumes, especially in patients with acute or chronic airway obstructions. In these patients high tidal volumes can lead to dynamic hyperinflation or can cause a severe barotrauma [14]. Furthermore, no clinical studies exist showing the beneficial effects of any particular ventilation mode on inhaled drug delivery [20 21]. Therefore, a new diagnostic and guiding tool for adequate optimization of ventilator settings prior to nebulization of inhalative drugs would be desirable. Hence, fast, non-invasive and reliable assessment at bedside in critical ill and ventilated patients is one of the cornerstones for modern intensive care monitoring. EIT, although with some constrains, may be a promising solution. EIT images are valid measurements of the regional distribution of ventilation and changes in lung volume in real-time. This dynamic evaluation makes EIT a promising tool for guided optimization

of ventilator parameters on an individualized base. Several studies in the last years have already demonstrated that EIT-guided respirator optimization results in significant improved respiratory mechanics and improved gas exchange [1 4 7 22]. However, a global standard based on a broad base of evidence was one of the most discussed topics in Respiratory Medicine over the last years. Therefore, the plausibility of EIT measurements highly depends on the correct belt position, proper impedance visualization, correct analysis and data interpretation [23].

The crucial step forward was the publication of recommendations of the TREND (Translational EIT Development Study) group [5]. These recommendations highlight the need for a consensus about examinations, consistent terminology and generally accepted approaches to EIT images and analysis. Based on this highly appreciated consensus statement we are now able to compare, understand and reproduce study findings from among different research groups and provide a standardized use in clinical routine.

A further limitation is that EIT captures only ventral-to-dorsal ventilation distribution. However, Bikker et al. also reported different ventilation distribution between cranial and caudal lung levels during decremental PEEP trials [24], concluding that existing EIT systems will not be able to cover the optimal PEEP titration for the whole lung.

Despite the possible limitations of EIT, this device can provide a remarkable advance in the field of individualized and guided mechanical ventilation adjustments. Therefore, this study can shed light on the extent to which the additional use of EIT for optimizing the ventilator settings can increase the effectiveness of inhaled salbutamol.

Outlook

EIT could help to visualize and verify an effective nebulization that could provide a safe, efficient and individualized way of inhalative drug application, e.g. by increasing the

effective dose reaching distal airway. Therefore, these results are also of great interest beyond salbutamol nebulization, e.g. for safe usage of inhalative antibiotics in critical ill and ventilated patients.

Trial status

The first patients were randomized in June 2018. The inclusion of participants is ongoing and is expected to continue until June 2019.

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List of abbreviations

ARDS	Acute respiratory distress syndrome
BMI	Body mass index
CRF	Case report form
delta-EELI	Change of end expiratory lung impedance
delta-EELV	Change of end expiratory lung volume
DRKS	Deutsches Register für klinische Studien
ECMO	Extracorporeal membrane oxygenation
EIT	Electrical impedance tomography
GDPR	General data protection regulation
ICD	Implantable cardioverter defibrillator
ICU	Intensive care unit
NYHA	New York Heart Association
p_aCO_2	Partial pressure of arterial carbon dioxide
p_aO_2	Partial pressure of arterial oxygen
PDMS	Patient data management systems
PEEP	Positive end-expiratory pressure
R	Resistance
ROI	Region of interest
SAPSII	Simplified acute physiology score II
SD	Standard deviation
SOFA score	Sepsis-related organ failure assessment score
Spirit	Standard Protocol Items - Recommendations for Interventional
TREND group	Translational EIT Development Study group

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of the Medical Faculty of the Ruhr-Universität Bochum (no. 17-6306) and written informed consent or a positive vote of an independent consultant are eligible for inclusion.

Consent for publication

Not applicable

Availability of data and material

The data of the described study will be available from the Dryad repository after publication.

Conflict of interests

None to declare

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Author Statement

Dr. med. Tim Rahmel: Main author of this manuscript, written and revising the manuscript

Alexandra Koniusch: Supporting methodical description and participated in the design of this study

Dr. med. Günther Oprea: Supporting data collection, participated in the design of this study, and revising the manuscript

Martin Schwertner: Supporting data collection, participated in the design of this study, and revising the manuscript

Prof. Dr. med. Michael Adamzik: Supporting data collection, participated in the design of this study and revising the manuscript

Dr. med. Hartmuth Nowak: Supporting data collection, participated in the design of this study, written and revising the manuscript

All authors read and approved the final manuscript.

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Not applicable

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Legends

Figure 1: Flowchart of interventional procedures on intervention and control group with duration of each step and performed measurements (EIT = electrical impedance tomography, ICU = intensive care unit)

Figure 2: Flowchart of EIT-guided optimization of ventilator settings (ROI = region of interest, Pmax = maximum airway pressure, Pinsp = inspiratory pressure, PEEP = positive end expiratory pressure)

Figure 3: Schedule of enrolment, interventions and assessments – SPIRIT Figure (SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials, EIT = electrical impedance tomography, ICU = intensive care unit)

Supplemental material

Supplemental material 1: Case report form of intervention group

Supplemental material 2: Case report form of control group

Supplemantal material 3: Additional information - EIT algorithm

Supplemental material 4: Spirit checklist

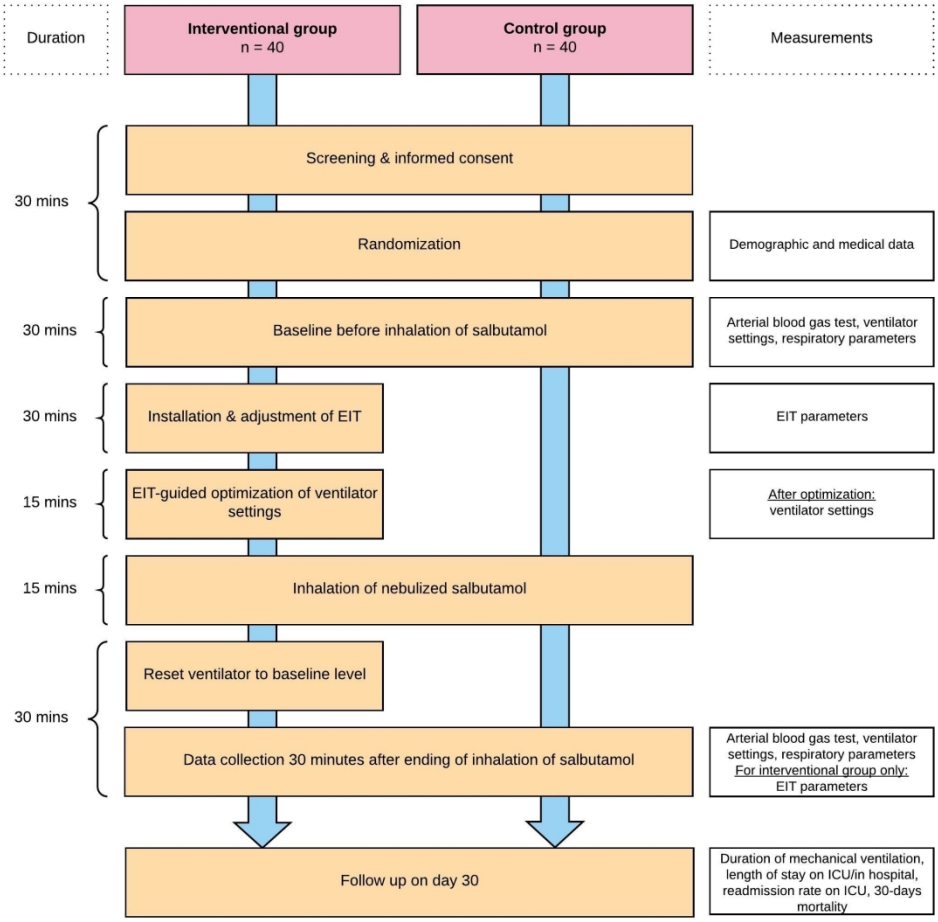


Figure 1: Flowchart of interventional procedures on intervention and control group with duration of each step and performed measurements (EIT = electrical impedance tomography, ICU = intensive care unit)

184x181mm (300 x 300 DPI)

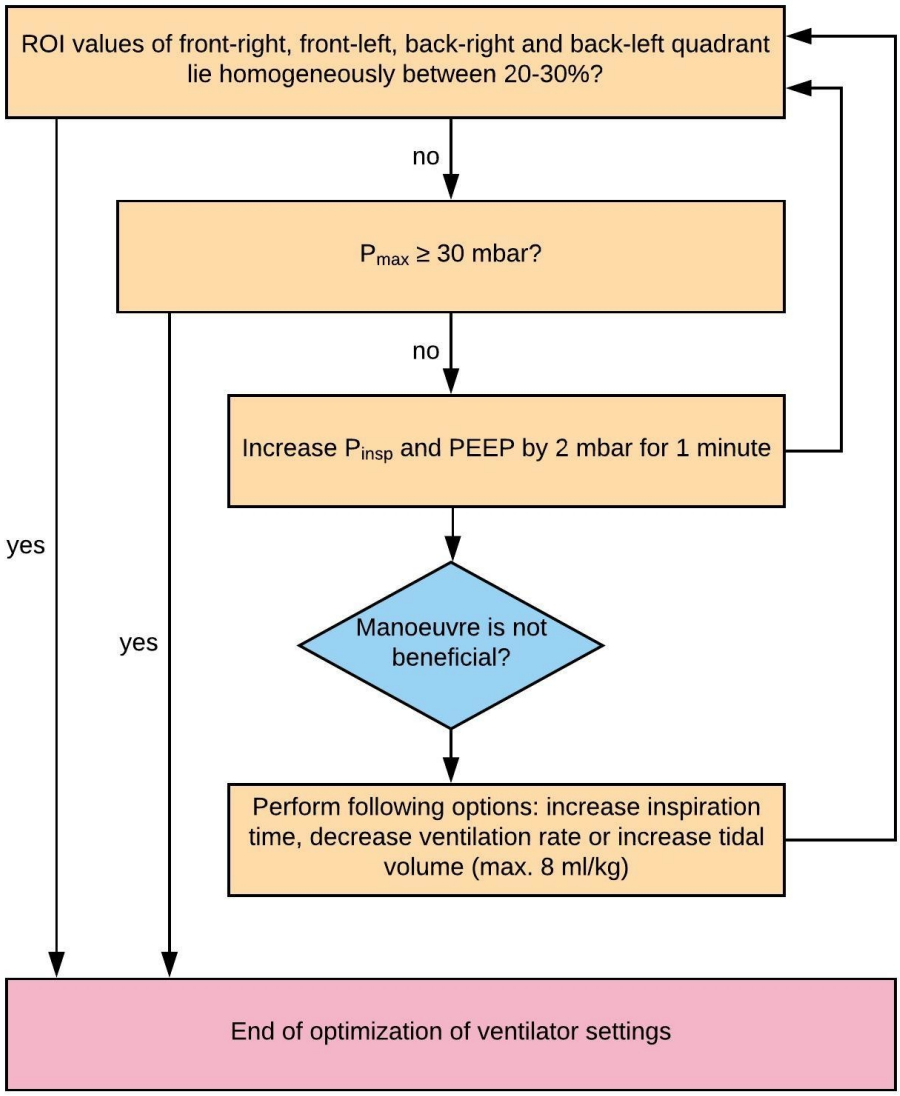


Figure 2: Flowchart of EIT-guided optimization of ventilator settings (ROI = region of interest, Pmax = maximum airway pressure, Pinsp = inspiratory pressure, PEEP = positive end expiratory pressure)

114x136mm (300 x 300 DPI)

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
TIMEPOINT	Prior randomization	0	Baseline	After Baseline	After intervention	30 days
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
INTERVENTIONS:						
EIT-guided optimization of ventilation, inhalation of nebulized salbutamol afterwards				X		
Inhalation of nebulized salbutamol				X		
ASSESSMENTS:						
Demographic & medical data			X			
Ventilator settings			X		X	
Respiratory parameters			X		X	
Arterial blood gas test			X		X	
EIT parameters (*for EIT group only*)			X		X	
Duration of mechanical ventilation, length of stay on ICU/in hospital, readmission rate on ICU						X
30-days mortality						X

Figure 3: Schedule of enrolment, interventions and assessments – SPIRIT Figure (SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials, EIT = electrical impedance tomography, ICU = intensive care unit)

139x224mm (300 x 300 DPI)

Randomization |__|__|.|__|__|.201__

No. |__|__| ***CRF EIT-Trial (intervention group)*** VU

Patient

Inclusion criteria	Yes	No
• Age ≥ 18 years	☐	☐
• Known obstructive airway disease or acute airway obstruction ***and*** • Medical indication for salbutamol inhalation	☐	☐
• Mechanical ventilated patient (<48h) and Horowitz index (p_aO_2/F_iO_2) < 400	☐	☐
• Written informed consent or positive vote of an independent consultant	☐	☐

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	☐	☐
• Lack of medical indication and/or contraindications to administration of salbutamol	☐	☐
• Age < 18 years	☐	☐
• Pre-existing conditions or operations: Patients with chest trauma or chest surgery; thoracic skin lesions and wound dressings; ARDS and/or ECMO therapy; neuromuscular diseases; severe cardiac diseases (e.g. NYHA III-IV); acute ischemic events; active implants (e.g. pacemakers, ICDs)	☐	☐
• Severe obesity (BMI > 35)	☐	☐
• Prior phase of long-term ventilation > 14 days	☐	☐
• Do-not-resuscitate order	☐	☐
• Pregnancy or lactation	☐	☐

- Copy patient file/printout! (Anamnesis, concomitant medications, concomitant diseases, physical examination, ECG, vital parameters ☐ carried out

  ☐ male ☐ female

  Height |__|__|__| cm **weight** |__|__|__|.|__| kg **BMI** |__|__|.|__| kg/m^2

- **Blood pressure** |__|__|__| / |__|__| **heart rate** |__|__|__| bpm

  body temperature |__|__|.|__| °C

- Pregnancy excluded ☐

- Note participation in the medical record! ☐ carried out

- **Procedure in the intervention group**
  - Study education including randomization (30 min) ☐
    - Measurement of SOFA-Score (_____), PCT (_____), CRP (_____), antibiotics (_____), vital parameters (_____), catecholamines (_____), sedation (_____) ☐
  - Data collection before inhalation (30 min)
    - Measurement of airway resistance before salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
  - Installation and adjustment of the EIT (30 min) ☐
    - Measurement of Region of Interest (ROI) (_____), changes of end-exspiratory lung volume (Delta-EELV) (_____) and changes of end-exspiratory lung impedance (Delta-EELI) (_____) ☐
  - Optimization of ventilator settings (15 min) ☐
    - Measurement of ventilator settings after EIT-guided optimization (P_{insp} (_____), PEEP (_____), I:E (_____), T_{insp} (_____), RR (_____), ventilation mode (_____)) ☐
  - Salbutamol nebulization and inhalation (15 min) ☐
  - Reset ventilator to baseline level ☐
  - Data collection after inhalation (30 min)
    - Measurement of airway resistance after salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
    - Measurement of Region of Interest (ROI) (_____), changes of end-exspiratory lung volume (Delta-EELV) (_____) and changes of end-exspiratory lung impedance (Delta-EELI) (_____) ☐

Date |__|__|.|__|__| 201__ Signature of the examiner _____

Randomization |__|__|.|__|__|.201__

No. |__|__| ***CRF EIT-Trial (control group)*** VU

Patient

Inclusion criteria	Yes	No
• Age ≥ 18 years	☐	☐
• Known obstructive airway disease or acute airway obstruction ***and*** • Medical indication for salbutamol inhalation	☐	☐
• Mechanical ventilated patient (<48h) and Horowitz index (p_aO_2/F_iO_2) < 400	☐	☐
• Written informed consent or positive vote of an independent consultant	☐	☐

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	☐	☐
• Lack of medical indication and/or contraindications to administration of salbutamol	☐	☐
• Age < 18 years	☐	☐
• Pre-existing conditions or operations: Patients with chest trauma or chest surgery; thoracic skin lesions and wound dressings; ARDS and/or ECMO therapy; neuromuscular diseases; severe cardiac diseases (e.g. NYHA III-IV); acute ischemic events; active implants (e.g. pacemakers, ICDs)	☐	☐
• Severe obesity (BMI > 35)	☐	☐
• Prior phase of long-term ventilation > 14 days	☐	☐
• Do-not-resuscitate order	☐	☐
• Pregnancy or lactation	☐	☐

- Copy patient file/printout! (Anamnesis, concomitant medications, concomitant diseases, physical examination, ECG, vital parameters ☐ carried out

  ☐ male ☐ female

  Height |__|__|__| cm **weight** |__|__|__|.|__| kg **BMI** |__|__|.|__| kg/m^2

- **Blood pressure** |__|__|__| / |__|__| **heart rate** |__|__|__| bpm

  body temperature |__|__|.|__| °C

- Pregnancy excluded ☐

- Note participation in the medical record! ☐ carried out

- **Procedure in the control group**
  - Study education including randomization (30 min) ☐
    - Measurement of SOFA-Score (_____), PCT (_____), CRP (_____), antibiotics (_____), vital parameters (_____),catecholamines (_____), sedation (_____) ☐
  - Data collection before inhalation (30 min)
    - Measurement of airway resistance before salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
  - Salbutamol nebulization and inhalation (15 min) ☐
  - Data collection after inhalation (30 min)
    - Measurement of airway resistance after salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐

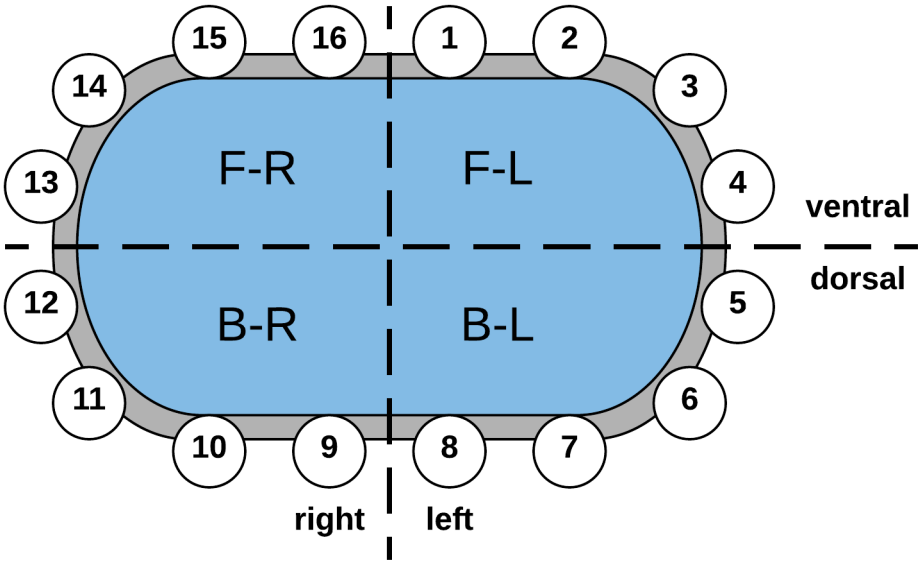
Date |__|__|.|__|__| 201__ Signature of the examiner _____

Additional information - EIT algorithm

Installation procedure for EIT (PulmoVista 500, Dräger Medical, Lübeck, Germany)		
1.	To turn on the EIT system press the green "Power on"-button in the left, lower corner of the screen (it will light up after switching on). Afterwards, the system will be in "Standby"-mode.	☐
2.	Connect the main plug of the trunk cable to the upper connection socket. Connect the color-coded plugs to the corresponding test socket (green = right/R), red = left/L).	☐
3.	Choose "System Test" on the touch screen. Press "Start" and confirm this selection by pressing the control knob in the right, lower corner of the screen. The EIT system will perform a self-check to ensure proper functioning of all components and the trunk cable.	☐
4.	Choose a belt according to the patient's circumference of chest (S = 70-85 cm, M = 80-96 cm, L = 92-110 cm, XL = 106-127 cm, XXL = 124-150 cm). Connect electrodes of the corresponding connection cable with the belt (number 1 to 1, number 2 to 2, …, number 16 to 16).	☐
5.	Placement of EIT belt: Between 8th and 9th electrode is a perceptible silicone mark, place this mark centrally over the spine between 4th and 6th intercostal space. Both lateral ends are folded forward towards the chest and connected in front of the sternum, so that electrode number 1 is placed left and number 16 right to the sternum (figure 1). Connect the "C"-electrode of the connection cable with the seal of the EIT belt. Place an ECG-electrode on the skin of the abdomen and connect it with the "REF"-electrode of the connection cable.	☐
6.	Plug the green and red color-coded plugs of the trunk cable out of the test socket and connect them to the connection cable of the EIT belt (ensure the correct connection: green to green and red to red).	☐
7.	Select the option "New Patient" on the touch screen in the Start/Standby menu. By choosing "Signal Check" skin resistance of each electrode is shown, a blue bar appears for all electrodes. If skin resistance is insufficiently high (> 300 ohms), the corresponding electrode is marked in red. In that case, prove the correct positioning of that electrode, moisturize the electrode with water or electrode gel where applicable. Move on to step 8 when all bars appear blue.	☐
8.	Register patient data by selecting "New Patient". Afterwards, press "Start" to start EIT measurements. A short calibration is performed (approximately 30 seconds), afterwards the system is ready for measuring.	☐

EIT algorithm Version 1.0

Figure 1: schematic cross-section image of thorax with positions of 16 EIT electrodes at the level of 4th to 6th intercostal space *(F-R = front-right quadrant, F-L = front-left quadrant, B-R = back-right quadrant, B-L = back-left quadrant)*



Measurement of EIT parameters (ROI, Delta-EELV and Delta-EELI)		
1.	ROI (Region of interest): Choose "Views" in right upper corner of the screen and tap on "Full Screen". Values for each quadrant (F-R, F-L, B-R, B-L) are displayed.	☐
2.	Delta-EELV (changes of end exspiratory lung volume): Choose "Views" in right upper corner of the screen and tap on "End exspiratory trend".	☐
3.	Delta-EELI (changes of end exspiratory lung impedance): Choose "Views" in right upper corner of the screen and tap on "Delta-EELI".	☐

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Evaluation of inhaled salbutamol effectiveness under supportive use of electrical impedance tomography in ventilated ICU patients: study protocol for a randomized controlled clinical trial ***(page 1)***
Trial registration	2	German trial register (DRKS.de); ID: DRKS00014706; registered on 14th May 2018 ***(page 6)***
Protocol version	3	10th March 2018, version 1.0
Funding	4	We acknowledge support by the DFG Open Access Publication Funds of the Ruhr-University Bochum (Ref. No. IN-1214264), just for financial support for publication costs. This will have no impact on our study design or collection, analysis and interpretation of our data. ***(page 19)***

Roles and responsibilities	5a	Dr. med. Tim Rahmel, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Principal investigator, main author of this manuscript, written and revising the manuscript Alexandra Koniusch, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting methodical description and participated in the design of this study Dr. med. Günther Oprea, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting data collection, participated in the design of this study, and revising the manuscript Martin Schwertner, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting data collection, participated in the design of this study, and revising the manuscript Prof. Dr. med. Michael Adamzik, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting data collection, participated in the design of this study and revising the manuscript Dr. med. Hartmuth Nowak, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Co-Principal investigator, supporting data collection, participated in the design of this study, written and revising the manuscript ***(pages 19-20)***
	5b	NA
	5c	Support is granted by the DFG Open Access Publication Funds of the Ruhr-University Bochum (Ref. No. IN-1214264), just for financial support for publication costs. This will have no impact on our study design or collection, analysis and interpretation of our data. ***(page 19)***
	5d	NA

Introduction

Background and rationale	6a	The inhalative administration of drugs is a non-invasive application form that is regularly used in the treatment of ventilated patients in critical care setting. However, assessment of effectiveness or distribution of nebulized drugs is one of the lacking cornerstones of modern intensive care monitoring as several studies could not show a benefit of inhaled medication. Unfortunately, these studies could not address the crucial issue whether the medication was distributed effectively in critical ill ventilated patients. To the present day, there is no established non-invasive real-time monitoring to measure or visualize the effectiveness or distribution of nebulized drugs in ventilated patients at bedside. Electrical impedance tomography (EIT) may provide a promising new monitoring and guiding tool for an adequate optimization of mechanical ventilation in critically ill patients. EIT makes use of changes in thoracic impedance, which in turn result in different concentrations of free ions due to changes in air content of the lung tissue. Therefore, EIT may assist in defining mechanical ventilation settings, assess distribution of tidal volume and evaluation of associated pathologies at bedside. Prior studies demonstrated that equivalent diagnostic findings between EIT and thoracic computed tomography could be achieved in critically ill patients in terms of regional ventilation in different thoracic regions, and also offered a valid examiner-independent test reproducibility of the results. ***(pages 4-5)***
	6b	As no non-invasive real-time monitoring for visualization of nebulized drugs in ventilated patients at bedside is established to the present day, comparator will be standard of care with no EIT-optimized application of salbutamol. ***(pages 4-5)***
Objectives	7	Our study wants to elucidate the extent to which the effectiveness of inhaled drugs, e.g. β2 sympathomimetics, can be optimized by the additional use of EIT for adjusting ventilator settings. Accordingly, we want to test the hypothesis whether EIT can increase the effectiveness of inhaled salbutamol. ***(page 5)***
Trial design	8	This study is a randomized, open-label superiority trial, comparing two groups of mechanically ventilated patients with an acute or chronic bronchial airway obstruction according the effectiveness of inhaled salbutamol with (intervention) or without (control) additional use of EIT for optimizing the ventilator settings. ***(page 6)***

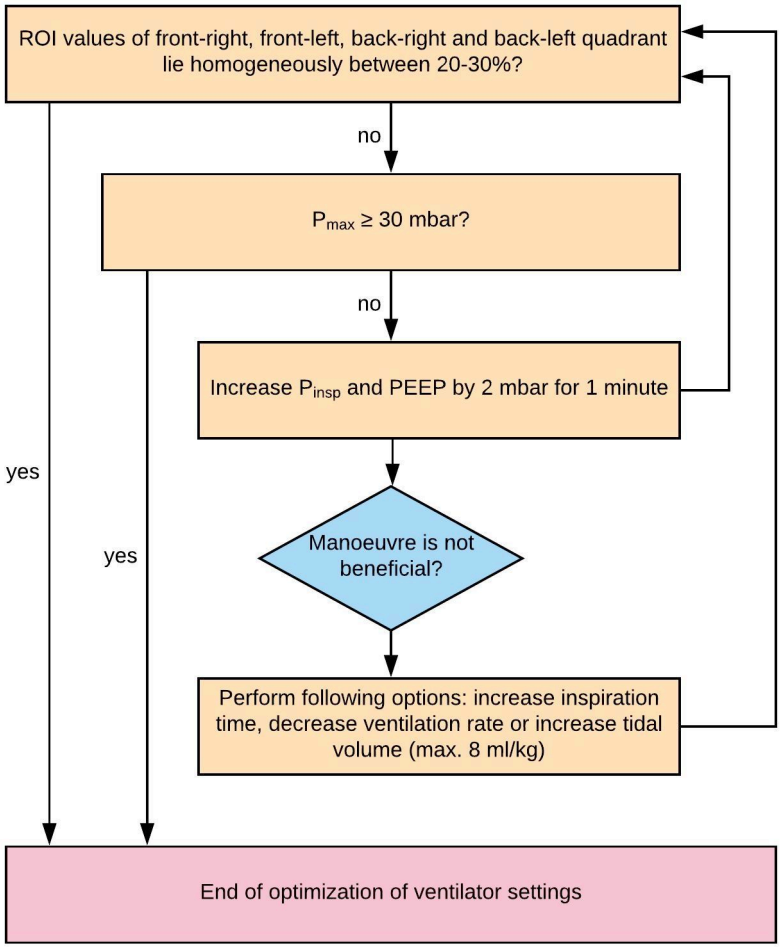
Methods: Participants, interventions, and outcomes

Study setting	9	This study will be conducted at the interdisciplinary, operative intensive care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum, a university hospital of Ruhr-University Bochum in Bochum, Germany. ***(page 6)***

Eligibility criteria	10	Patients at the age of 18 years or more, diagnosed with an acute airway obstruction or known chronic obstructive pulmonary disease under mechanical ventilation for less than 48 hours and providing written informed consent or a positive vote of an independent consultant are eligible for inclusion. ***(page 6)***
		Exclusion criteria are: pregnancy or lactation, severe obesity (body mass index > 35), missing medical indication and/or contraindication for inhaled salbutamol administration, Horowitz index ≥ 400, prior phase of long-term ventilation > 14 days, a study-independent medical indication for salbutamol nebulization in obstructive pulmonary disease and/or an acute obstructive condition and procedure of withdrawing life-sustaining therapy. Furthermore, patients with the following pre-existing conditions and operations will be excluded: patients with chest trauma or surgery (e.g. pneumectomy), pneumonia, ARDS with or without ECMO therapy, neuromuscular diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic events, active implants (e.g. pacemakers, ICD) or thoracic skin lesions and wound dressings. ***(page 6-7)***

Interventions	11a	EIT and control group undergo an arterial blood gas analysis and corresponding airway measurements to determine baseline parameters before salbutamol inhalation. Therefore, 1.25 mg / 2.5 mL salbutamol (Sultanol®, Glaxo Smith Kline plc., Brentford, United Kingdom) is applied with a vibrating mesh nebulizer (Solo®, Aerogen, Galway, Ireland). ***(page 9)***
		In the control group, baseline measurement is followed by ultrasound nebulization and inhalation with salbutamol for 15 minutes, following measurements and arterial blood gas analysis 30 minutes after inhalation. In addition, all study-relevant data are documented pseudonymised in the case report form (CRF) to ensure a standardized operating. This CRF will be handed over to the principal investigator immediately after collection of data. The principal investigator keeps the study documents in a study folder not accessible to third parties. ***(page 9)***
		In the intervention group, baseline measurements are followed by the standardized setup and adjustment of EIT, where a belt with 16 integrated electrodes is attached circularly to the thorax. This is followed by the optimization of the respirator settings by means of EIT using a defined algorithm, according the recommendations of the Translational EIT Development Study Group (TREND) (see below, figure 2). The EIT algorithm focuses on homogenisation of lung ventilation described by the fast-response parameter ROI (region of interest) to titrate protective PEEP and tidal volume combinations. The next step is nebulization and inhalation of salbutamol for 15 minutes. Subsequently, ventilator settings are reset to baseline as before EIT adjustment. After a period of 30 minutes, a new data collection after salbutamol administration including EIT measurement is done and an arterial blood gas analysis is performed (figure 1). Data is documented in the CRF. ***(page 9-10)***

EIT algorithm for optimization of respirator settings (figure 2):



11b As study procedure is only done once, no specific criteria for discontinuing or modifying allocated interventions is needed.

11c NA

11d NA

Outcomes	12	The primary objective is to assess if additional use of EIT can increase the effectiveness of inhaled salbutamol, and therefore decrease the airway resistance 30 minutes after salbutamol inhalation more effective than without usage of EIT. ***(page 10)***
		The secondary objectives will be to compare the EIT-intervention group and the control group regarding: Before and 30 minutes after salbutamol inhalation [Changes made in ventilator settings under EIT, tidal volume, compliance, resistance, arterial oxygen partial pressure (paO2), Horowitz index, arterial carbon dioxide partial pressure (paCO2), peripheral and arterial oxygen saturation, upper and lower inflection point of the pressure-volume curve, EIT parameters: Region of Interest (ROI), changes of end expiratory lung volume (Delta-EELV) and changes of end expiratory lung impedance (Delta-EELI), heart rate, blood pressure]; duration of mechanical ventilation; length of stay on ICU and hospital, readmission rate on ICU; 30-days mortality. ***(pages 10-11)***
		Additionally, after pseudonymization a large body of clinical and demographic data will be entered into a database for later analysis, including pre-existing morbidities, Simplified Acute Physiology Score II (SAPSII), Sepsis-related Organ Failure Assessment Score (SOFA), body mass index (BMI), necessity for renal replacement therapy, ventilator settings, PaO2/FiO2 ratio (Horowitz index), vital parameters, medications and dosage of vasoactive drugs and blood chemistry values. ***(page 7)***

Participant timeline 13 Study schedule is presented in the following table (figure 3):

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
TIMEPOINT	Prior randomization	0	Baseline	After Baseline	After intervention	30 days
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
INTERVENTIONS:						
EIT-guided optimization of ventilation, inhalation of nebulized salbutamol afterwards				X		
Inhalation of nebulized salbutamol				X		
ASSESSMENTS:						
Demographic & medical data			X			
Ventilator settings			X		X	
Respiratory parameters			X		X	
Arterial blood gas test			X		X	
EIT parameters (*for EIT group only*)			X		X	
Duration of mechanical ventilation, length of stay on ICU/in hospital, readmission rate on ICU						X
30-days mortality						X

Sample size 14 A total of 80 mechanically ventilated patients will be included in the study, with 40 patients in the intervention group and 40 patients in the control group. With a total cohort size of n=80, a power of > 95% (alpha error p = 0.05, beta error < 0.05) will be reached, referring to the data from a reference work (table 1) by Malliotakis et al. Calculations from these values indicate that 76 participants (38 per group) are required to achieve a power of 95% with an alpha error of 5%. ***(pages 7-8)***

Variable	**R_{int}**	**R_{rs}**
$n_{Baseline}$	10	10
n_{30min}	10	10
$Mean_{Baseline}$ ± SD	18.4±4.0 [cmH2O/l/sec]	26.5±4.1 [cmH2O/l/sec]
$Mean_{30min}$ ± SD	15.5±3.6 [cmH2O/l/sec]	23.1±3.6 [cmH2O/l/sec]
Effect-size	0.762	0.881
n_{total} Power 80%	44	34
n_{total} Power 90%	62	46
n_{total} Power 95%	76	58

Airway resistance and related sample size (n) before and 30 min after salbutamol administration in ventilated patients of reference work 18; Ri_{nt}, R_{rs}: minimum and maximum inspiratory resistance (cm H2O/l/s), respectively

Recruitment 15 We will ensure patient recruitment by screening patients on ICU daily. Eligible patients will be approached by the principal inverstigator and/or one of the eligible physicians.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a Block-balanced randomization, in a 1:1 ratio, will be computer-generated by StatsDirect (StatsDirect Ltd., Cambridge, United Kingdom) with random block sizes between n = 10 and n = 20, additionally using random permutations of treatments within each block. Investigators will be blinded to the allocation according to the randomization list until the study patient has been included. ***(page 9)***

Allocation concealment mechanism 16b Concealment of allocation mechanism will be performed by using sealed envelopes. For each patient included, a sealed envelope will be drawn and opened.

Implementation	16c	A physician who is independent to this trial will generate allocation sequence. Enrolment and assignment will be done by the principal investigator and/or eligible physicians.
Blinding (masking)	17a	No blinding will be performed.
	17b	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	The documentation of the data will be pseudonymized and computer-assisted from our patient data management system (PDMS) (Dräger ICM, Dräger Medical, Lübeck, Germany) in a central offline database. ***(page 11)***
	18b	All above mentioned parameters will be collected during the patients stay in hospital until discharge, death or 30th day of stay on ICU. In case of discharge from ICU, follow-up to evaluate 30-days survival will be performed by visit on normal ward or a phone call by one of the investigators. ***(page 11)***
Data management	19	All collected data will solely be provided in pseudonymized form for further study analyzation. Access to the pseudonymization key, which is password protected, is only available to the principal investigator of this study. ***(page 11)***

Statistical methods	20a	Since this is a study designed to demonstrate superiority of the primary endpoint (change in airway resistance 30 minutes after salbutamol inhalation), whether an additional use of EIT increases the effectiveness of inhaled salbutamol, we will perform an intention-to-treat and additionally a per-protocol analysis as recommended by the CONSORT guidelines. The per-protocol population will be defined as randomized patients without major protocol deviations, such as non-considerations of exclusion criteria or missing data for the primary endpoint. Baseline characteristics of all patients will be described per group. Qualitative data will be described as frequencies and percentages. Continuous variables are presented as means ± standard deviation in case of normal distribution and as median and interquartile range (25th; 75th percentile) in case of non-normally distributed variables. Continuous variables will be compared using parametric Student's t-test or non-parametric Mann-Whitney-U-Test. Categorical variables will be characterized by numbers with percentages and will be compared using the Chi-square test or a Fisher's exact test. Superiority will be assumed, if the 95% confidence interval for the difference between the means excludes zero or p-values are statistically significantly different at an a priori alpha error of less than 0.05. The graphical processing of variables will be performed depending on the measurement level of the variables as histograms, mean value curves with corresponding standard deviations or box whisker plots. ***(pages 11-12)***
	20b	NA
	20c	We will perform an intention-to-treat and additionally a per-protocol analysis as recommended by the CONSORT guidelines. ***(page 11)***
Methods: Monitoring		
Data monitoring	21a	Data entered in the central offline database will be monitored by an independent clinical research associate and checked for consistency and missing values. ***(page 11)***
	21b	No interim analyses are planned.
Harms	22	During study conduct and follow-up patients will be continuously monitored for possible adverse events. Those will be recorded in the database.
Auditing	23	NA
Ethics and dissemination		
Research ethics approval	24	This study was reviewed and approved by the Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306). ***(page 6)***

Protocol amendments	25	Prinicipal investigator will communicate all important modifications to study personnel.
Consent or assent	26a	Informed consent will be obtained by principal investigator and/or eligible physicians.
	26b	NA
Confidentiality	27	All records, subjects' identities and data management will remain confidential with the General Data Protection Regulation (GDPR) of the European Parliament and the Council of the European Union. ***(page 11)***
Declaration of interests	28	None to declare ***(page 19)***
Access to data	29	The data of the described study will be available from the Dryad repository after publication. ***(page 19)***
Ancillary and post-trial care	30	No arrangements have been made for compensation to those who suffer harm from trial participation. This has been stated in the informed consent.
Dissemination policy	31a	A manuscript with the results of the study will be published in a peer-reviewed journal. ***(page 12)***
	31b	NA
	31c	A publication of this study protocol in BMJ Open is submitted.
Appendices		
Informed consent materials	32	An informed consent form is available in German language can be obtained from the authors.
Biological specimens	33	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Evaluation of inhaled salbutamol effectiveness under supportive use of electrical impedance tomography in ventilated ICU patients: study protocol for a randomized controlled clinical trial

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Keywords:	optimization of ventilation, inhalation, nebulization, region of interest, end expiratory lung volume, end expiratory lung impedance

Evaluation of inhaled salbutamol effectiveness under supportive use of electrical impedance tomography in ventilated ICU patients: study protocol for a randomized controlled clinical trial

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Running head: EIT-guided ventilator optimization for salbutamol inhalation

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Abstract

Introduction: The inhalative administration of drugs is a non-invasive application form that is regularly used in the treatment of ventilated patients in critical care setting. However, assessment of effectiveness or distribution of nebulized drugs is one of the lacking cornerstones of modern intensive care monitoring. Electrical impedance tomography (EIT) may provide a promising new monitoring and guiding tool for an adequate optimization of mechanical ventilation in critically ill patients. EIT may assist in defining mechanical ventilation settings, assess distribution of tidal volume and evaluation of associated pathologies at bedside. This study wants to elucidate the extent to which the effectiveness of inhaled salbutamol can be increased by the additional use of EIT for optimization of respirator settings.

Methods and analysis: This study is a randomized, open-label superiority trial, conducted on an intensive care unit of a German university hospital, comparing two groups of mechanically ventilated patients with an acute or chronic bronchial airway obstruction according the effectiveness of inhaled salbutamol with (intervention) or without (control) additional use of EIT for optimizing the ventilator settings. Primary outcome is change in airway resistance 30 minutes after salbutamol inhalation.

Ethics and dissemination: The study has received the following approvals: Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306). Results will be made available to critical care survivors, their caregivers, the funders, the critical care societies and other researchers by publication in a peer-reviewed journal.

Trial registration: German trial register (DRKS.de); ID: DRKS00014706; registered on 14th May 2018

Article Summary

Strengths and limitations of this study

- This is the first interventional trial assessing, whether the additional usage of EIT can improve the effectiveness of inhalative drug administration in critical ill and ventilated patients.
- EIT could help to visualize and verify an effective nebulization that could provide a safe, efficient and individualized way of inhalative drug application, e.g. by increasing the effective dose for reaching the distal airway.
- Despite few possible limitations of EIT, this device can provide a remarkable advance in the field of individualized and guided mechanical ventilation adjustments at bedside.
- The secondary outcomes of this study will possibly offer a opportunity to recommend standard respirator settings for inhalative drug application.
- The lack of blinding of the assessors collecting data on EIT usage is a limitation to the study design.

Keywords: EIT, optimization of ventilation, inhalation, nebulization, region of interest, end expiratory lung volume, end expiratory lung impedance

Introduction

Electrical impedance tomography (EIT) is an imaging method that is already used in clinical setting. For several years it has been mainly used for monitoring of lung function [1]. With regard to lung monitoring, EIT makes use of changes in thoracic impedance, which in turn result in different concentrations of free ions due to changes in air content of the lung tissue [2]. In brief, the principle of EIT is based on the application of very small alternating electrical currents, which are applied and measured via alternating pairs of electrodes. With a scan rate of 50 images per second, voltage profiles from 16 electrode positions are continuously combined to a cross-sectional image [2]. With these cross-sectional images, the EIT enables a continuous real-time monitoring of lung function at bedside [3]. With its high resolution, EIT enables reliably the immediate and non-invasive assessment of changes in regional lung tissue [4 5]. It can also help to optimize ventilation settings to prevent regional overinflating of the lungs and atelectasis [6]. Prior studies demonstrated that equivalent diagnostic findings between EIT and thoracic computed tomography could be achieved in critically ill patients in terms of regional ventilation in different thoracic regions, and also offered a valid examiner-independent test reproducibility of the results [5 7-9]. In addition, the bedside applicability of EIT can eliminate the logistical burden of diagnostic transports with several associated risk factors and could even reduce treatment costs [1 10].

There are only a few contraindications for EIT, like the usage in active implants (e.g. pacemaker or implantable cardioverter-defibrillator) due to the lack of experience of interactions with the generated alternating electric field of EIT [11]. Furthermore, a certain amount of expertise and a sufficient level of experience of the nursing and medical staff is needed to ensure the correct interpretation of EIT values and avoidance of technical errors [5 12].

The inhalative administration of drugs is an established, non-invasive and painless application form, which is used in treatment of obstructive airways diseases. An important advantage is that significant higher local concentrations of the drug at the site of action are achieved without significant systemic exposure [13 14]. Several studies could not show a benefit of inhaled medication [15-17]. Unfortunately, these studies could not address the crucial issue whether the medication was distributed effectively in critical ill ventilated patients. To the present day, there is no established non-invasive real-time monitoring to measure or visualize the effectiveness or distribution of nebulized drugs in ventilated patients at bedside [14].

Based on this issue, our study wants to elucidate the extent to which the effectiveness of inhaled drugs, e.g. β2 sympathomimetics, can be optimized by the additional use of EIT for adjusting ventilator settings. Accordingly, we want to test the hypothesis whether EIT can increase the effectiveness of inhaled salbutamol.

Methods and analysis

This study is a randomized, open-label superiority trial comparing an interventional group with optimization of respirator settings under use of EIT and a control group without optimization of respirator settings. Ventilation distribution images will be obtained with a commercially available EIT system (PulmoVista™ , Dräger Medical, Lübeck, Germany).

Study population and general data acquisition

This study was reviewed and approved by the Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306) and registered in the German Clinical Trial Register (DRKS00014706). It will be conducted in accordance with the Declaration of Helsinki and German laws and regulations. All patients will be admitted to the intensive care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum and will be recruited from June 2018 to June 2019. We will perform EIT measurements with PulmoVista™ (Dräger Medical, Lübeck, Germany) and a size adjusted chest belt with 16 electrodes. The diagnosis of acute or chronic airway obstruction will include clinical examination and expiration-flow analyzation. Patients at the age of 18 years or more, diagnosed with an acute airway obstruction or known chronic obstructive pulmonary disease under mechanical ventilation for less than 48 hours and providing written informed consent or a positive vote of an independent consultant are eligible for inclusion. Exclusion criteria are: pregnancy or lactation, severe obesity (body mass index > 35), missing medical indication and/or contraindication for inhaled salbutamol administration, Horowitz index ≥ 400, prior phase of long-term ventilation > 14 days, a study-independent medical indication for salbutamol nebulization in obstructive pulmonary disease and/or an acute obstructive condition and procedure of withdrawing life-sustaining therapy. Furthermore, patients with the following pre-existing conditions

and operations will be excluded: patients with chest trauma or surgery (e.g. pneumectomy), pneumonia, ARDS with or without ECMO therapy, neuromuscular diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic events, active implants (e.g. pacemakers, ICD) or thoracic skin lesions and wound dressings.

Patients will be treated generally with a multimodal concept, which includes analgesia and sedation, fluid administration, lung-protective mechanical ventilation, anticoagulation, as well as hemodynamic, antibiotic and diagnostic management as recommended by guidelines, standard operating procedures or evidence based best practice. Additionally, after pseudonymization a large body of clinical and demographic data will be entered into a database for later analysis, including pre-existing morbidities, Simplified Acute Physiology Score II (SAPSII), Sepsis-related Organ Failure Assessment Score (SOFA), body mass index (BMI), necessity for renal replacement therapy, ventilator settings, PaO2/FiO2 ratio (Horowitz index), vital parameters, medications and dosage of vasoactive drugs and blood chemistry values.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measures or study design.

Sample size calculation

A total of 80 mechanically ventilated patients will be included in the study, with 40 patients in the intervention group and 40 patients in the control group. With a total cohort size of n=80, a power of > 95% (alpha error p = 0.05, beta error < 0.05) will be reached, referring to the data about the salbutamol treatment effect from a reference work (table 1) by Malliotakis et al. [18], and according to our estimation of a clinically meaningful effect size. Calculations from these values indicate that 76 participants (38

per group) are required to achieve a power of 95% with an alpha error of 5%. To compensate a potential insufficiency of our a-priori sample size calculation, due to the lack of comparable studies, we will also perform a post-hoc power analysis to evaluate our beta-error. Additionally, all results will be presented with an effect size estimation described as standardized mean difference.

Table 1: Baseline characteristics of sample size calculation

Variable	R_{int}	R_{rs}
$n_{Baseline}$	10	10
n_{30min}	10	10
$Mean_{Baseline}$ ± SD	18.4±4.0 [cmH2O/l/sec]	26.5±4.1 [cmH2O/l/sec]
$Mean_{30min}$ ± SD	15.5±3.6 [cmH2O/l/sec]	23.1±3.6 [cmH2O/l/sec]
Effect-size	0.762	0.881
n_{total} Power 80%	44	34
n_{total} Power 90%	62	46
n_{total} Power 95%	76	58

Airway resistance and related sample size (n) before and 30 min after salbutamol administration in ventilated patients of reference work [18]; R_{int}, R_{rs}: minimum and maximum inspiratory resistance (cm H2O/l/s), respectively

Study design

The total study duration is planned for 18 months. It will take 12 months for recruitment of patients and collection of data, last 6 months are scheduled for analyzation. For each patient an individual study duration is assigned of one day. In the control group, 1.75 hours are scheduled per patient. These include study education and randomization (30 mins), data collection before inhalation (30 mins), drug nebulization and inhalation (15 mins) and measurements after inhalation (30 mins; figure 1). In the interventional group, study explanation and randomization (30 mins), data collection before inhalation

(30 mins), the installation and adjustment of EIT (30 mins), the optimization of ventilator settings (15 mins), drug nebulization and inhalation (15 mins), resetting ventilator settings to baseline and measurements 30 minutes after inhalation add up to a total duration of 2.5 hours (figure 1).

Randomization

Block-balanced randomization, in a 1:1 ratio, will be computer-generated by StatsDirect (StatsDirect Ltd., Cambridge, United Kingdom) with random block sizes between n = 10 and n = 20, additionally using random permutations of treatments within each block. Investigators will be blinded to the allocation according to the randomization list until the study patient has been included.

Interventional procedure

EIT and control group undergo an arterial blood gas analysis and corresponding airway measurements to determine baseline parameters before salbutamol inhalation (figure 1; Supplemental material 1+2). Therefore, 1.25 mg / 2.5 mL salbutamol (Sultanol®, Glaxo Smith Kline plc., Brentford, United Kingdom) is applied with a vibrating mesh nebulizer (Solo®, Aerogen, Galway, Ireland).

In the control group, baseline measurement is followed by ultrasound nebulization and inhalation with salbutamol for 15 minutes, following measurements and arterial blood gas analysis 30 minutes after inhalation (figure 1). In addition, all study-relevant data are documented pseudonymised in the case report form (CRF) to ensure a standardized operating (Supplemental material 2). This CRF will be handed over to the principal investigator immediately after collection of data. The principal investigator keeps the study documents in a study folder not accessible to third parties.

In the intervention group, baseline measurements are followed by the standardized setup and adjustment of EIT, where a belt with 16 integrated electrodes is attached circularly to the thorax (Supplemental material 3). This is followed by the optimization of the respirator settings by means of EIT using a defined algorithm (figure 2), according the recommendations of the Translational EIT Development Study Group (TREND) [5]. The EIT algorithm focuses on homogenisation of lung ventilation described by the fast-response parameter ROI (region of interest) to titrate protective PEEP and tidal volume combinations (figure 2). The next step is nebulization and inhalation of salbutamol for 15 minutes. Subsequently, ventilator settings are reset to baseline as before EIT adjustment. After a period of 30 minutes, a new data collection after salbutamol administration including EIT measurement is done and an arterial blood gas analysis is performed (figure 1). Data is documented in the CRF (Supplemental material 1).

Objectives

The primary objective is to assess if additional use of EIT can increase the effectiveness of inhaled salbutamol, and therefore decrease the airway resistance 30 minutes after salbutamol inhalation more effective than without usage of EIT. The secondary objectives will be to compare the EIT-intervention group and the control group regarding:

- Before and 30 minutes after salbutamol inhalation:
  - Changes made in ventilator settings under EIT,
  - tidal volume, compliance, resistance, arterial oxygen partial pressure (p_aO2), Horowitz index, arterial carbon dioxide partial pressure (p_aCO_2), peripheral and arterial oxygen saturation,
  - upper and lower inflection point of the pressure-volume curve,

- EIT parameters: Region of Interest (ROI), changes of end expiratory lung volume (Delta-EELV) and changes of end expiratory lung impedance (Delta-EELI),
- heart rate, blood pressure

- duration of mechanical ventilation,
- length of stay on ICU and hospital, readmission rate on ICU.
- 30-days mortality

Data collection

The documentation of the data will be pseudonymized and computer-assisted from our patient data management system (PDMS) (Dräger ICM, Dräger Medical, Lübeck, Germany) in a central offline database. Therefore, all collected data will solely be provided in pseudonymized form for further study analyzation. Access to the pseudonymization key, which is password protected, is only available to the principal investigator of this study. All above mentioned parameters will be collected during the patients stay in hospital until discharge, death or 30th day of stay on ICU. In case of discharge from ICU, follow-up to evaluate 30-days survival will be performed by visit on normal ward or a phone call by one of the investigators. Data entered in the central offline database will be monitored by an independent clinical research associate and checked for consistency and missing values. All records, subjects' identities and data management will remain confidential with the General Data Protection Regulation (GDPR) of the European Parliament and the Council of the European Union. Furthermore, this protocol was designed following the recommendations for interventional trials (SPIRIT; figure 3; Supplemental material 4).

Statistical analysis

Since this is a study designed to demonstrate superiority of the primary endpoint (change in airway resistance 30 minutes after salbutamol inhalation), whether an additional use of EIT increases the effectiveness of inhaled salbutamol, we will perform an intention-to-treat and additionally a per-protocol analysis as recommended by the CONSORT guidelines [19]. The per-protocol population will be defined as randomized patients without major protocol deviations, such as non-considerations of exclusion criteria or missing data for the primary endpoint. Baseline characteristics of all patients will be described per group. Qualitative data will be described as frequencies and percentages. Continuous variables are presented as means ± standard deviation in case of normal distribution and as median and interquartile range (25th; 75th percentile) in case of non-normally distributed variables. Continuous variables will be compared using parametric Student's t-test or non-parametric Mann-Whitney-U-Test. Categorical variables will be characterized by numbers with percentages and will be compared using the Chi-square test or a Fisher's exact test. Superiority will be assumed, if the 95% confidence interval for the difference between the means excludes zero or p-values are statistically significantly different at an a priori alpha error of less than 0.05.

The graphical processing of variables will be performed depending on the measurement level of the variables as histograms, mean value curves with corresponding standard deviations or box whisker plots.

Ethics and dissemination

A manuscript with the results of the study will be published in a peer-reviewed journal. The study has received the following approvals: Ethics Committee of the Medical

Faculty of Ruhr-University Bochum (17-6306). On completion of the trial, and after publication of the primary manuscript, data will be made availabele in a free accessable online repository.

Discussion

This study, to our knowledge, is the first interventional trial assessing, whether the additional usage of EIT can improve the effectiveness of inhalative drug administration in critical ill and ventilated patients.

The administration of inhaled drugs is routinely used in intensive care units, due to the advantage of delivering high drug concentrations to the airway, along with rapid onset of action and fewer systemic side effects. However, it is believed that the beneficial effects of inhaled drugs are smaller in patients on mechanical ventilation than in those breathing spontaneously. In this regard, a previous study could demonstrate that only 2.9% of the administered drug dose reached the distal airway in ventilated patients, compared to 11.9% in patients without artificial airway [16]. A recently published review, regarding inhalative drug therapy in mechanical ventilation, stated that ventilator settings play an crucial role in inhaled drug delivery [14]. A tidal volume of at least 500 mL, increased inspiratory time and a low inspiratory flow are general recommendations in order to optimize drug distribution in the lungs [14 20 21]. Nevertheless, attention should be paid to serious adverse effects of high (> 500 mL) tidal volumes, especially in patients with acute or chronic airway obstructions. In these patients high tidal volumes can lead to dynamic hyperinflation or can cause a severe barotrauma [14]. Furthermore, no clinical studies exist showing the beneficial effects of any particular ventilation mode on inhaled drug delivery [20 21]. Therefore, a new diagnostic and guiding tool for adequate optimization of ventilator settings prior to nebulization of inhalative drugs would be desirable. Hence, fast, non-invasive and reliable assessment at bedside in critical ill and ventilated patients is one of the cornerstones for modern intensive care monitoring. EIT, although with some constrains, may be a promising solution. EIT images are valid measurements of the regional distribution of ventilation and changes in lung volume in real-time. This dynamic evaluation makes EIT a promising tool for guided optimization

of ventilator parameters on an individualized base. Several studies in the last years have already demonstrated that EIT-guided respirator optimization results in significant improved respiratory mechanics and improved gas exchange [1 4 7 22]. However, a global standard based on a broad base of evidence was one of the most discussed topics in Respiratory Medicine over the last years. Therefore, the plausibility of EIT measurements highly depends on the correct belt position, proper impedance visualization, correct analysis and data interpretation [23].

The crucial step forward was the publication of recommendations of the TREND (Translational EIT Development Study) group [5]. These recommendations highlight the need for a consensus about examinations, consistent terminology and generally accepted approaches to EIT images and analysis. Based on this highly appreciated consensus statement we are now able to compare, understand and reproduce study findings from among different research groups and provide a standardized use in clinical routine.

A further limitation is that EIT captures only ventral-to-dorsal ventilation distribution. However, Bikker et al. also reported different ventilation distribution between cranial and caudal lung levels during decremental PEEP trials [24], concluding that existing EIT systems will not be able to cover the optimal PEEP titration for the whole lung.

Despite the possible limitations of EIT, this device can provide a remarkable advance in the field of individualized and guided mechanical ventilation adjustments. Therefore, this study can shed light on the extent to which the additional use of EIT for optimizing the ventilator settings can increase the effectiveness of inhaled salbutamol.

Outlook

EIT could help to visualize and verify an effective nebulization that could provide a safe, efficient and individualized way of inhalative drug application, e.g. by increasing the

effective dose reaching distal airway. Therefore, these results are also of great interest beyond salbutamol nebulization, e.g. for safe usage of inhalative antibiotics in critical ill and ventilated patients.

Trial status

The first patients were randomized in June 2018. The inclusion of participants is ongoing and is expected to continue until June 2019.

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List of abbreviations

ARDS	Acute respiratory distress syndrome
BMI	Body mass index
CRF	Case report form
delta-EELI	Change of end expiratory lung impedance
delta-EELV	Change of end expiratory lung volume
DRKS	Deutsches Register für klinische Studien
ECMO	Extracorporeal membrane oxygenation
EIT	Electrical impedance tomography
GDPR	General data protection regulation
ICD	Implantable cardioverter defibrillator
ICU	Intensive care unit
NYHA	New York Heart Association
p_aCO_2	Partial pressure of arterial carbon dioxide
p_aO_2	Partial pressure of arterial oxygen
PDMS	Patient data management systems
PEEP	Positive end-expiratory pressure
R	Resistance
ROI	Region of interest
SAPSII	Simplified acute physiology score II
SD	Standard deviation
SOFA score	Sepsis-related organ failure assessment score
Spirit	Standard Protocol Items - Recommendations for Interventional
TREND group	Translational EIT Development Study group

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of the Medical Faculty of the Ruhr-Universität Bochum (no. 17-6306) and written informed consent or a positive vote of an independent consultant are eligible for inclusion.

Consent for publication

Not applicable

Availability of data and material

The data of the described study will be available from the Dryad repository after publication.

Conflict of interests

None to declare

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Author Statement

Dr. med. Tim Rahmel: Main author of this manuscript, written and revising the manuscript

Alexandra Koniusch: Supporting methodical description and participated in the design of this study

Dr. med. Günther Oprea: Supporting data collection, participated in the design of this study, and revising the manuscript

Martin Schwertner: Supporting data collection, participated in the design of this study, and revising the manuscript

Prof. Dr. med. Michael Adamzik: Supporting data collection, participated in the design of this study and revising the manuscript

Dr. med. Hartmuth Nowak: Supporting data collection, participated in the design of this study, written and revising the manuscript

All authors read and approved the final manuscript.

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Legends

Figure 1: Flowchart of interventional procedures on intervention and control group with duration of each step and performed measurements (EIT = electrical impedance tomography, ICU = intensive care unit)

Figure 2: Flowchart of EIT-guided optimization of ventilator settings (ROI = region of interest, Pmax = maximum airway pressure, Pinsp = inspiratory pressure, PEEP = positive end expiratory pressure)

Figure 3: Schedule of enrolment, interventions and assessments – SPIRIT Figure (SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials, EIT = electrical impedance tomography, ICU = intensive care unit)

Supplemental material

Supplemental material 1: Case report form of intervention group

Supplemental material 2: Case report form of control group

Supplemantal material 3: Additional information - EIT algorithm

Supplemental material 4: Spirit checklist

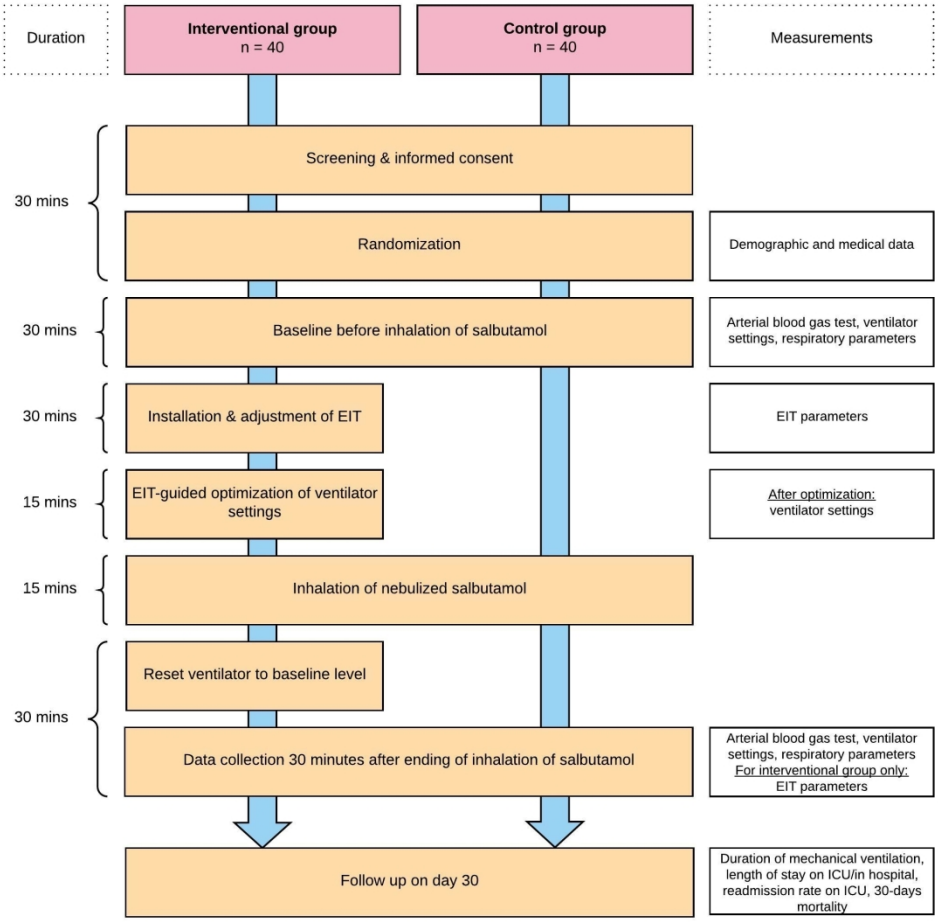


Figure 1: Flowchart of interventional procedures on intervention and control group with duration of each step and performed measurements (EIT = electrical impedance tomography, ICU = intensive care unit)

184x181mm (300 x 300 DPI)

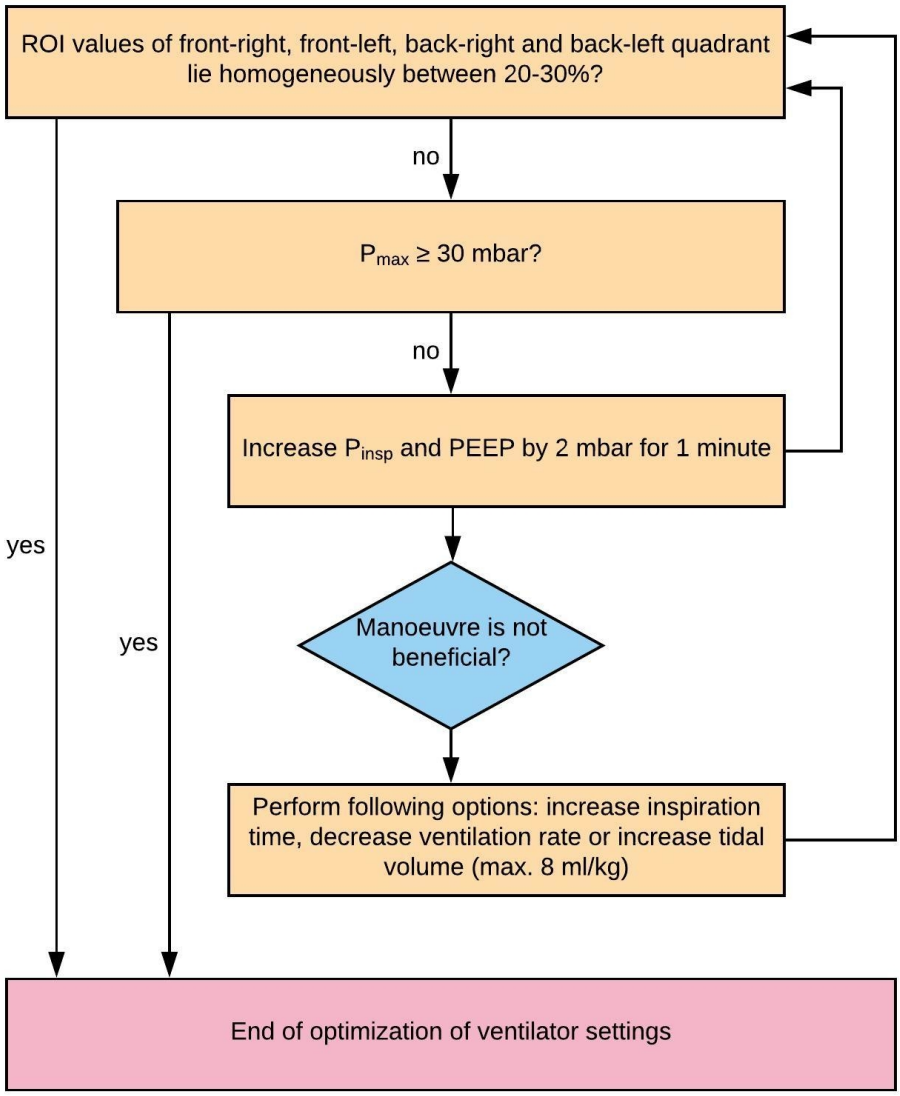


Figure 2: Flowchart of EIT-guided optimization of ventilator settings (ROI = region of interest, Pmax = maximum airway pressure, Pinsp = inspiratory pressure, PEEP = positive end expiratory pressure)

114x136mm (300 x 300 DPI)

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
TIMEPOINT	Prior randomization	0	Baseline	After Baseline	After intervention	30 days
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
INTERVENTIONS:						
EIT-guided optimization of ventilation, inhalation of nebulized salbutamol afterwards				X		
Inhalation of nebulized salbutamol				X		
ASSESSMENTS:						
Demographic & medical data			X			
Ventilator settings			X		X	
Respiratory parameters			X		X	
Arterial blood gas test			X		X	
EIT parameters (*for EIT group only*)			X		X	
Duration of mechanical ventilation, length of stay on ICU/in hospital, readmission rate on ICU						X
30-days mortality						X

Figure 3: Schedule of enrolment, interventions and assessments – SPIRIT Figure (SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials, EIT = electrical impedance tomography, ICU = intensive care unit)

139x224mm (300 x 300 DPI)

Randomization |__|__|.|__|__|.201__

No. |__|__| ***CRF EIT-Trial (intervention group)*** VU

Patient

Inclusion criteria	Yes	No
• Age ≥ 18 years	☐	☐
• Known obstructive airway disease or acute airway obstruction ***and*** • Medical indication for salbutamol inhalation	☐	☐
• Mechanical ventilated patient (<48h) and Horowitz index (p_aO_2/F_iO_2) < 400	☐	☐
• Written informed consent or positive vote of an independent consultant	☐	☐

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	☐	☐
• Lack of medical indication and/or contraindications to administration of salbutamol	☐	☐
• Age < 18 years	☐	☐
• Pre-existing conditions or operations: Patients with chest trauma or chest surgery; thoracic skin lesions and wound dressings; ARDS and/or ECMO therapy; neuromuscular diseases; severe cardiac diseases (e.g. NYHA III-IV); acute ischemic events; active implants (e.g. pacemakers, ICDs)	☐	☐
• Severe obesity (BMI > 35)	☐	☐
• Prior phase of long-term ventilation > 14 days	☐	☐
• Do-not-resuscitate order	☐	☐
• Pregnancy or lactation	☐	☐

- Copy patient file/printout! (Anamnesis, concomitant medications, concomitant diseases, physical examination, ECG, vital parameters ☐ carried out

  ☐ male ☐ female

  Height |__|__|__| cm **weight** |__|__|__|.|__| kg **BMI** |__|__|.|__| kg/m^2

- **Blood pressure** |__|__|__| / |__|__| **heart rate** |__|__|__| bpm

  body temperature |__|__|.|__| °C

- Pregnancy excluded ☐

- Note participation in the medical record! ☐ carried out

- **Procedure in the intervention group**
  - Study education including randomization (30 min) ☐
    - Measurement of SOFA-Score (_____), PCT (_____), CRP (_____), antibiotics (_____), vital parameters (_____), catecholamines (_____), sedation (_____) ☐
  - Data collection before inhalation (30 min)
    - Measurement of airway resistance before salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
  - Installation and adjustment of the EIT (30 min) ☐
    - Measurement of Region of Interest (ROI) (_____), changes of end-exspiratory lung volume (Delta-EELV) (_____) and changes of end-exspiratory lung impedance (Delta-EELI) (_____) ☐
  - Optimization of ventilator settings (15 min) ☐
    - Measurement of ventilator settings after EIT-guided optimization (P_{insp} (_____), PEEP (_____), I:E (_____), T_{insp} (_____), RR (_____), ventilation mode (_____)) ☐
  - Salbutamol nebulization and inhalation (15 min) ☐
  - Reset ventilator to baseline level ☐
  - Data collection after inhalation (30 min)
    - Measurement of airway resistance after salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
    - Measurement of Region of Interest (ROI) (_____), changes of end-exspiratory lung volume (Delta-EELV) (_____) and changes of end-exspiratory lung impedance (Delta-EELI) (_____) ☐

Date |__|__|.|__|__| 201__ Signature of the examiner _____

Randomization |__|__|.|__|__|.201__

No. |__|__| ***CRF EIT-Trial (control group)*** VU

Patient

Inclusion criteria	Yes	No
• Age ≥ 18 years	☐	☐
• Known obstructive airway disease or acute airway obstruction ***and*** • Medical indication for salbutamol inhalation	☐	☐
• Mechanical ventilated patient (<48h) and Horowitz index (p_aO_2/F_iO_2) < 400	☐	☐
• Written informed consent or positive vote of an independent consultant	☐	☐

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	☐	☐
• Lack of medical indication and/or contraindications to administration of salbutamol	☐	☐
• Age < 18 years	☐	☐
• Pre-existing conditions or operations: Patients with chest trauma or chest surgery; thoracic skin lesions and wound dressings; ARDS and/or ECMO therapy; neuromuscular diseases; severe cardiac diseases (e.g. NYHA III-IV); acute ischemic events; active implants (e.g. pacemakers, ICDs)	☐	☐
• Severe obesity (BMI > 35)	☐	☐
• Prior phase of long-term ventilation > 14 days	☐	☐
• Do-not-resuscitate order	☐	☐
• Pregnancy or lactation	☐	☐

- Copy patient file/printout! (Anamnesis, concomitant medications, concomitant diseases, physical examination, ECG, vital parameters ☐ carried out

  ☐ male ☐ female

  Height |__|__|__| cm **weight** |__|__|__|.|__| kg **BMI** |__|__|.|__| kg/m^2

- **Blood pressure** |__|__|__| / |__|__| **heart rate** |__|__|__| bpm

  body temperature |__|__|.|__| °C

- Pregnancy excluded ☐

- Note participation in the medical record! ☐ carried out

- **Procedure in the control group**
  - Study education including randomization (30 min) ☐
    - Measurement of SOFA-Score (_____), PCT (_____), CRP (_____), antibiotics (_____), vital parameters (_____),catecholamines (_____), sedation (_____) ☐
  - Data collection before inhalation (30 min)
    - Measurement of airway resistance before salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐
  - Salbutamol nebulization and inhalation (15 min) ☐
  - Data collection after inhalation (30 min)
    - Measurement of airway resistance after salbutamol inhalation (_____) ☐
    - Measurement of tidal volume (_____), lung compliance (_____), arterial oxygen partial pressure (paO_2) (_____), Horowitz index (_____), arterial carbon dioxide partial pressure ($paCO_2$) (_____), peripheral oxygen saturation (_____), arterial oxygen saturation (_____), upper (_____) and lower (_____) inflectionpoint of the pressure-volume-curve ☐
    - Arterial blood sampling ☐

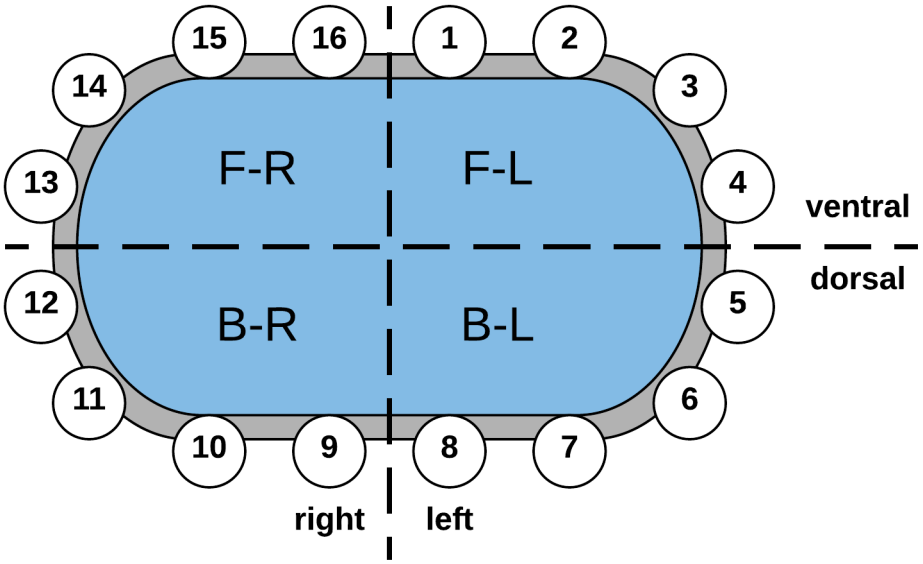
Date |__|__|.|__|__| 201__ Signature of the examiner _____

Additional information - EIT algorithm

Installation procedure for EIT (PulmoVista 500, Dräger Medical, Lübeck, Germany)		
1.	To turn on the EIT system press the green "Power on"-button in the left, lower corner of the screen (it will light up after switching on). Afterwards, the system will be in "Standby"-mode.	☐
2.	Connect the main plug of the trunk cable to the upper connection socket. Connect the color-coded plugs to the corresponding test socket (green = right/R), red = left/L).	☐
3.	Choose "System Test" on the touch screen. Press "Start" and confirm this selection by pressing the control knob in the right, lower corner of the screen. The EIT system will perform a self-check to ensure proper functioning of all components and the trunk cable.	☐
4.	Choose a belt according to the patient's circumference of chest (S = 70-85 cm, M = 80-96 cm, L = 92-110 cm, XL = 106-127 cm, XXL = 124-150 cm). Connect electrodes of the corresponding connection cable with the belt (number 1 to 1, number 2 to 2, …, number 16 to 16).	☐
5.	Placement of EIT belt: Between 8th and 9th electrode is a perceptible silicone mark, place this mark centrally over the spine between 4th and 6th intercostal space. Both lateral ends are folded forward towards the chest and connected in front of the sternum, so that electrode number 1 is placed left and number 16 right to the sternum (figure 1). Connect the "C"-electrode of the connection cable with the seal of the EIT belt. Place an ECG-electrode on the skin of the abdomen and connect it with the "REF"-electrode of the connection cable.	☐
6.	Plug the green and red color-coded plugs of the trunk cable out of the test socket and connect them to the connection cable of the EIT belt (ensure the correct connection: green to green and red to red).	☐
7.	Select the option "New Patient" on the touch screen in the Start/Standby menu. By choosing "Signal Check" skin resistance of each electrode is shown, a blue bar appears for all electrodes. If skin resistance is insufficiently high (> 300 ohms), the corresponding electrode is marked in red. In that case, prove the correct positioning of that electrode, moisturize the electrode with water or electrode gel where applicable. Move on to step 8 when all bars appear blue.	☐
8.	Register patient data by selecting "New Patient". Afterwards, press "Start" to start EIT measurements. A short calibration is performed (approximately 30 seconds), afterwards the system is ready for measuring.	☐

EIT algorithm Version 1.0

Figure 1: schematic cross-section image of thorax with positions of 16 EIT electrodes at the level of 4th to 6th intercostal space *(F-R = front-right quadrant, F-L = front-left quadrant, B-R = back-right quadrant, B-L = back-left quadrant)*



Measurement of EIT parameters (ROI, Delta-EELV and Delta-EELI)		
1.	ROI (Region of interest): Choose "Views" in right upper corner of the screen and tap on "Full Screen". Values for each quadrant (F-R, F-L, B-R, B-L) are displayed.	☐
2.	Delta-EELV (changes of end exspiratory lung volume): Choose "Views" in right upper corner of the screen and tap on "End exspiratory trend".	☐
3.	Delta-EELI (changes of end exspiratory lung impedance): Choose "Views" in right upper corner of the screen and tap on "Delta-EELI".	☐

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Evaluation of inhaled salbutamol effectiveness under supportive use of electrical impedance tomography in ventilated ICU patients: study protocol for a randomized controlled clinical trial ***(page 1)***
Trial registration	2	German trial register (DRKS.de); ID: DRKS00014706; registered on 14th May 2018 ***(page 6)***
Protocol version	3	10th March 2018, version 1.0
Funding	4	We acknowledge support by the DFG Open Access Publication Funds of the Ruhr-University Bochum (Ref. No. IN-1214264), just for financial support for publication costs. This will have no impact on our study design or collection, analysis and interpretation of our data. ***(page 19)***

Roles and responsibilities	5a	Dr. med. Tim Rahmel, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Principal investigator, main author of this manuscript, written and revising the manuscript Alexandra Koniusch, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting methodical description and participated in the design of this study Dr. med. Günther Oprea, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting data collection, participated in the design of this study, and revising the manuscript Martin Schwertner, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting data collection, participated in the design of this study, and revising the manuscript Prof. Dr. med. Michael Adamzik, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting data collection, participated in the design of this study and revising the manuscript Dr. med. Hartmuth Nowak, Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital Knappschaftskrankenhaus Bochum, Bochum, Germany: Co-Principal investigator, supporting data collection, participated in the design of this study, written and revising the manuscript ***(pages 19-20)***
	5b	NA
	5c	Support is granted by the DFG Open Access Publication Funds of the Ruhr-University Bochum (Ref. No. IN-1214264), just for financial support for publication costs. This will have no impact on our study design or collection, analysis and interpretation of our data. ***(page 19)***
	5d	NA

Introduction

Background and rationale	6a	The inhalative administration of drugs is a non-invasive application form that is regularly used in the treatment of ventilated patients in critical care setting. However, assessment of effectiveness or distribution of nebulized drugs is one of the lacking cornerstones of modern intensive care monitoring as several studies could not show a benefit of inhaled medication. Unfortunately, these studies could not address the crucial issue whether the medication was distributed effectively in critical ill ventilated patients. To the present day, there is no established non-invasive real-time monitoring to measure or visualize the effectiveness or distribution of nebulized drugs in ventilated patients at bedside. Electrical impedance tomography (EIT) may provide a promising new monitoring and guiding tool for an adequate optimization of mechanical ventilation in critically ill patients. EIT makes use of changes in thoracic impedance, which in turn result in different concentrations of free ions due to changes in air content of the lung tissue. Therefore, EIT may assist in defining mechanical ventilation settings, assess distribution of tidal volume and evaluation of associated pathologies at bedside. Prior studies demonstrated that equivalent diagnostic findings between EIT and thoracic computed tomography could be achieved in critically ill patients in terms of regional ventilation in different thoracic regions, and also offered a valid examiner-independent test reproducibility of the results. ***(pages 4-5)***
	6b	As no non-invasive real-time monitoring for visualization of nebulized drugs in ventilated patients at bedside is established to the present day, comparator will be standard of care with no EIT-optimized application of salbutamol. ***(pages 4-5)***
Objectives	7	Our study wants to elucidate the extent to which the effectiveness of inhaled drugs, e.g. β2 sympathomimetics, can be optimized by the additional use of EIT for adjusting ventilator settings. Accordingly, we want to test the hypothesis whether EIT can increase the effectiveness of inhaled salbutamol. ***(page 5)***
Trial design	8	This study is a randomized, open-label superiority trial, comparing two groups of mechanically ventilated patients with an acute or chronic bronchial airway obstruction according the effectiveness of inhaled salbutamol with (intervention) or without (control) additional use of EIT for optimizing the ventilator settings. ***(page 6)***

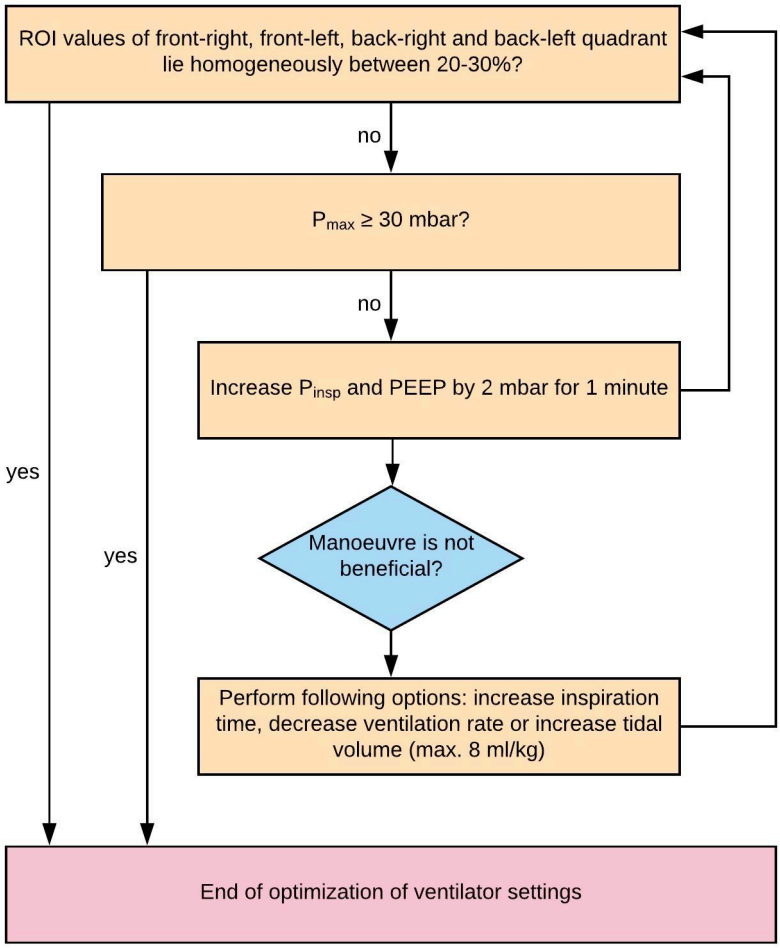
Methods: Participants, interventions, and outcomes

Study setting	9	This study will be conducted at the interdisciplinary, operative intensive care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum, a university hospital of Ruhr-University Bochum in Bochum, Germany. ***(page 6)***

Eligibility criteria	10	Patients at the age of 18 years or more, diagnosed with an acute airway obstruction or known chronic obstructive pulmonary disease under mechanical ventilation for less than 48 hours and providing written informed consent or a positive vote of an independent consultant are eligible for inclusion. ***(page 6)***
		Exclusion criteria are: pregnancy or lactation, severe obesity (body mass index > 35), missing medical indication and/or contraindication for inhaled salbutamol administration, Horowitz index ≥ 400, prior phase of long-term ventilation > 14 days, a study-independent medical indication for salbutamol nebulization in obstructive pulmonary disease and/or an acute obstructive condition and procedure of withdrawing life-sustaining therapy. Furthermore, patients with the following pre-existing conditions and operations will be excluded: patients with chest trauma or surgery (e.g. pneumectomy), pneumonia, ARDS with or without ECMO therapy, neuromuscular diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic events, active implants (e.g. pacemakers, ICD) or thoracic skin lesions and wound dressings. ***(page 6-7)***

Interventions	11a	EIT and control group undergo an arterial blood gas analysis and corresponding airway measurements to determine baseline parameters before salbutamol inhalation. Therefore, 1.25 mg / 2.5 mL salbutamol (Sultanol®, Glaxo Smith Kline plc., Brentford, United Kingdom) is applied with a vibrating mesh nebulizer (Solo®, Aerogen, Galway, Ireland). ***(page 9)***
		In the control group, baseline measurement is followed by ultrasound nebulization and inhalation with salbutamol for 15 minutes, following measurements and arterial blood gas analysis 30 minutes after inhalation. In addition, all study-relevant data are documented pseudonymised in the case report form (CRF) to ensure a standardized operating. This CRF will be handed over to the principal investigator immediately after collection of data. The principal investigator keeps the study documents in a study folder not accessible to third parties. ***(page 9)***
		In the intervention group, baseline measurements are followed by the standardized setup and adjustment of EIT, where a belt with 16 integrated electrodes is attached circularly to the thorax. This is followed by the optimization of the respirator settings by means of EIT using a defined algorithm, according the recommendations of the Translational EIT Development Study Group (TREND) (see below, figure 2). The EIT algorithm focuses on homogenisation of lung ventilation described by the fast-response parameter ROI (region of interest) to titrate protective PEEP and tidal volume combinations. The next step is nebulization and inhalation of salbutamol for 15 minutes. Subsequently, ventilator settings are reset to baseline as before EIT adjustment. After a period of 30 minutes, a new data collection after salbutamol administration including EIT measurement is done and an arterial blood gas analysis is performed (figure 1). Data is documented in the CRF. ***(page 9-10)***

EIT algorithm for optimization of respirator settings (figure 2):



11b As study procedure is only done once, no specific criteria for discontinuing or modifying allocated interventions is needed.

11c NA

11d NA

Outcomes	12	The primary objective is to assess if additional use of EIT can increase the effectiveness of inhaled salbutamol, and therefore decrease the airway resistance 30 minutes after salbutamol inhalation more effective than without usage of EIT. ***(page 10)***
		The secondary objectives will be to compare the EIT-intervention group and the control group regarding: Before and 30 minutes after salbutamol inhalation [Changes made in ventilator settings under EIT, tidal volume, compliance, resistance, arterial oxygen partial pressure (paO2), Horowitz index, arterial carbon dioxide partial pressure (paCO2), peripheral and arterial oxygen saturation, upper and lower inflection point of the pressure-volume curve, EIT parameters: Region of Interest (ROI), changes of end expiratory lung volume (Delta-EELV) and changes of end expiratory lung impedance (Delta-EELI), heart rate, blood pressure]; duration of mechanical ventilation; length of stay on ICU and hospital, readmission rate on ICU; 30-days mortality. ***(pages 10-11)***
		Additionally, after pseudonymization a large body of clinical and demographic data will be entered into a database for later analysis, including pre-existing morbidities, Simplified Acute Physiology Score II (SAPSII), Sepsis-related Organ Failure Assessment Score (SOFA), body mass index (BMI), necessity for renal replacement therapy, ventilator settings, PaO2/FiO2 ratio (Horowitz index), vital parameters, medications and dosage of vasoactive drugs and blood chemistry values. ***(page 7)***

Participant timeline 13 Study schedule is presented in the following table (figure 3):

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
TIMEPOINT	Prior randomization	0	Baseline	After Baseline	After intervention	30 days
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
INTERVENTIONS:						
EIT-guided optimization of ventilation, inhalation of nebulized salbutamol afterwards				X		
Inhalation of nebulized salbutamol				X		
ASSESSMENTS:						
Demographic & medical data			X			
Ventilator settings			X		X	
Respiratory parameters			X		X	
Arterial blood gas test			X		X	
EIT parameters (*for EIT group only*)			X		X	
Duration of mechanical ventilation, length of stay on ICU/in hospital, readmission rate on ICU						X
30-days mortality						X

Sample size 14 A total of 80 mechanically ventilated patients will be included in the study, with 40 patients in the intervention group and 40 patients in the control group. With a total cohort size of n=80, a power of > 95% (alpha error p = 0.05, beta error < 0.05) will be reached, referring to the data from a reference work (table 1) by Malliotakis et al. Calculations from these values indicate that 76 participants (38 per group) are required to achieve a power of 95% with an alpha error of 5%. ***(pages 7-8)***

Variable	**R_{int}**	**R_{rs}**
$n_{Baseline}$	10	10
n_{30min}	10	10
$Mean_{Baseline}$ ± SD	18.4±4.0 [cmH2O/l/sec]	26.5±4.1 [cmH2O/l/sec]
$Mean_{30min}$ ± SD	15.5±3.6 [cmH2O/l/sec]	23.1±3.6 [cmH2O/l/sec]
Effect-size	0.762	0.881
n_{total} Power 80%	44	34
n_{total} Power 90%	62	46
n_{total} Power 95%	76	58

Airway resistance and related sample size (n) before and 30 min after salbutamol administration in ventilated patients of reference work 18; Ri_{nt}, R_{rs}: minimum and maximum inspiratory resistance (cm H2O/l/s), respectively

Recruitment 15 We will ensure patient recruitment by screening patients on ICU daily. Eligible patients will be approached by the principal inverstigator and/or one of the eligible physicians.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a Block-balanced randomization, in a 1:1 ratio, will be computer-generated by StatsDirect (StatsDirect Ltd., Cambridge, United Kingdom) with random block sizes between n = 10 and n = 20, additionally using random permutations of treatments within each block. Investigators will be blinded to the allocation according to the randomization list until the study patient has been included. ***(page 9)***

Allocation concealment mechanism 16b Concealment of allocation mechanism will be performed by using sealed envelopes. For each patient included, a sealed envelope will be drawn and opened.

Implementation	16c	A physician who is independent to this trial will generate allocation sequence. Enrolment and assignment will be done by the principal investigator and/or eligible physicians.
Blinding (masking)	17a	No blinding will be performed.
	17b	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	The documentation of the data will be pseudonymized and computer-assisted from our patient data management system (PDMS) (Dräger ICM, Dräger Medical, Lübeck, Germany) in a central offline database. ***(page 11)***
	18b	All above mentioned parameters will be collected during the patients stay in hospital until discharge, death or 30th day of stay on ICU. In case of discharge from ICU, follow-up to evaluate 30-days survival will be performed by visit on normal ward or a phone call by one of the investigators. ***(page 11)***
Data management	19	All collected data will solely be provided in pseudonymized form for further study analyzation. Access to the pseudonymization key, which is password protected, is only available to the principal investigator of this study. ***(page 11)***

Statistical methods	20a	Since this is a study designed to demonstrate superiority of the primary endpoint (change in airway resistance 30 minutes after salbutamol inhalation), whether an additional use of EIT increases the effectiveness of inhaled salbutamol, we will perform an intention-to-treat and additionally a per-protocol analysis as recommended by the CONSORT guidelines. The per-protocol population will be defined as randomized patients without major protocol deviations, such as non-considerations of exclusion criteria or missing data for the primary endpoint. Baseline characteristics of all patients will be described per group. Qualitative data will be described as frequencies and percentages. Continuous variables are presented as means ± standard deviation in case of normal distribution and as median and interquartile range (25th; 75th percentile) in case of non-normally distributed variables. Continuous variables will be compared using parametric Student's t-test or non-parametric Mann-Whitney-U-Test. Categorical variables will be characterized by numbers with percentages and will be compared using the Chi-square test or a Fisher's exact test. Superiority will be assumed, if the 95% confidence interval for the difference between the means excludes zero or p-values are statistically significantly different at an a priori alpha error of less than 0.05. The graphical processing of variables will be performed depending on the measurement level of the variables as histograms, mean value curves with corresponding standard deviations or box whisker plots. ***(pages 11-12)***
	20b	NA
	20c	We will perform an intention-to-treat and additionally a per-protocol analysis as recommended by the CONSORT guidelines. ***(page 11)***
Methods: Monitoring		
Data monitoring	21a	Data entered in the central offline database will be monitored by an independent clinical research associate and checked for consistency and missing values. ***(page 11)***
	21b	No interim analyses are planned.
Harms	22	During study conduct and follow-up patients will be continuously monitored for possible adverse events. Those will be recorded in the database.
Auditing	23	NA
Ethics and dissemination		
Research ethics approval	24	This study was reviewed and approved by the Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306). ***(page 6)***

Protocol amendments	25	Prinicipal investigator will communicate all important modifications to study personnel.
Consent or assent	26a	Informed consent will be obtained by principal investigator and/or eligible physicians.
	26b	NA
Confidentiality	27	All records, subjects' identities and data management will remain confidential with the General Data Protection Regulation (GDPR) of the European Parliament and the Council of the European Union. ***(page 11)***
Declaration of interests	28	None to declare ***(page 19)***
Access to data	29	The data of the described study will be available from the Dryad repository after publication. ***(page 19)***
Ancillary and post-trial care	30	No arrangements have been made for compensation to those who suffer harm from trial participation. This has been stated in the informed consent.
Dissemination policy	31a	A manuscript with the results of the study will be published in a peer-reviewed journal. ***(page 12)***
	31b	NA
	31c	A publication of this study protocol in BMJ Open is submitted.
Appendices		
Informed consent materials	32	An informed consent form is available in German language can be obtained from the authors.
Biological specimens	33	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.