

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

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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 nebulised 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 optimisation of mechanical ventilation in critically ill patients. EIT may assist in defining mechanical ventilation settings, assess distribution of tidal volume and evaluate associated pathologies at bedside. This study aims to elucidate the extent to which the effectiveness of inhaled salbutamol can be increased by the additional use of EIT for optimisation of respirator settings.

Methods and analysis This study is a randomised, 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 to the effectiveness of inhaled salbutamol with (intervention) or without (control) additional use of EIT for optimising ventilator settings. The primary outcome is change in airway resistance 30 min after salbutamol inhalation.

Ethics and dissemination The study has received approval from the Ethics Committee of the Medical Faculty of Ruhr-University Bochum (17-6306). The 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 number DRKS00014706; Pre-results.

INTRODUCTION

Electrical impedance tomography (EIT) is an imaging method that is already used in clinical setting. For several years it has been mainly used to monitor 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 the air content of the lung

Strengths and limitations of this study

- This is the first interventional trial assessing whether the additional usage of electrical impedance tomography (EIT) can improve the effectiveness of inhalative drug administration in critically ill and ventilated patients.
- EIT could help to visualise and verify an effective nebulisation that could provide a safe, efficient and individualised way of inhalative drug application, for example, 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 individualised and guided mechanical ventilation adjustments at bedside.
- The secondary outcomes of this study will possibly offer 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.

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 reliably enables the immediate and non-invasive assessment of changes in regional lung tissue.^{4 5} It can also help to optimise ventilation settings to prevent regional overinflating of the lungs and atelectasis.⁶ Prior studies demonstrated that equivalent diagnostic findings between EIT and thoracic CT 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, such as usage in active implants (eg, 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 are 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 the treatment of obstructive airways diseases. An important advantage is that significantly 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 critically ill and ventilated patients. To the present day, there is no established non-invasive real-time monitoring to measure or visualise the effectiveness or distribution of nebulised drugs in ventilated patients at bedside.¹⁴

Based on this issue, our study aims to elucidate the extent to which the effectiveness of inhaled drugs, for example, β_2 sympathomimetics, can be optimised by the additional use of EIT for adjusting ventilator settings. Accordingly, we want to test the hypothesis on whether EIT can increase the effectiveness of inhaled salbutamol.

METHODS AND ANALYSIS

This study is a randomised, open-label, superiority trial comparing an interventional group with optimisation of respirator settings under the use of EIT and a control group without optimisation 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

All patients admitted to the intensive care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum will be recruited from June 2018 to June 2019. We will perform EIT measurements with PulmoVista (Dräger Medical) and a size-adjusted chest belt with 16 electrodes. The diagnosis of acute or chronic airway obstruction will include clinical examination and expiration flow analysis. Patients aged 18 years or older 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 [BMI] >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 nebulisation in obstructive pulmonary disease and/or an acute obstructive condition, and in the process of withdrawing life-sustaining therapy. Furthermore, patients with the following pre-existing conditions and operations will be excluded: patients with chest trauma or surgery (eg, pneumonectomy), pneumonia, acute respiratory distress syndrome with or without extracorporeal membrane oxygenation therapy, neuromuscular diseases, severe cardiac diseases (eg, New York Heart Association III–IV), acute ischaemic events, active implants (eg, pacemakers, implantable cardioverter-defibrillator), 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 haemodynamic, antibiotic and diagnostic management as recommended by guidelines, standard operating procedures or evidence-based best practice. Additionally, after pseudonymisation 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, Sepsis-related Organ Failure Assessment score, BMI, necessity for renal replacement therapy, ventilator settings, ratio of arterial oxygen partial pressure to fractional inspired oxygen (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 standardised 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 (cmH ₂ O/L/s)	26.5±4.1 (cmH ₂ O/L/s)
Mean _{30min} ± SD	15.5±3.6 (cmH ₂ O/L/s)	23.1±3.6 (cmH ₂ O/L/s)
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 from a reference work by Malliotakis *et al.*¹⁸

R_{int}, R_{rs}, minimum and maximum inspiratory resistance (cmH₂O/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, and the last 6 months are scheduled for analysis. For each patient an individual study duration is 1 day. In the control group, 1.75 hours are scheduled per patient. These include study education and randomisation (30 min), data collection before inhalation (30 min), drug nebulisation and inhalation (15 min), and measurements after inhalation (30 min; [figure 1](#)). In the interventional group, study explanation and randomisation (30 min), data collection before inhalation (30 min), installation and adjustment of EIT (30 min), optimisation of ventilator settings (15 min), drug nebulisation and inhalation (15 min), and resetting ventilator settings to baseline and measurements 30 min after inhalation add up to a total duration of 2.5 hours ([figure 1](#)).

Randomisation

Block-balanced randomisation, in a 1:1 ratio, will be computer-generated by StatsDirect (StatsDirect, Cambridge, UK) 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 randomisation list until the study patient has been included.

Interventional procedure

The EIT and control groups undergo an arterial blood gas analysis and corresponding airway measurements to determine baseline parameters before salbutamol inhalation ([figure 1](#); [online supplementary materials 1 and 2](#)). Therefore, 1.25 mg/2.5 mL salbutamol (Sultanol, GlaxoSmith-Kline, Brentford, UK) is applied with a vibrating mesh nebuliser (Solo, Aerogen, Galway, Ireland).

In the control group, baseline measurement is followed by ultrasound nebulisation and inhalation with salbutamol for 15 min, following measurements and arterial

blood gas analysis 30 min after inhalation ([figure 1](#)). In addition, all study-relevant data are documented pseudonymised on the case report form (CRF) to ensure a standardised operating procedure ([online supplementary 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 standardised set-up and adjustment of EIT, where a belt with 16 integrated electrodes is attached circularly to the thorax ([online supplementary material 3](#)). This is followed by the optimisation of the respirator settings by means of EIT using a defined algorithm ([figure 2](#)), according to 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 region of interest (ROI) to titrate protective positive end-expiratory pressure (PEEP) and tidal volume combinations ([figure 2](#)). The next step is nebulisation and inhalation of salbutamol for 15 min. Subsequently, ventilator settings are reset to baseline as before EIT adjustment. After a period of 30 min, a new data collection after salbutamol administration including EIT measurement is done and an arterial blood gas analysis is performed ([figure 1](#)). Data are documented on the CRF ([online supplementary 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 min after salbutamol inhalation more effectively than without usage of EIT. The secondary objectives will be to compare the EIT intervention group and the control group with regard to the following:

- ▶ Before and 30 min after salbutamol inhalation:
 - Changes made in ventilator settings under EIT.
 - Tidal volume, compliance, resistance, arterial oxygen partial pressure, Horowitz index, arterial carbon dioxide partial pressure, and peripheral and arterial oxygen saturation.
 - Upper and lower inflection point of the pressure-volume curve.
 - EIT parameters: ROI, changes in end expiratory lung volume (delta-EELV) and changes in end expiratory lung impedance (delta-EELI).
 - Heart rate and blood pressure.
- ▶ Duration of mechanical ventilation.
- ▶ Length of stay on ICU and hospital and readmission rate on ICU.
- ▶ 30-day mortality.

Data collection

The documentation of the data will be pseudonymised and computer-assisted from our patient data management system (Dräger ICM, Dräger Medical) in a central

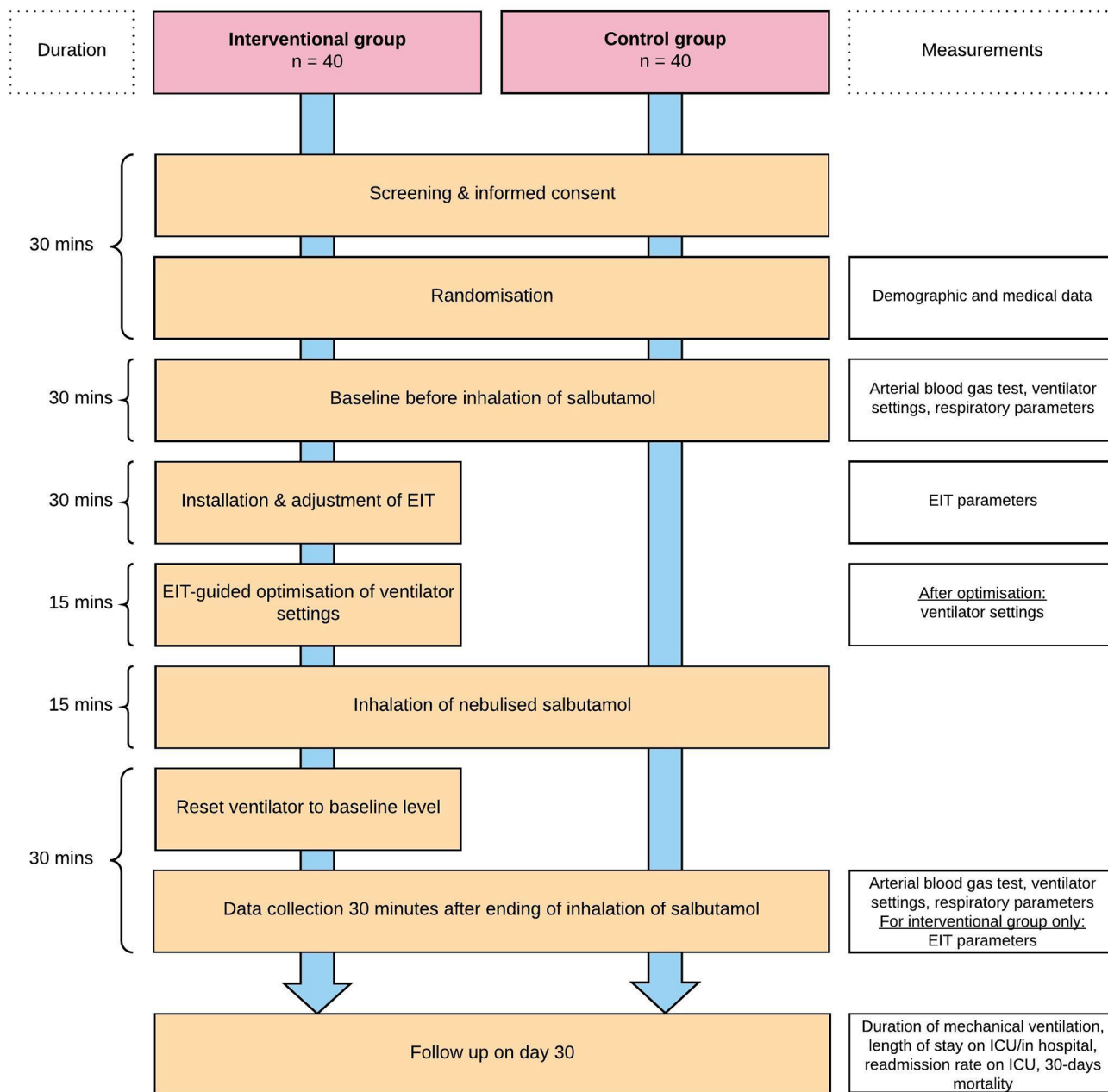


Figure 1 Flow chart of interventional procedures on the intervention and control groups with duration of each step and performed measurements. EIT, electrical impedance tomography; ICU, intensive care unit.

offline database. Therefore, all collected data will solely be provided in pseudonymised form for further study analysis. Access to the pseudonymisation key, which is password-protected, is only available to the principal investigator of this study. All above-mentioned parameters will be collected during the patient's stay in the hospital until discharge, death or the 30th day of stay on the ICU. In case of discharge from the ICU, follow-up to evaluate 30-day survival will be performed by visit on normal ward or a phone call by one of the investigators. Data entered into 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 of the European Parliament and the Council of the European Union. Furthermore, this protocol was designed following the recommendations for interventional trials (Standard Protocol Items: Recommendations for Interventional Trials; [figure 3](#) and online supplementary material 4).

Statistical analysis

Since this is a study designed to demonstrate superiority of the primary endpoint (change in airway resistance 30 min 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

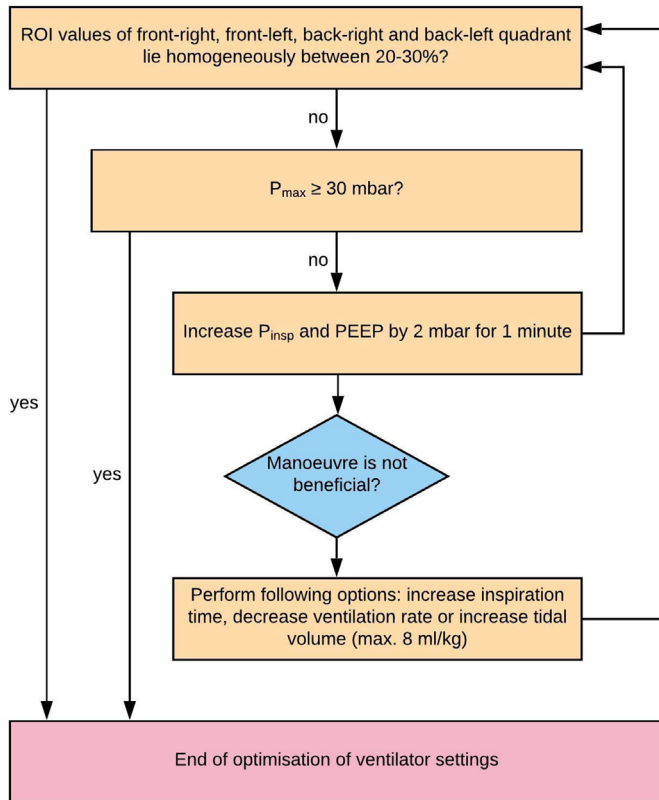


Figure 2 Flow chart of EIT-guided optimisation of ventilator settings. EIT, electrical impedance tomography; PEEP, positive end-expiratory pressure; P_{insp} , inspiratory pressure; P_{max} , maximum airway pressure; ROI, region of interest.

the Consolidated Standards of Reporting Trials guidelines.¹⁹ The per-protocol population will be defined as randomised 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 mean±SD in case of normal distribution and as median and IQR (25th and 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 characterised by numbers with percentages and will be compared using the χ^2 test or a Fisher’s exact test. Superiority will be assumed, if the 95% CI 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 SD 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

	STUDY PERIOD					
	Enrolment		Post-allocation			Close out
	Prior randomisation	0	Baseline	After Baseline	After intervention	
TIMEPOINT					30 days	
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomisation		X				
INTERVENTIONS:						
EIT-guided optimization of ventilation, inhalation of nebulised salbutamol afterwards				X		
Inhalation of nebulised 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. EIT, electrical impedance tomography; ICU, intensive care unit; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

received approval from the 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 available in a free accessible 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 critically ill and ventilated patients.

The administration of inhaled drugs is routinely used in ICUs, 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 with 11.9% in patients without artificial airway.¹⁶ A recently published review on inhalative drug therapy in mechanical ventilation stated that ventilator settings play a 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 optimise 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 optimisation of ventilator settings prior to nebulisation of inhalative drugs would be desirable. Hence, fast, non-invasive and reliable assessment at bedside in critically ill and ventilated patients is one of the cornerstones for modern intensive care monitoring. EIT, although with some constraints, 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 optimisation of ventilator parameters on an individualised base. Several studies in the last years have already demonstrated that EIT-guided respirator optimisation results in significantly improved respiratory mechanics and improved gas exchange.^{1 4 7 22} However, a global standard based on a broad base of evidence has been 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 visualisation, correct analysis and data interpretation.²³

The crucial step forward was the publication of the recommendations of TREND.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 standardised use in clinical routine.

A further limitation is that EIT captures only ventral to dorsal ventilation distribution. However, Bikker *et al.*²⁴ also reported a different ventilation distribution between the cranial and caudal lung levels during decremental PEEP trials, 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 individualised and guided mechanical ventilation adjustments. Therefore, this study can shed light on the extent to which

the additional use of EIT for optimising ventilator settings can increase the effectiveness of inhaled salbutamol.

Outlook

EIT could help to visualise and verify an effective nebulisation that could provide a safe, efficient and individualised way of inhalative drug application, for example, by increasing the effective dose reaching the distal airway. Therefore, these results are also of great interest beyond salbutamol nebulisation, for example, for safe usage of inhalative antibiotics in critically ill and ventilated patients.

Trial status

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

Contributors TR: main author of this manuscript, wrote and revised the manuscript. AK: supporting methodical description and participated in the design of this study. GO: supporting data collection, participated in the design of this study and revised the manuscript. MS: supporting data collection, participated in the design of this study and revised the manuscript. MA: supporting data collection, participated in the design of this study and revised the manuscript. HN: supporting data collection, participated in the design of this study, wrote and revised the manuscript. All authors read and approved the final manuscript and the first revision.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was reviewed and approved by the Ethics Committee of the Medical Faculty of the Ruhr-Universität Bochum (no 17-6306). It will be conducted in accordance with the Declaration of Helsinki and German laws and regulations. Patients with written informed consent or a positive vote of an independent consultant are eligible for inclusion.

Provenance and peer review Not commissioned; externally peer reviewed.

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