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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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Manuscripts

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

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13 **Running head:** EIT-guided ventilator optimization for salbutamol inhalation

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30 **Abstract**

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

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

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

51 **Trial registration:** German trial register (DRKS.de); ID: DRKS00014706; registered on
52 14th May 2018

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56 Article Summary

57 *Strengths and limitations of this study*

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

82 Introduction

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

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

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3 107 The inhalative administration of drugs is an established, non-invasive and painless
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5 108 application form, which is used in treatment of obstructive airways diseases. An
6
7 109 important advantage is that significant higher local concentrations of the drug at the site
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9 110 of action are achieved without significant systemic exposure^{13 14}. Several studies could
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11 111 not show a benefit of inhaled medication¹⁵⁻¹⁷. Unfortunately, all these studies could not
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13 112 address the crucial issue whether the medication itself or its distribution was less
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15 113 effective. To the present day, there is no established non-invasive real-time monitoring
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17 114 to measure or visualize the effectiveness or distribution of nebulized drugs in ventilated
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19 115 patients at bedside¹⁴.

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23 116 Based on this issue, our study wants to elucidate the extent to which the effectiveness
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25 117 of inhaled drugs, e.g. β 2 sympathomimetics, can be optimized by the additional use of
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27 118 EIT for adjusting ventilator settings. Accordingly, we want to test the hypothesis
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29 119 whether EIT can increase the effectiveness of inhaled salbutamol.

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121 **Methods and analysis**

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

127

128 **Study population and general data acquisition**

129 This study was reviewed and approved by the Ethics Committee of the Medical Faculty
130 of Ruhr-University Bochum (17-6306) and registered in the German Clinical Trial
131 Register (DRKS00014706). It will be conducted in accordance with the Declaration of
132 Helsinki and German laws and regulations. All patients will be admitted to the intensive
133 care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum and will be
134 recruited from June 2018 to June 2019. We will perform EIT measurements with
135 PulmoVista™ (Dräger Medical, Lübeck, Germany) and a size adjusted chest belt with
136 16 electrodes. The diagnosis of acute or chronic airway obstruction will include clinical
137 examination and expiration-flow analyzation. Patients at the age of 18 years or more,
138 diagnosed with an acute airway obstruction or known chronic obstructive pulmonary
139 disease under mechanical ventilation and providing written informed consent or a
140 positive vote of an independent consultant are eligible for inclusion. Exclusion criteria
141 are: pregnancy or lactation, severe obesity (body mass index > 35), missing medical
142 indication and/or contraindication for inhaled salbutamol administration, Horowitz index
143 ≥ 400 , long-term ventilation > 14 days, a study-independent medical indication for
144 salbutamol nebulization in obstructive pulmonary disease and/or an acute obstructive
145 condition and procedure of withdrawing life-sustaining therapy. Furthermore, patients
146 with the following pre-existing conditions and operations will be excluded: patients with

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3 147 chest trauma or surgery (e.g. pneumectomy), pneumonia, ARDS with or without ECMO
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5 148 therapy, neuromuscular diseases, severe cardiac diseases (e.g. NYHA III-IV), acute
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7 149 ischemic events, active implants (e.g. pacemakers, ICD) or thoracic skin lesions and
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9 150 wound dressings.

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11 151 Patients will be treated generally with a multimodal concept, which includes analgesia
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13 152 and sedation, fluid administration, lung-protective mechanical ventilation,
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15 153 anticoagulation, as well as hemodynamic, antibiotic and diagnostic management as
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17 154 recommended by guidelines, standard operating procedures or evidence based best
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19 155 practice. Additionally, after pseudonymization a large body of clinical and demographic
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21 156 data will be entered into a database for later analysis, including pre-existing morbidities,
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23 157 Simplified Acute Physiology Score II (SAPSII), Sepsis-related Organ Failure
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25 158 Assessment Score (SOFA), body mass index (BMI), necessity for renal replacement
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27 159 therapy, ventilator settings, PaO₂/FiO₂ ratio (Horowitz index), vital parameters,
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29 160 medications and dosage of vasoactive drugs and blood chemistry values.
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34 35 162 **Sample size calculation**

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37 163 A total of 80 mechanically ventilated patients will be included in the study, with 40
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39 164 patients in the intervention group and 40 patients in the control group. With a total
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41 165 cohort size of n=80, a power of > 95% (alpha error p = 0.05, beta error < 0.05) will be
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43 166 reached, referring to the data from a reference work (table 1) by Malliotakis et al.¹⁸.
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45 167 Calculations from these values indicate that 76 participants (38 per group) are required
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47 168 to achieve a power of 95% with an alpha error of 5%.

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173 **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

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

180 The total study duration is planned for 18 months. It will take 12 months for recruitment
 181 of patients and collection of data, last 6 months are scheduled for analyzation. For each
 182 patient an individual study duration is assigned of one day. In the control group, 1.75
 183 hours are scheduled per patient. These include study education and randomization (30
 184 mins), data collection before inhalation (30 mins), drug nebulization and inhalation (15
 185 mins) and measurements after inhalation (30 mins; figure 1). In the interventional
 186 group, study explanation and randomization (30 mins), data collection before inhalation
 187 (30 mins), the installation and adjustment of EIT (30 mins), the optimization of ventilator
 188 settings (15 mins), drug nebulization and inhalation (15 mins), resetting ventilator
 189 settings to baseline and measurements 30 minutes after inhalation add up to a total
 190 duration of 2.5 hours (figure 1).

191

192

193 **Randomization**

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

199

200 **Interventional procedure**

201 EIT and control group undergo an arterial blood gas analysis and corresponding airway
202 measurements to determine baseline parameters before salbutamol inhalation (figure
203 1; Supplemental material 1+2). Therefore, 1.25 mg / 2.5 mL salbutamol (Sultanol[®],
204 Glaxo Smith Kline plc., Brentford, United Kingdom) is applied with a vibrating mesh
205 nebulizer (Solo[®], Aerogen, Galway, Ireland).

206

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

214

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

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3 219 material 3), according the recommendations of the Translational EIT Development
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5 220 Study Group (TREND)⁵. The next step is nebulization and inhalation of salbutamol for
6
7 221 15 minutes. Subsequently, ventilator settings are reset to baseline as before EIT
8
9 222 adjustment. After a period of 30 minutes, a new data collection after salbutamol
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11 223 administration including EIT measurement is done and an arterial blood gas analysis is
12
13 224 performed (figure 1). Data is documented in the CRF (Supplemental material 1).
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226 Objectives

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

- 232 • Before and 30 minutes after salbutamol inhalation:
 - 233 ○ Changes made in ventilator settings under EIT,
 - 234 ○ tidal volume, compliance, resistance, arterial oxygen partial pressure
 - 235 (p_aO₂), Horowitz index, arterial carbon dioxide partial pressure (p_aCO₂),
 - 236 peripheral and arterial oxygen saturation,
 - 237 ○ upper and lower inflection point of the pressure-volume curve,
 - 238 ○ EIT parameters: Region of Interest (ROI), changes of end expiratory lung
 - 239 volume (Delta-EELV) and changes of end expiratory lung impedance
 - 240 (Delta-EELI),
 - 241 ○ heart rate, blood pressure
- 242 • duration of mechanical ventilation,
- 243 • length of stay on ICU and hospital, readmission rate on ICU.
- 244 • 30-days mortality

245 **Data collection**

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

261

262 **Statistical analysis**

263 Since this is a study designed to demonstrate superiority of the composite endpoint,
264 whether an additional use of EIT increases the effectiveness of inhaled salbutamol, we
265 will perform an intention-to-treat and additionally a per-protocol analysis as
266 recommended by the CONSORT guidelines¹⁹. The per-protocol population will be
267 defined as randomized patients without major protocol deviations, such as non-
268 considerations of exclusion criteria or missing data for the primary endpoint. Baseline
269 characteristics of all patients will be described per group. Qualitative data will be
270 described as frequencies and percentages. Continuous variables are presented as

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3 271 means \pm standard deviation in case of normal distribution and as median and
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5 272 interquartile range (25th; 75th percentile) in case of non-normally distributed variables.
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7 273 Continuous variables will be compared using parametric Student's t-test or non-
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9 274 parametric Mann-Whitney-U-Test. Categorical variables will be characterized by
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11 275 numbers with percentages and will be compared using the Chi-square test or a Fisher's
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13 276 exact test.

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15 277 The graphical processing of variables will be performed depending on the
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17 278 measurement level of the variables as histograms, mean value curves with
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19 279 corresponding standard deviations or box whisker plots.
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23 281 **Ethics and dissemination**

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26 282 A manuscript with the results of the study will be published in a peer-reviewed journal.

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28 283 The study has received the following approvals: Ethics Committee of the Medical
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30 284 Faculty of Ruhr-University Bochum (17-6306). On completion of the trial, and after
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32 285 publication of the primary manuscript, data will be made available in a free accessible
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34 286 online repository.
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295 Discussion

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

299 The administration of inhaled drugs is routinely used in intensive care units, due to the
300 advantage of delivering high drug concentrations to the airway, along with rapid onset
301 of action and fewer systemic side effects. However, it is believed that the beneficial
302 effects of inhaled drugs are smaller in patients on mechanical ventilation than in those
303 breathing spontaneously. In this regard, a previous study could demonstrate that only
304 2.9% of the administered drug dose reached the distal airway in ventilated patients,
305 compared to 11.9% in patients without artificial airway¹⁶. A recently published review,
306 regarding inhalative drug therapy in mechanical ventilation, stated that ventilator
307 settings play an crucial role in inhaled drug delivery¹⁴. A tidal volume of at least 500
308 mL, increased inspiratory time and a low inspiratory flow are general recommendations
309 in order to optimize drug distribution in the lungs^{14 20 21}. Nevertheless, attention should
310 be paid to serious adverse effects of high (> 500 mL) tidal volumes, especially in
311 patients with acute or chronic airway obstructions. In these patients high tidal volumes
312 can lead to dynamic hyperinflation or can cause a severe barotrauma¹⁴. Furthermore,
313 no clinical studies exist showing the beneficial effects of any particular ventilation mode
314 on inhaled drug delivery^{20 21}. Therefore, a new diagnostic and guiding tool for adequate
315 optimization of ventilator settings prior to nebulization of inhalative drugs would be
316 desirable. Hence, fast, non-invasive and reliable assessment at bedside in critical ill
317 and ventilated patients is one of the cornerstones for modern intensive care monitoring.
318 EIT, although with some constrains, may be a promising solution. EIT images are valid
319 measurements of the regional distribution of ventilation and changes in lung volume in
320 real-time. This dynamic evaluation makes EIT a promising tool for guided optimization

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3 321 of ventilator parameters on an individualized base. Several studies in the last years
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5 322 have already demonstrated that EIT-guided respirator optimization results in significant
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7 323 improved respiratory mechanics and improved gas exchange^{1 4 7 22}. However, a global
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9 324 standard based on a broad base of evidence was one of the most discussed topics in
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11 325 Respiratory Medicine over the last years. Therefore, the plausibility of EIT
12
13 326 measurements highly depends on the correct belt position, proper impedance
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15 327 visualization, correct analysis and data interpretation²³.

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18 328 The crucial step forward was the publication of recommendations of the TREND
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20 329 (Translational EIT Development Study) group⁵. These recommendations highlight the
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22 330 need for a consensus about examinations, consistent terminology and generally
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24 331 accepted approaches to EIT images and analysis. Based on this highly appreciated
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26 332 consensus statement we are now able to compare, understand and reproduce study
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28 333 findings from among different research groups and provide a standardized use in
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30 334 clinical routine.

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33 335 A further limitation is that EIT captures only ventral-to-dorsal ventilation distribution.
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35 336 However, Bikker et al. also reported different ventilation distribution between cranial
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37 337 and caudal lung levels during decremental PEEP trials²⁴, concluding that existing EIT
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39 338 systems will not be able to cover the optimal PEEP titration for the whole lung.

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42 339 Despite the possible limitations of EIT, this device can provide a remarkable advance in
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44 340 the field of individualized and guided mechanical ventilation adjustments. Therefore,
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46 341 this study can shed light on the extent to which the additional use of EIT for optimizing
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48 342 the ventilator settings can increase the effectiveness of inhaled salbutamol.

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3 347 **Outlook**

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5 348 EIT could help to visualize and verify an effective nebulization that could provide a safe,
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7 349 efficient and individualized way of inhalative drug application, e.g. by increasing the
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9 350 effective dose reaching distal airway.

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13 352 **Trial status**

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15 353 The first patients were randomized in June 2018. The inclusion of participants is
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17 354 ongoing and is expected to continue until June 2019.

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440 **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
$p_a\text{CO}_2$	Partial pressure of arterial carbon dioxide
$p_a\text{O}_2$	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

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3 442 **Declarations**

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7 444 **Ethics approval and consent to participate**

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9 445 This study was reviewed and approved by the Ethics Committee of the Medical Faculty
10 446 of the Ruhr-Universität Bochum (no. 17-6306) and written informed consent or a
11 447 positive vote of an independent consultant are eligible for inclusion.
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17 449 **Consent for publication**

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19 450 Not applicable

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23 452 **Availability of data and material**

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25 453 The data of the described study will be available from the Dryad repository after
26 454 publication.
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32 456 **Conflict of interests**

33
34 457 None to declare

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37
38 459 **Funding**

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41 461 University Bochum (Ref. No. IN-1214264), just for financial support for publication
42 462 costs. This will have no impact on our study design or collection, analysis and
43 463 interpretation of our data.
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49 465 **Author Statement**

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51 466 Dr. med. Tim Rahmel: Main author of this manuscript, written and revising the
52 467 manuscript
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3 468 Alexandra Koniusch: Supporting methodical description and participated in the design
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5 469 of this study

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7 470 Dr. med. Günther Oprea: Supporting data collection, participated in the design of this
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9 471 study, and revising the manuscript

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11 472 Martin Schwertner: Supporting data collection, participated in the design of this study,
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13 473 and revising the manuscript

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15 474 Prof. Dr. med. Michael Adamzik: Supporting data collection, participated in the design
16
17 475 of this study and revising the manuscript

18
19 476 Dr. med. Hartmuth Nowak: Supporting data collection, participated in the design of this
20
21 477 study, written and revising the manuscript

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23 478 All authors read and approved the final manuscript.

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25
26 479

27 28 480 **Acknowledgements**

29
30 481 Not applicable

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32 482

33 34 483 **Authors' information**

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46 489 ¹ Received from the Klinik für Anästhesiologie, Intensivmedizin und
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3 494 **Legends**

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5 495 **Figure 1:** Flowchart of interventional procedures on intervention and control group with
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7 496 duration of each step and performed measurements (EIT = electrical impedance
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9 497 tomography, ICU = intensive care unit)

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14 499 **Figure 2:** Schedule of enrolment, interventions and assessments – SPIRIT Figure
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16 500 (SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials, EIT =
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18 501 electrical impedance tomography, ICU = intensive care unit)

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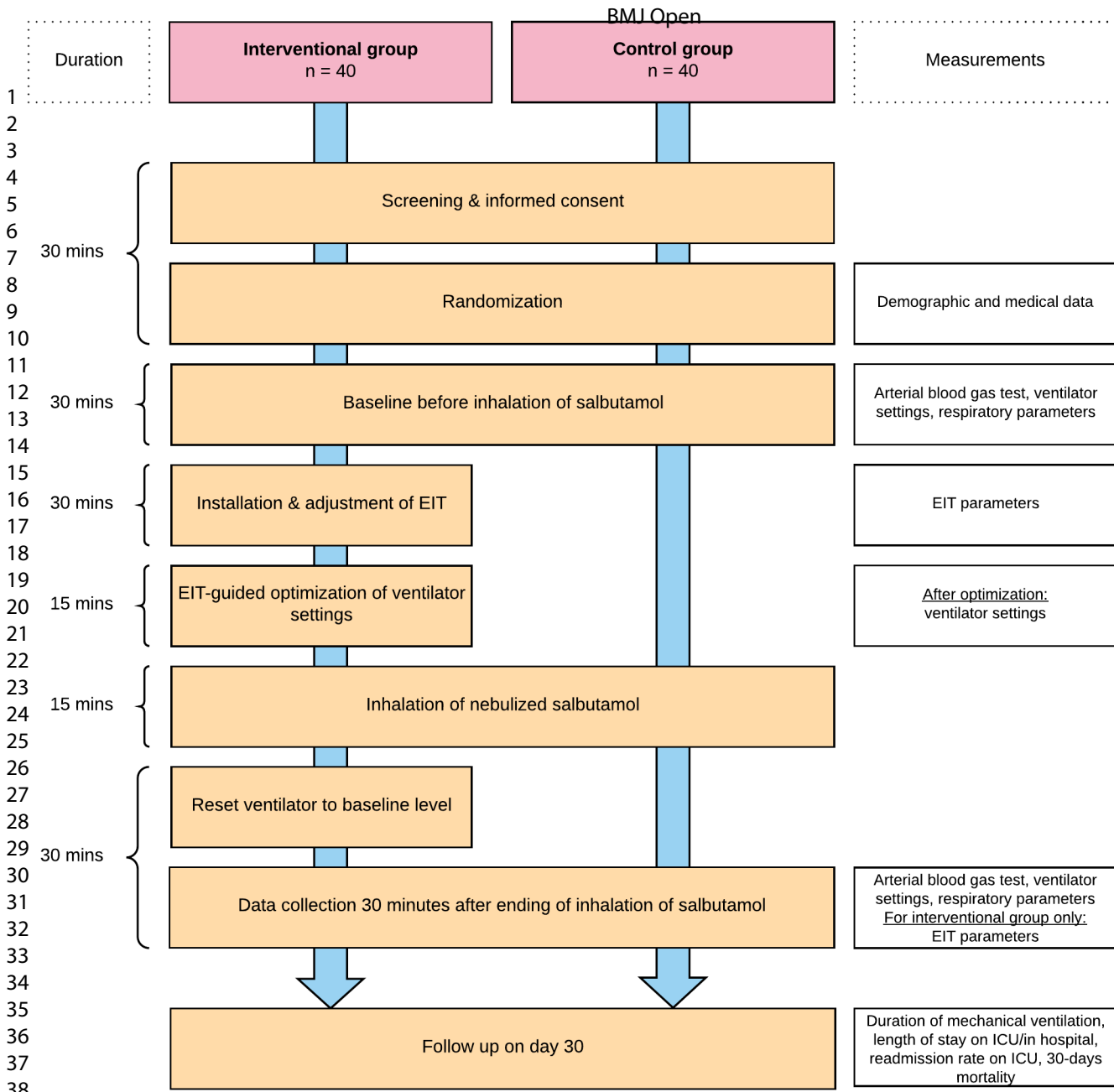
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23 503 **Supplemental material**

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25 504 **Supplemental material 1:** Case report form of intervention group

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27 505 **Supplemental material 2:** Case report form of control group

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29 506 **Supplemental material 3:** EIT algorithm for standardized EIT application and

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32 507 assessment
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TIMEPOINT	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
	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 (<i>for EIT group only</i>)			X		X	
Duration of mechanical ventilation, length of stay on ICU/in hospital, readmission rate on ICU						X
30-days mortality						X

Randomization

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No. |_|_|

CRF EIT-Trial (intervention group)

VU

Patient

Inclusion criteria	Yes	No
• Age ≥ 18 years	<input type="checkbox"/>	<input type="checkbox"/>
• Known obstructive airway disease or acute airway obstruction and	<input type="checkbox"/>	<input type="checkbox"/>
• Medical indication for salbutamol inhalation	<input type="checkbox"/>	<input type="checkbox"/>
• Mechanical ventilated patient and Horowitz index (p _a O ₂ /F _i O ₂) < 400	<input type="checkbox"/>	<input type="checkbox"/>
• Written informed consent or positive vote of an independent consultant	<input type="checkbox"/>	<input type="checkbox"/>

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	<input type="checkbox"/>	<input type="checkbox"/>
• Lack of medical indication and/or contraindications to administration of salbutamol	<input type="checkbox"/>	<input type="checkbox"/>
• Age < 18 years	<input type="checkbox"/>	<input type="checkbox"/>
• 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)	<input type="checkbox"/>	<input type="checkbox"/>
• Severe obesity (BMI > 35)	<input type="checkbox"/>	<input type="checkbox"/>
• Long-term ventilation > 14 days	<input type="checkbox"/>	<input type="checkbox"/>
• Do-not-resuscitate order	<input type="checkbox"/>	<input type="checkbox"/>
• Pregnancy or lactation	<input type="checkbox"/>	<input type="checkbox"/>

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

male female

Height |_|_|_| cm **weight** |_|_|_|. |_| kg **BMI** |_|_|. |_| kg/m²

- **Blood pressure** |_|_|_| / |_|_| **heart rate** |_|_|_| bpm
body temperature |_|_|. |_| °C

- Pregnancy excluded

- Note participation in the medical record! carried out

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- **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 (paO₂) (____), Horowitz index (____), arterial carbon dioxide partial pressure (paCO₂) (____), 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-expiratory lung volume (Delta-EELV) (____) and changes of end-expiratory 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 (paO₂) (____), Horowitz index (____), arterial carbon dioxide partial pressure (paCO₂) (____), 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-expiratory lung volume (Delta-EELV) (____) and changes of end-expiratory 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	<input type="checkbox"/>	<input type="checkbox"/>
• Known obstructive airway disease or acute airway obstruction and • Medical indication for salbutamol inhalation	<input type="checkbox"/>	<input type="checkbox"/>
• Mechanical ventilated patient and Horowitz index (p _a O ₂ /F _i O ₂) < 400	<input type="checkbox"/>	<input type="checkbox"/>
• Written informed consent or positive vote of an independent consultant	<input type="checkbox"/>	<input type="checkbox"/>

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	<input type="checkbox"/>	<input type="checkbox"/>
• Lack of medical indication and/or contraindications to administration of salbutamol	<input type="checkbox"/>	<input type="checkbox"/>
• Age < 18 years	<input type="checkbox"/>	<input type="checkbox"/>
• 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)	<input type="checkbox"/>	<input type="checkbox"/>
• Severe obesity (BMI > 35)	<input type="checkbox"/>	<input type="checkbox"/>
• Long-term ventilation > 14 days	<input type="checkbox"/>	<input type="checkbox"/>
• Do-not-resuscitate order	<input type="checkbox"/>	<input type="checkbox"/>
• Pregnancy or lactation	<input type="checkbox"/>	<input type="checkbox"/>

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

male female

Height |_|_|_| cm **weight** |_|_|_|. |_| kg **BMI** |_|_|. |_| kg/m²

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

body temperature |_|_|. |_| °C

- Pregnancy excluded

- Note participation in the medical record! carried out

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3 • **Procedure in the control group**

- 4 ○ Study education including randomization (30 min)
- 5
- 6 ▪ Measurement of SOFA-Score (____), PCT (____), CRP (____), antibiotics
7 (____), vital parameters (____), catecholamines (____), sedation (____)
- 8
- 9 ○ Data collection before inhalation (30 min)
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- 11 ▪ Measurement of airway resistance before salbutamol inhalation (____)
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- 13 ▪ Measurement of tidal volume (____), lung compliance (____), arterial oxygen
14 partial pressure (paO₂) (____), Horowitz index (____), arterial carbon dioxide
15 partial pressure (paCO₂) (____), peripheral oxygen saturation (____), arterial
16 oxygen saturation (____), upper (____) and lower (____) inflectionpoint of the
17 pressure-volume-curve
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- 19 ▪ Arterial blood sampling
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- 21 ○ Salbutamol nebulization and inhalation (15 min)
- 22
- 23 ○ Data collection after inhalation (30 min)
- 24
- 25 ▪ Measurement of airway resistance after salbutamol inhalation (____)
- 26
- 27 ▪ Measurement of tidal volume (____), lung compliance (____), arterial oxygen
28 partial pressure (paO₂) (____), Horowitz index (____), arterial carbon dioxide
29 partial pressure (paCO₂) (____), peripheral oxygen saturation (____), arterial
30 oxygen saturation (____), upper (____) and lower (____) inflectionpoint of the
31 pressure-volume-curve
- 32
- 33 ▪ Arterial blood sampling
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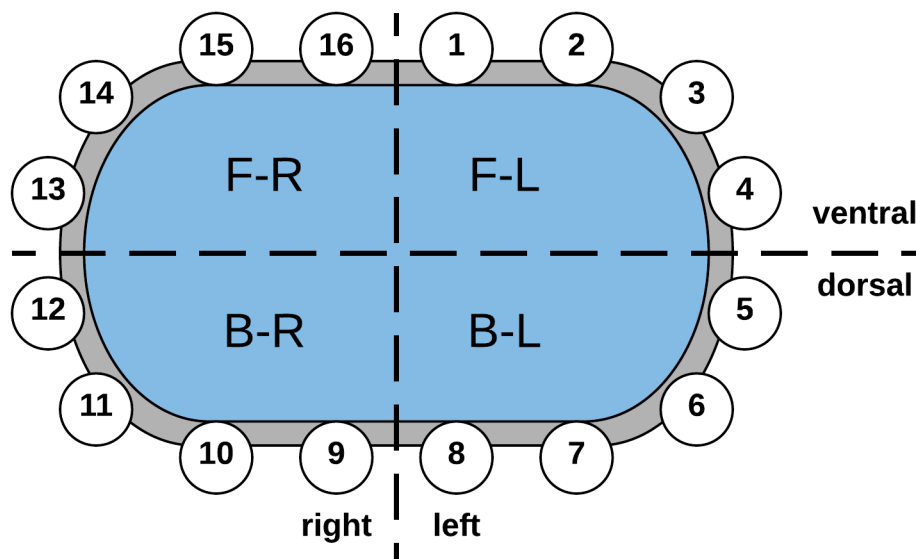
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56 Signature of the examiner _____

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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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.	<input type="checkbox"/>

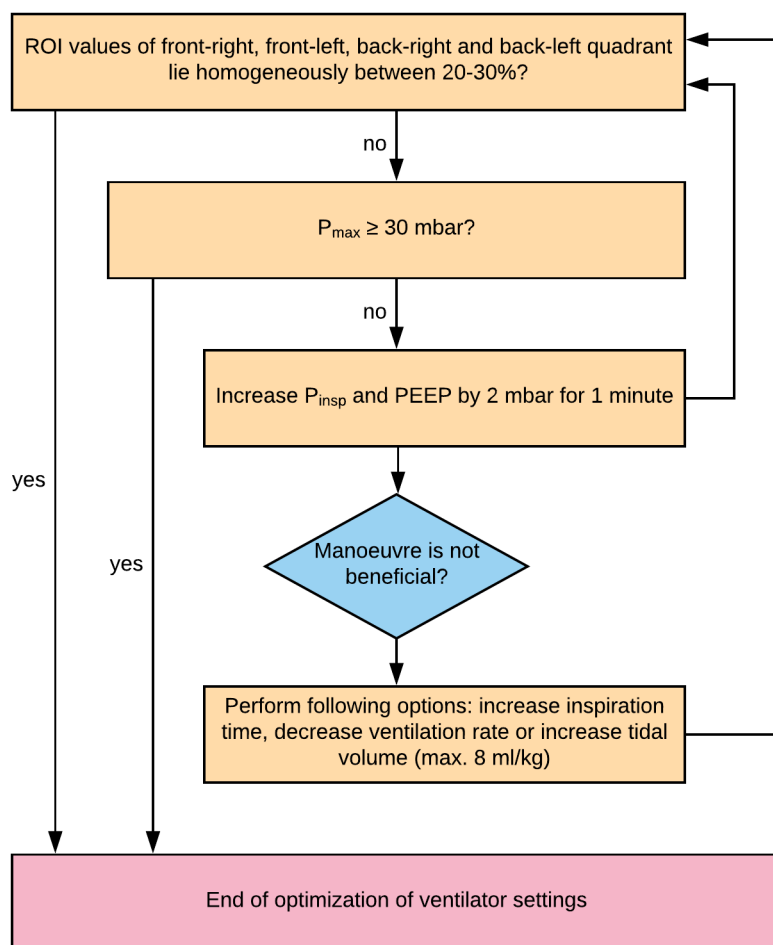
Figure 1: schematic cross-section image of thorax with positions of 16 EIT electrodes at the level of 4th to 6th intercostal space (*F-R* = front-right quadrant, *F-L* = front-left quadrant, *B-R* = back-right quadrant, *B-L* = back-left quadrant)



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.	<input type="checkbox"/>
2.	Delta-EELV (changes of end expiratory lung volume): Choose "Views" in right upper corner of the screen and tap on "End expiratory trend".	<input type="checkbox"/>
3.	Delta-EELI (changes of end expiratory lung impedance): Choose "Views" in right upper corner of the screen and tap on "Delta-EELI".	<input type="checkbox"/>

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*)



only

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

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Diagnostics, Pharmacology and therapeutics, Respiratory medicine
Keywords:	optimization of ventilation, inhalation, nebulization, region of interest, end expiratory lung volume, end expiratory lung impedance

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Manuscripts

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1 Evaluation of inhaled salbutamol effectiveness under 2 supportive use of electrical impedance tomography in 3 ventilated ICU patients: study protocol for a randomized 4 controlled clinical trial

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12
13 **Running head:** EIT-guided ventilator optimization for salbutamol inhalation

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17 **Word count:** 2828 (Introduction: 466; Methods/Design: 1704; Discussion: 658)

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7
8 30 **Abstract**

9
10 31 **Introduction:** The inhalative administration of drugs is a non-invasive application form that
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12 32 is regularly used in the treatment of ventilated patients in critical care setting. However,
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14 33 assessment of effectiveness or distribution of nebulized drugs is one of the lacking
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16 34 cornerstones of modern intensive care monitoring. Electrical impedance tomography (EIT)
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18 35 may provide a promising new monitoring and guiding tool for an adequate optimization of
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20 36 mechanical ventilation in critically ill patients. EIT may assist in defining mechanical
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22 37 ventilation settings, assess distribution of tidal volume and evaluation of associated
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24 38 pathologies at bedside. This study wants to elucidate the extent to which the effectiveness
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26 39 of inhaled salbutamol can be increased by the additional use of EIT for optimization of
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28 40 respirator settings.

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31 41 **Methods and analysis:** This study is a randomized, open-label superiority trial, conducted
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33 42 on an intensive care unit of a German university hospital, comparing two groups of
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35 43 mechanically ventilated patients with an acute or chronic bronchial airway obstruction
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37 44 according the effectiveness of inhaled salbutamol with (intervention) or without (control)
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39 45 additional use of EIT for optimizing the ventilator settings. Primary outcome is change in
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41 46 airway resistance 30 minutes after salbutamol inhalation.

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43 47 **Ethics and dissemination:** The study has received the following approvals: Ethics
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45 48 Committee of the Medical Faculty of Ruhr-University Bochum (17-6306). Results will be
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47 49 made available to critical care survivors, their caregivers, the funders, the critical care
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49 50 societies and other researchers by publication in a peer-reviewed journal.

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3 51 **Trial registration:** German trial register (DRKS.de); ID: DRKS00014706; registered on 14th
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14 56 **Article Summary**

17 57 ***Strengths and limitations of this study***

- 19 58 • This is the first interventional trial assessing, whether the additional usage of EIT can
20 59 improve the effectiveness of inhalative drug administration in critical ill and ventilated
21 60 patients.
 - 22 61 • EIT could help to visualize and verify an effective nebulization that could provide a
23 62 safe, efficient and individualized way of inhalative drug application, e.g. by increasing
24 63 the effective dose for reaching the distal airway.
 - 25 64 • Despite few possible limitations of EIT, this device can provide a remarkable advance
26 65 in the field of individualized and guided mechanical ventilation adjustments at
27 66 bedside.
 - 28 67 • The secondary outcomes of this study will possibly offer a opportunity to recommend
29 68 standard respirator settings for inhalative drug application.
 - 30 69 • The lack of blinding of the assessors collecting data on EIT usage is a limitation to
31 70 the study design.
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3 74 **Keywords: EIT, optimization of ventilation, inhalation, nebulization, region of interest,**
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5 75 **end expiratory lung volume, end expiratory lung impedance**
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20 82 **Introduction**

23
24 83 Electrical impedance tomography (EIT) is an imaging method that is already used in clinical
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26 84 setting. For several years it has been mainly used for monitoring of lung function ¹. With
27
28 85 regard to lung monitoring, EIT makes use of changes in thoracic impedance, which in turn
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30 86 result in different concentrations of free ions due to changes in air content of the lung tissue
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32 87 ². In brief, the principle of EIT is based on the application of very small alternating electrical
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34 88 currents, which are applied and measured via alternating pairs of electrodes. With a scan
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36 89 rate of 50 images per second, voltage profiles from 16 electrode positions are continuously
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38 90 combined to a cross-sectional image ². With these cross-sectional images, the EIT enables
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40 91 a continuous real-time monitoring of lung function at bedside ³. With its high resolution, EIT
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42 92 enables reliably the immediate and non-invasive assessment of changes in regional lung
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44 93 tissue ^{4 5}. It can also help to optimize ventilation settings to prevent regional overinflating of
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46 94 the lungs and atelectasis ⁶. Prior studies demonstrated that equivalent diagnostic findings
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48 95 between EIT and thoracic computed tomography could be achieved in critically ill patients
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50 96 in terms of regional ventilation in different thoracic regions, and also offered a valid
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52 97 examiner-independent test reproducibility of the results ^{5 7-9}. In addition, the bedside
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3 98 applicability of EIT can eliminate the logistical burden of diagnostic transports with several
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5 99 associated risk factors and could even reduce treatment costs ^{1 10}.
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9 100 There are only a few contraindications for EIT, like the usage in active implants (e.g.
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11 101 pacemaker or implantable cardioverter-defibrillator) due to the lack of experience of
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13 102 interactions with the generated alternating electric field of EIT ¹¹. Furthermore, a certain
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15 103 amount of expertise and a sufficient level of experience of the nursing and medical staff is
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17 104 needed to ensure the correct interpretation of EIT values and avoidance of technical errors
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20 105 ^{5 12}.
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24 106 The inhalative administration of drugs is an established, non-invasive and painless
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26 107 application form, which is used in treatment of obstructive airways diseases. An important
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28 108 advantage is that significant higher local concentrations of the drug at the site of action are
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30 109 achieved without significant systemic exposure ^{13 14}. Several studies could not show a benefit
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32 110 of inhaled medication ¹⁵⁻¹⁷. Unfortunately, these studies could not address the crucial issue
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34 111 whether the medication was distributed effectively in critical ill ventilated patients. To the
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36 112 present day, there is no established non-invasive real-time monitoring to measure or
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38 113 visualize the effectiveness or distribution of nebulized drugs in ventilated patients at bedside
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46 115 Based on this issue, our study wants to elucidate the extent to which the effectiveness of
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48 116 inhaled drugs, e.g. β_2 sympathomimetics, can be optimized by the additional use of EIT for
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50 117 adjusting ventilator settings. Accordingly, we want to test the hypothesis whether EIT can
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52 118 increase the effectiveness of inhaled salbutamol.
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132 **Methods and analysis**

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

138 **Study population and general data acquisition**

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

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3 145 Lübeck, Germany) and a size adjusted chest belt with 16 electrodes. The diagnosis of acute
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5 146 or chronic airway obstruction will include clinical examination and expiration-flow
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7 147 analyzation. Patients at the age of 18 years or more, diagnosed with an acute airway
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9 148 obstruction or known chronic obstructive pulmonary disease under mechanical ventilation
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11 149 for less than 48 hours and providing written informed consent or a positive vote of an
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13 150 independent consultant are eligible for inclusion. Exclusion criteria are: pregnancy or
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15 151 lactation, severe obesity (body mass index > 35), missing medical indication and/or
16
17 152 contraindication for inhaled salbutamol administration, Horowitz index ≥ 400 , prior phase of
18
19 153 long-term ventilation > 14 days, a study-independent medical indication for salbutamol
20
21 154 nebulization in obstructive pulmonary disease and/or an acute obstructive condition and
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23 155 procedure of withdrawing life-sustaining therapy. Furthermore, patients with the following
24
25 156 pre-existing conditions and operations will be excluded: patients with chest trauma or
26
27 157 surgery (e.g. pneumectomy), pneumonia, ARDS with or without ECMO therapy,
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29 158 neuromuscular diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic events,
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31 159 active implants (e.g. pacemakers, ICD) or thoracic skin lesions and wound dressings.
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33 160 Patients will be treated generally with a multimodal concept, which includes analgesia and
34
35 161 sedation, fluid administration, lung-protective mechanical ventilation, anticoagulation, as
36
37 162 well as hemodynamic, antibiotic and diagnostic management as recommended by
38
39 163 guidelines, standard operating procedures or evidence based best practice. Additionally,
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41 164 after pseudonymization a large body of clinical and demographic data will be entered into a
42
43 165 database for later analysis, including pre-existing morbidities, Simplified Acute Physiology
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45 166 Score II (SAPSI), Sepsis-related Organ Failure Assessment Score (SOFA), body mass
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47 167 index (BMI), necessity for renal replacement therapy, ventilator settings, PaO₂/FiO₂ ratio
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168 (Horowitz index), vital parameters, medications and dosage of vasoactive drugs and blood
 169 chemistry values.

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171 Patient and public involvement

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

174

175 Sample size calculation

176 A total of 80 mechanically ventilated patients will be included in the study, with 40 patients
 177 in the intervention group and 40 patients in the control group. With a total cohort size of
 178 $n=80$, a power of $> 95\%$ (alpha error $p = 0.05$, beta error < 0.05) will be reached, referring
 179 to the data from a reference work (table 1) by Malliotakis et al. ¹⁸. Calculations from these
 180 values indicate that 76 participants (38 per group) are required to achieve a power of 95%
 181 with an alpha error of 5%.

182 **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/sec]	26.5±4.1 [cmH ₂ O/l/sec]
Mean_{30min} ± SD	15.5±3.6 [cmH ₂ O/l/sec]	23.1±3.6 [cmH ₂ O/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

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

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188 **Study design**

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

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202 **Randomization**

203 Block-balanced randomization, in a 1:1 ratio, will be computer-generated by StatsDirect
204 (StatsDirect Ltd., Cambridge, United Kingdom) with random block sizes between $n = 10$ and
205 $n = 20$, additionally using random permutations of treatments within each block. Investigators
206 will be blinded to the allocation according to the randomization list until the study patient has
207 been included.

208

209 **Interventional procedure**

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3 210 EIT and control group undergo an arterial blood gas analysis and corresponding airway
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5 211 measurements to determine baseline parameters before salbutamol inhalation (figure 1;
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7 212 Supplemental material 1+2). Therefore, 1.25 mg / 2.5 mL salbutamol (Sultanol®, Glaxo
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10 213 Smith Kline plc., Brentford, United Kingdom) is applied with a vibrating mesh nebulizer
11
12 214 (Solo®, Aerogen, Galway, Ireland).

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17 216 In the control group, baseline measurement is followed by ultrasound nebulization and
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19 217 inhalation with salbutamol for 15 minutes, following measurements and arterial blood gas
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21 218 analysis 30 minutes after inhalation (figure 1). In addition, all study-relevant data are
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23 219 documented pseudonymised in the case report form (CRF) to ensure a standardized
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25 220 operating (Supplemental material 2). This CRF will be handed over to the principal
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27 221 investigator immediately after collection of data. The principal investigator keeps the study
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29 222 documents in a study folder not accessible to third parties.
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35 224 In the intervention group, baseline measurements are followed by the standardized setup
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37 225 and adjustment of EIT, where a belt with 16 integrated electrodes is attached circularly to
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39 226 the thorax (Supplemental material 3). This is followed by the optimization of the respirator
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41 227 settings by means of EIT using a defined algorithm (figure 2), according the
42
43 228 recommendations of the Translational EIT Development Study Group (TREND)⁵. The EIT
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45 229 algorithm focuses on homogenisation of lung ventilation described by the fast-response
46
47 230 parameter ROI (region of interest) to titrate protective PEEP and tidal volume combinations
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49 231 (figure 2). The next step is nebulization and inhalation of salbutamol for 15 minutes.
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51 232 Subsequently, ventilator settings are reset to baseline as before EIT adjustment. After a
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53 233 period of 30 minutes, a new data collection after salbutamol administration including EIT
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234 measurement is done and an arterial blood gas analysis is performed (figure 1). Data is
235 documented in the CRF (Supplemental material 1).

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237 Objectives

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

- 242 • Before and 30 minutes after salbutamol inhalation:
 - 243 ○ Changes made in ventilator settings under EIT,
 - 244 ○ tidal volume, compliance, resistance, arterial oxygen partial pressure (p_aO_2),
 - 245 Horowitz index, arterial carbon dioxide partial pressure (p_aCO_2), peripheral
 - 246 and arterial oxygen saturation,
 - 247 ○ upper and lower inflection point of the pressure-volume curve,
 - 248 ○ EIT parameters: Region of Interest (ROI), changes of end expiratory lung
 - 249 volume (Delta-EELV) and changes of end expiratory lung impedance (Delta-
 - 250 EELI),
 - 251 ○ heart rate, blood pressure
- 252 • duration of mechanical ventilation,
- 253 • length of stay on ICU and hospital, readmission rate on ICU.
- 254 • 30-days mortality

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256 Data collection

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3 257 The documentation of the data will be pseudonymized and computer-assisted from our
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5 258 patient data management system (PDMS) (Dräger ICM, Dräger Medical, Lübeck, Germany)
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7 259 in a central offline database. Therefore, all collected data will solely be provided in
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10 260 pseudonymized form for further study analyzation. Access to the pseudonymization key,
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12 261 which is password protected, is only available to the principal investigator of this study. All
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14 262 above mentioned parameters will be collected during the patients stay in hospital until
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16 263 discharge, death or 30th day of stay on ICU. In case of discharge from ICU, follow-up to
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18 264 evaluate 30-days survival will be performed by visit on normal ward or a phone call by one
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20 265 of the investigators. Data entered in the central offline database will be monitored by an
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22 266 independent clinical research associate and checked for consistency and missing values.
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24 267 All records, subjects' identities and data management will remain confidential with the
25
26 268 General Data Protection Regulation (GDPR) of the European Parliament and the Council of
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28 269 the European Union. Furthermore, this protocol was designed following the
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30 270 recommendations for interventional trials (SPIRIT; figure 3; Supplemental material 4).
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272 **Statistical analysis**

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40 273 Since this is a study designed to demonstrate superiority of the primary endpoint (change in
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42 274 airway resistance 30 minutes after salbutamol inhalation), whether an additional use of EIT
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44 275 increases the effectiveness of inhaled salbutamol, we will perform an intention-to-treat and
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46 276 additionally a per-protocol analysis as recommended by the CONSORT guidelines¹⁹. The
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48 277 per-protocol population will be defined as randomized patients without major protocol
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50 278 deviations, such as non-considerations of exclusion criteria or missing data for the primary
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52 279 endpoint. Baseline characteristics of all patients will be described per group. Qualitative data
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54 280 will be described as frequencies and percentages. Continuous variables are presented as
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3 281 means \pm standard deviation in case of normal distribution and as median and interquartile
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5 282 range (25th; 75th percentile) in case of non-normally distributed variables. Continuous
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7 283 variables will be compared using parametric Student's t-test or non-parametric Mann-
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9 284 Whitney-U-Test. Categorical variables will be characterized by numbers with percentages
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11 285 and will be compared using the Chi-square test or a Fisher's exact test. Superiority will be
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13 286 assumed, if the 95% confidence interval for the difference between the means excludes zero
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15 287 or p-values are statistically significantly different at an a priori alpha error of less than 0.05.
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17 288 The graphical processing of variables will be performed depending on the measurement
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19 289 level of the variables as histograms, mean value curves with corresponding standard
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21 290 deviations or box whisker plots.
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29 292 **Ethics and dissemination**

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32 293 A manuscript with the results of the study will be published in a peer-reviewed journal. The
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34 294 study has received the following approvals: Ethics Committee of the Medical Faculty of
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36 295 Ruhr-University Bochum (17-6306). On completion of the trial, and after publication of the
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38 296 primary manuscript, data will be made available in a free accessible online repository.
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55 302 **Discussion**

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3 303 This study, to our knowledge, is the first interventional trial assessing, whether the additional
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5 304 usage of EIT can improve the effectiveness of inhalative drug administration in critical ill and
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8 305 ventilated patients.

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10 306 The administration of inhaled drugs is routinely used in intensive care units, due to the
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12 307 advantage of delivering high drug concentrations to the airway, along with rapid onset of
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14 308 action and fewer systemic side effects. However, it is believed that the beneficial effects of
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17 309 inhaled drugs are smaller in patients on mechanical ventilation than in those breathing
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19 310 spontaneously. In this regard, a previous study could demonstrate that only 2.9% of the
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21 311 administered drug dose reached the distal airway in ventilated patients, compared to 11.9%
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23 312 in patients without artificial airway¹⁶. A recently published review, regarding inhalative drug
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25 313 therapy in mechanical ventilation, stated that ventilator settings play an crucial role in inhaled
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27 314 drug delivery¹⁴. A tidal volume of at least 500 mL, increased inspiratory time and a low
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29 315 inspiratory flow are general recommendations in order to optimize drug distribution in the
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31 316 lungs^{14 20 21}. Nevertheless, attention should be paid to serious adverse effects of high (>
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33 317 500 mL) tidal volumes, especially in patients with acute or chronic airway obstructions. In
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35 318 these patients high tidal volumes can lead to dynamic hyperinflation or can cause a severe
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37 319 barotrauma¹⁴. Furthermore, no clinical studies exist showing the beneficial effects of any
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39 320 particular ventilation mode on inhaled drug delivery^{20 21}. Therefore, a new diagnostic and
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41 321 guiding tool for adequate optimization of ventilator settings prior to nebulization of inhalative
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43 322 drugs would be desirable. Hence, fast, non-invasive and reliable assessment at bedside in
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45 323 critical ill and ventilated patients is one of the cornerstones for modern intensive care
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47 324 monitoring. EIT, although with some constrains, may be a promising solution. EIT images
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49 325 are valid measurements of the regional distribution of ventilation and changes in lung volume
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51 326 in real-time. This dynamic evaluation makes EIT a promising tool for guided optimization of
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3 327 ventilator parameters on an individualized base. Several studies in the last years have
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5 328 already demonstrated that EIT-guided respirator optimization results in significant improved
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7 329 respiratory mechanics and improved gas exchange ^{14 7 22}. However, a global standard based
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10 330 on a broad base of evidence was one of the most discussed topics in Respiratory Medicine
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12 331 over the last years. Therefore, the plausibility of EIT measurements highly depends on the
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14 332 correct belt position, proper impedance visualization, correct analysis and data interpretation
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17 333 ²³.

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19 334 The crucial step forward was the publication of recommendations of the TREND
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21 335 (Translational EIT Development Study) group ⁵. These recommendations highlight the need
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23 336 for a consensus about examinations, consistent terminology and generally accepted
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25 337 approaches to EIT images and analysis. Based on this highly appreciated consensus
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27 338 statement we are now able to compare, understand and reproduce study findings from
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29 339 among different research groups and provide a standardized use in clinical routine.
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33 340 A further limitation is that EIT captures only ventral-to-dorsal ventilation distribution.
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35 341 However, Bikker et al. also reported different ventilation distribution between cranial and
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37 342 caudal lung levels during decremental PEEP trials ²⁴, concluding that existing EIT systems
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39 343 will not be able to cover the optimal PEEP titration for the whole lung.
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42 344 Despite the possible limitations of EIT, this device can provide a remarkable advance in the
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44 345 field of individualized and guided mechanical ventilation adjustments. Therefore, this study
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46 346 can shed light on the extent to which the additional use of EIT for optimizing the ventilator
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48 347 settings can increase the effectiveness of inhaled salbutamol.
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54 349 **Outlook**

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3 350 EIT could help to visualize and verify an effective nebulization that could provide a safe,
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5 351 efficient and individualized way of inhalative drug application, e.g. by increasing the effective
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7 352 dose reaching distal airway. Therefore, these results are also of great interest beyond
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10 353 salbutamol nebulization, e.g. for safe usage of inhalative antibiotics in critical ill and
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12 354 ventilated patients.
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17 356 ***Trial status***

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19 357 The first patients were randomized in June 2018. The inclusion of participants is ongoing
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21 358 and is expected to continue until June 2019.
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10 440 a decremental positive end-expiratory lung pressure trial. *Crit Care* 2011;15:R193.
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16 443 **List of abbreviations**

19	ARDS	Acute respiratory distress syndrome
21	BMI	Body mass index
23	CRF	Case report form
26	delta-EELI	Change of end expiratory lung impedance
28	delta-EELV	Change of end expiratory lung volume
30	DRKS	Deutsches Register für klinische Studien
32	ECMO	Extracorporeal membrane oxygenation
34	EIT	Electrical impedance tomography
36	GDPR	General data protection regulation
38	ICD	Implantable cardioverter defibrillator
40	ICU	Intensive care unit
42	NYHA	New York Heart Association
44	$p_a\text{CO}_2$	Partial pressure of arterial carbon dioxide
46	$p_a\text{O}_2$	Partial pressure of arterial oxygen
48	PDMS	Patient data management systems
50	PEEP	Positive end-expiratory pressure
52	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

444

445 **Declarations**

446

447 **Ethics approval and consent to participate**

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

451

452 **Consent for publication**

453 Not applicable

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455 **Availability of data and material**

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

457

458 **Conflict of interests**

459 None to declare

460

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2
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4
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6
7 464 This will have no impact on our study design or collection, analysis and interpretation of our
8
9 data.
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12 466

14 467 **Author Statement**

16
17 468 Dr. med. Tim Rahmel: Main author of this manuscript, written and revising the manuscript

18
19 469 Alexandra Koniusch: Supporting methodical description and participated in the design of this
20
21 study
22

23
24 471 Dr. med. Günther Oprea: Supporting data collection, participated in the design of this study,
25
26 and revising the manuscript
27

28
29 473 Martin Schwertner: Supporting data collection, participated in the design of this study, and
30
31 revising the manuscript
32

33 475 Prof. Dr. med. Michael Adamzik: Supporting data collection, participated in the design of this
34
35 study and revising the manuscript
36

37
38 477 Dr. med. Hartmuth Nowak: Supporting data collection, participated in the design of this
39
40 study, written and revising the manuscript
41

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43

44 480

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47
48 482 Not applicable
49

50 483

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14 490 ¹ Received from the Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie,
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18 492 Germany
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26 495 **Legends**

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29 496 **Figure 1:** Flowchart of interventional procedures on intervention and control group with
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31 497 duration of each step and performed measurements (EIT = electrical impedance
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33 498 tomography, ICU = intensive care unit)
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38 500 **Figure 2:** Flowchart of EIT-guided optimization of ventilator settings (ROI = region of
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40 501 interest, Pmax = maximum airway pressure, P_{insp} = inspiratory pressure, PEEP = positive
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42 502 end expiratory pressure)
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47 504 **Figure 3:** Schedule of enrolment, interventions and assessments – SPIRIT Figure (SPIRIT
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49 505 = Standard Protocol Items: Recommendations for Interventional Trials, EIT = electrical
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51 506 impedance tomography, ICU = intensive care unit)
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54 507 55 508 **Supplemental material**

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- 509 **Supplemental material 1:** Case report form of intervention group
- 510 **Supplemental material 2:** Case report form of control group
- 511 **Supplemental material 3:** Additional information - EIT algorithm
- 512 **Supplemental material 4:** Spirit checklist

For peer review only

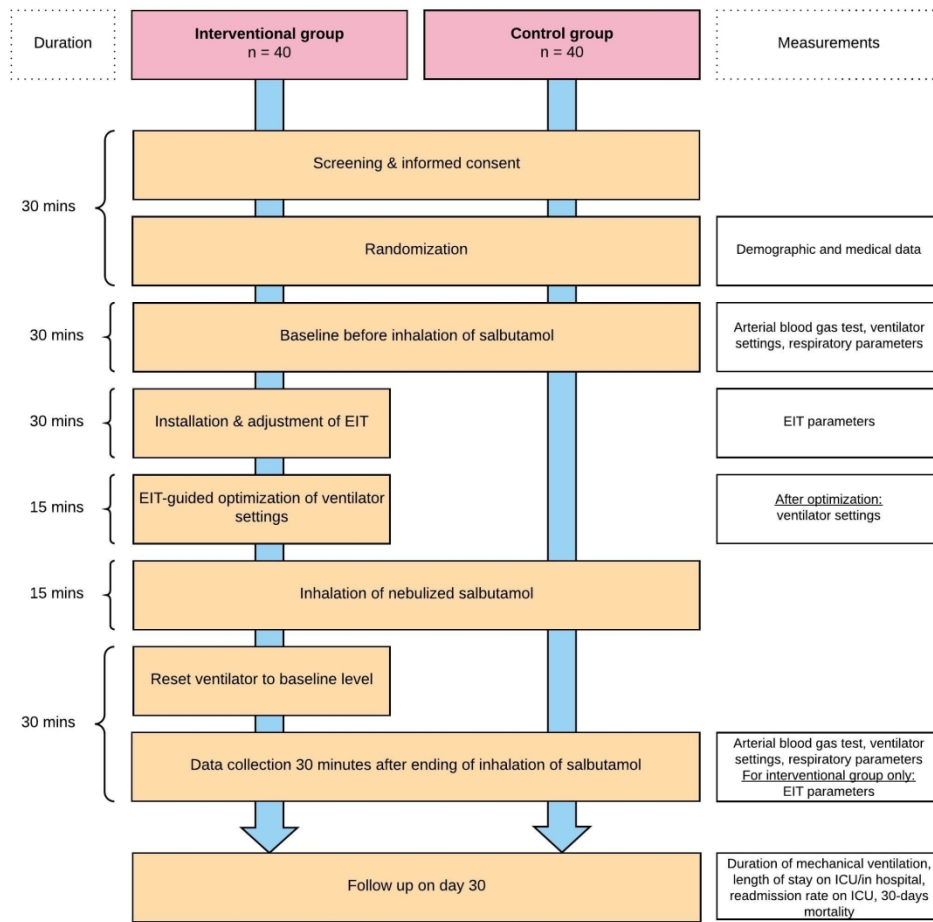


Figure 1: Flowchart of interventional procedures on intervention and control group with duration of each step and performed measurements (EIT = electrical impedance tomography, ICU = intensive care unit)

184x181mm (300 x 300 DPI)

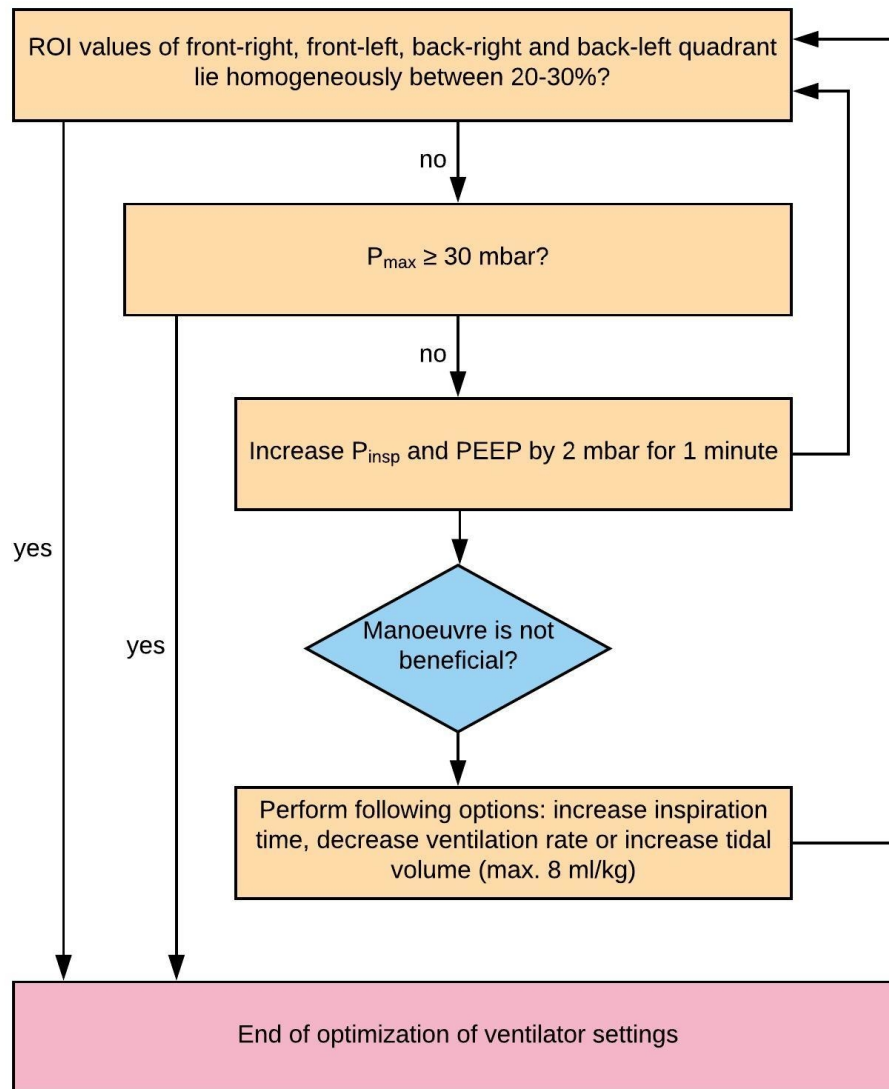


Figure 2: Flowchart of EIT-guided optimization of ventilator settings (ROI = region of interest, P_{max} = maximum airway pressure, P_{insp} = inspiratory pressure, PEEP = positive end expiratory pressure)

114x136mm (300 x 300 DPI)

TIMEPOINT	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
	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)

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Patient

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

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	<input type="checkbox"/>	<input type="checkbox"/>
• Lack of medical indication and/or contraindications to administration of salbutamol	<input type="checkbox"/>	<input type="checkbox"/>
• Age < 18 years	<input type="checkbox"/>	<input type="checkbox"/>
• 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)	<input type="checkbox"/>	<input type="checkbox"/>
• Severe obesity (BMI > 35)	<input type="checkbox"/>	<input type="checkbox"/>
• Prior phase of long-term ventilation > 14 days	<input type="checkbox"/>	<input type="checkbox"/>
• Do-not-resuscitate order	<input type="checkbox"/>	<input type="checkbox"/>
• Pregnancy or lactation	<input type="checkbox"/>	<input type="checkbox"/>

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

male female

Height |_|_|_| cm **weight** |_|_|_|. |_| kg **BMI** |_|_|. |_| kg/m²

- **Blood pressure** |_|_|_| / |_|_| **heart rate** |_|_|_| bpm
body temperature |_|_|. |_| °C

- Pregnancy excluded

- Note participation in the medical record! carried out

1
2
3 • **Procedure in the intervention group**
4

- 5 ○ Study education including randomization (30 min)
- 6 ▪ Measurement of SOFA-Score (____), PCT (____), CRP (____), antibiotics
7 (____), vital parameters (____), catecholamines (____), sedation (____)
- 8
- 9 ○ Data collection before inhalation (30 min)
- 10 ▪ Measurement of airway resistance before salbutamol inhalation (____)
- 11 ▪ Measurement of tidal volume (____), lung compliance (____), arterial oxygen
12 partial pressure (paO₂) (____), Horowitz index (____), arterial carbon dioxide
13 partial pressure (paCO₂) (____), peripheral oxygen saturation (____), arterial
14 oxygen saturation (____), upper (____) and lower (____) inflectionpoint of the
15 pressure-volume-curve
- 16 ▪ Arterial blood sampling
- 17
- 18 ○ Installation and adjustment of the EIT (30 min)
- 19 ▪ Measurement of Region of Interest (ROI) (____), changes of end-expiratory lung
20 volume (Delta-EELV) (____) and changes of end-expiratory lung impedance (Delta-
21 EELI) (____)
- 22
- 23 ○ Optimization of ventilator settings (15 min)
- 24 ▪ Measurement of ventilator settings after EIT-guided optimization (P_{insp} (____), PEEP
25 (____), I:E (____), T_{insp} (____), RR (____), ventilation mode (____))
- 26
- 27 ○ Salbutamol nebulization and inhalation (15 min)
- 28
- 29 ○ Reset ventilator to baseline level
- 30
- 31 ○ Data collection after inhalation (30 min)
- 32 ▪ Measurement of airway resistance after salbutamol inhalation (____)
- 33 ▪ Measurement of tidal volume (____), lung compliance (____), arterial oxygen
34 partial pressure (paO₂) (____), Horowitz index (____), arterial carbon dioxide
35 partial pressure (paCO₂) (____), peripheral oxygen saturation (____), arterial
36 oxygen saturation (____), upper (____) and lower (____) inflectionpoint of the
37 pressure-volume-curve
- 38 ▪ Arterial blood sampling
- 39 ▪ Measurement of Region of Interest (ROI) (____), changes of end-expiratory lung
40 volume (Delta-EELV) (____) and changes of end-expiratory lung impedance (Delta-
41 EELI) (____)
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Date |__|__|.|__|__| 201__

Signature of the examiner _____

Randomization

|_|_|_|. |_|_|_|.201__

No. |_|_|

CRF EIT-Trial (control group)

VU

Patient

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

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	<input type="checkbox"/>	<input type="checkbox"/>
• Lack of medical indication and/or contraindications to administration of salbutamol	<input type="checkbox"/>	<input type="checkbox"/>
• Age < 18 years	<input type="checkbox"/>	<input type="checkbox"/>
• 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)	<input type="checkbox"/>	<input type="checkbox"/>
• Severe obesity (BMI > 35)	<input type="checkbox"/>	<input type="checkbox"/>
• Prior phase of long-term ventilation > 14 days	<input type="checkbox"/>	<input type="checkbox"/>
• Do-not-resuscitate order	<input type="checkbox"/>	<input type="checkbox"/>
• Pregnancy or lactation	<input type="checkbox"/>	<input type="checkbox"/>

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

male female

Height |_|_|_| cm **weight** |_|_|_|. |_| kg **BMI** |_|_|. |_| kg/m²

- **Blood pressure** |_|_|_| / |_|_| **heart rate** |_|_|_| bpm
body temperature |_|_|. |_| °C

- Pregnancy excluded

- Note participation in the medical record! carried out

1
2
3 • **Procedure in the control group**
4

- 5 ○ Study education including randomization (30 min)
- 6 ▪ Measurement of SOFA-Score (____), PCT (____), CRP (____), antibiotics
7 (____), vital parameters (____), catecholamines (____), sedation (____)
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- 9
- 10 ○ Data collection before inhalation (30 min)
- 11 ▪ Measurement of airway resistance before salbutamol inhalation (____)
- 12
- 13 ▪ Measurement of tidal volume (____), lung compliance (____), arterial oxygen
14 partial pressure (paO₂) (____), Horowitz index (____), arterial carbon dioxide
15 partial pressure (paCO₂) (____), peripheral oxygen saturation (____), arterial
16 oxygen saturation (____), upper (____) and lower (____) inflectionpoint of the
17 pressure-volume-curve
- 18
- 19 ▪ Arterial blood sampling
- 20
- 21
- 22 ○ Salbutamol nebulization and inhalation (15 min)
- 23
- 24 ○ Data collection after inhalation (30 min)
- 25 ▪ Measurement of airway resistance after salbutamol inhalation (____)
- 26
- 27 ▪ Measurement of tidal volume (____), lung compliance (____), arterial oxygen
28 partial pressure (paO₂) (____), Horowitz index (____), arterial carbon dioxide
29 partial pressure (paCO₂) (____), peripheral oxygen saturation (____), arterial
30 oxygen saturation (____), upper (____) and lower (____) inflectionpoint of the
31 pressure-volume-curve
- 32
- 33 ▪ Arterial blood sampling
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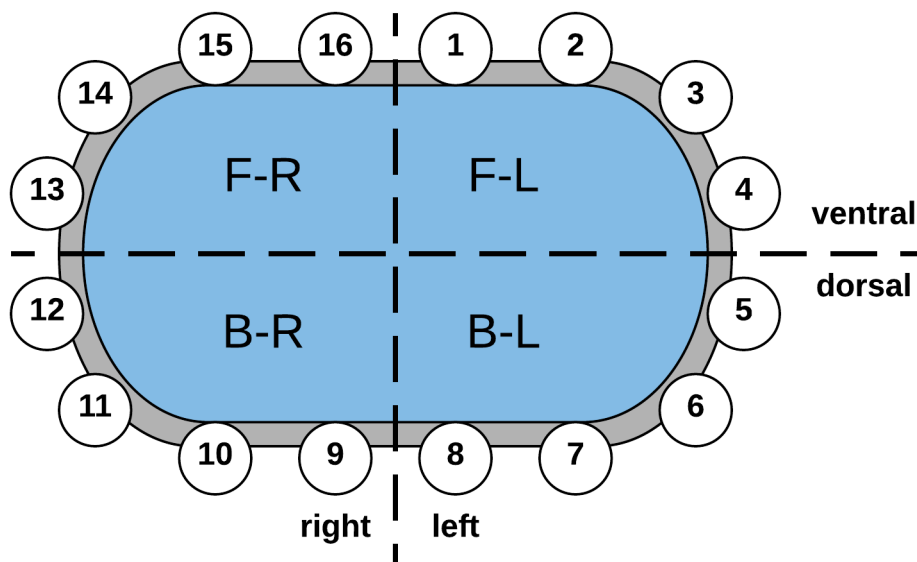
Date |__|__|. |__|__| 201__

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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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.	<input type="checkbox"/>

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.	<input type="checkbox"/>
2.	Delta-EELV (changes of end expiratory lung volume): Choose "Views" in right upper corner of the screen and tap on "End expiratory trend".	<input type="checkbox"/>
3.	Delta-EELI (changes of end expiratory lung impedance): Choose "Views" in right upper corner of the screen and tap on "Delta-EELI".	<input type="checkbox"/>



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 14 th May 2018 (page 6)
Protocol version	3	10 th 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)

- 1
2 Roles and 5a Dr. med. Tim Rahmel, Department of Anaesthesiology, Intensive Care
3 responsibilities and Pain Medicine, University Hospital Knappschaftskrankenhaus
4 Bochum, Bochum, Germany: Principal investigator, main author of
5 this manuscript, written and revising the manuscript
6
7 Alexandra Koniusch, Department of Anaesthesiology, Intensive Care
8 and Pain Medicine, University Hospital Knappschaftskrankenhaus
9 Bochum, Bochum, Germany: Supporting methodical description and
10 participated in the design of this study
11
12 Dr. med. Günther Oprea, Department of Anaesthesiology, Intensive
13 Care and Pain Medicine, University Hospital
14 Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting
15 data collection, participated in the design of this study, and revising
16 the manuscript
17
18 Martin Schwertner, Department of Anaesthesiology, Intensive Care
19 and Pain Medicine, University Hospital Knappschaftskrankenhaus
20 Bochum, Bochum, Germany: Supporting data collection, participated
21 in the design of this study, and revising the manuscript
22
23 Prof. Dr. med. Michael Adamzik, Department of Anaesthesiology,
24 Intensive Care and Pain Medicine, University Hospital
25 Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting
26 data collection, participated in the design of this study and revising the
27 manuscript
28
29 Dr. med. Hartmuth Nowak, Department of Anaesthesiology, Intensive
30 Care and Pain Medicine, University Hospital
31 Knappschaftskrankenhaus Bochum, Bochum, Germany: Co-Principal
32 investigator, supporting data collection, participated in the design of
33 this study, written and revising the manuscript (**pages 19-20**)
34
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36 5b NA
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38 5c Support is granted by the DFG Open Access Publication Funds of the
39 Ruhr-University Bochum (Ref. No. IN-1214264), just for financial
40 support for publication costs. This will have no impact on our study
41 design or collection, analysis and interpretation of our data. (**page 19**)
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49 Introduction

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2 Background and 6a The inhalative administration of drugs is a non-invasive application
3 rationale form that is regularly used in the treatment of ventilated patients in
4 critical care setting. However, assessment of effectiveness or
5 distribution of nebulized drugs is one of the lacking cornerstones of
6 modern intensive care monitoring as several studies could not show a
7 benefit of inhaled medication. Unfortunately, these studies could not
8 address the crucial issue whether the medication was distributed
9 effectively in critical ill ventilated patients. To the present day, there is
10 no established non-invasive real-time monitoring to measure or
11 visualize the effectiveness or distribution of nebulized drugs in
12 ventilated patients at bedside. Electrical impedance tomography (EIT)
13 may provide a promising new monitoring and guiding tool for an
14 adequate optimization of mechanical ventilation in critically ill patients.
15 EIT makes use of changes in thoracic impedance, which in turn result
16 in different concentrations of free ions due to changes in air content of
17 the lung tissue. Therefore, EIT may assist in defining mechanical
18 ventilation settings, assess distribution of tidal volume and evaluation
19 of associated pathologies at bedside. Prior studies demonstrated that
20 equivalent diagnostic findings between EIT and thoracic computed
21 tomography could be achieved in critically ill patients in terms of
22 regional ventilation in different thoracic regions, and also offered a
23 valid examiner-independent test reproducibility of the results. **(pages**
24 **4-5)**

31 6b As no non-invasive real-time monitoring for visualization of nebulized
32 drugs in ventilated patients at bedside is established to the present
33 day, comparator will be standard of care with no EIT-optimized
34 application of salbutamol. **(pages 4-5)**

37 Objectives 7 Our study wants to elucidate the extent to which the effectiveness of
38 inhaled drugs, e.g. β 2 sympathomimetics, can be optimized by the
39 additional use of EIT for adjusting ventilator settings. Accordingly, we
40 want to test the hypothesis whether EIT can increase the
41 effectiveness of inhaled salbutamol. **(page 5)**

44 Trial design 8 This study is a randomized, open-label superiority trial, comparing two
45 groups of mechanically ventilated patients with an acute or chronic
46 bronchial airway obstruction according the effectiveness of inhaled
47 salbutamol with (intervention) or without (control) additional use of EIT
48 for optimizing the ventilator settings. **(page 6)**

52 **Methods: Participants, interventions, and outcomes**

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

1
2 Eligibility criteria 10 Patients at the age of 18 years or more, diagnosed with an acute
3 airway obstruction or known chronic obstructive pulmonary disease
4 under mechanical ventilation for less than 48 hours and providing
5 written informed consent or a positive vote of an independent
6 consultant are eligible for inclusion. **(page 6)**
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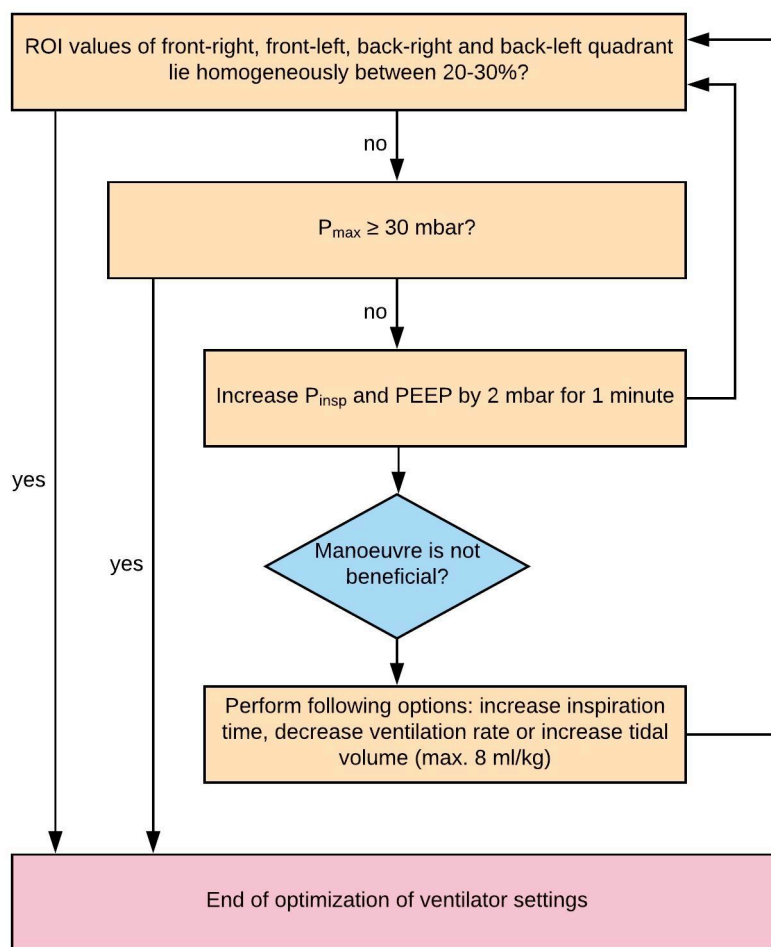
8
9 Exclusion criteria are: pregnancy or lactation, severe obesity (body
10 mass index > 35), missing medical indication and/or contraindication
11 for inhaled salbutamol administration, Horowitz index \geq 400, prior
12 phase of long-term ventilation > 14 days, a study-independent medical
13 indication for salbutamol nebulization in obstructive pulmonary
14 disease and/or an acute obstructive condition and procedure of
15 withdrawing life-sustaining therapy. Furthermore, patients with the
16 following pre-existing conditions and operations will be excluded:
17 patients with chest trauma or surgery (e.g. pneumectomy),
18 pneumonia, ARDS with or without ECMO therapy, neuromuscular
19 diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic
20 events, active implants (e.g. pacemakers, ICD) or thoracic skin lesions
21 and wound dressings. **(page 6-7)**
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2 Interventions 11a EIT and control group undergo an arterial blood gas analysis and
3 corresponding airway measurements to determine baseline
4 parameters before salbutamol inhalation. Therefore, 1.25 mg / 2.5 mL
5 salbutamol (Sultanol®, Glaxo Smith Kline plc., Brentford, United
6 Kingdom) is applied with a vibrating mesh nebulizer (Solo®, Aerogen,
7 Galway, Ireland). **(page 9)**
8
9

10
11 In the control group, baseline measurement is followed by ultrasound
12 nebulization and inhalation with salbutamol for 15 minutes, following
13 measurements and arterial blood gas analysis 30 minutes after
14 inhalation. In addition, all study-relevant data are documented
15 pseudonymised in the case report form (CRF) to ensure a
16 standardized operating. This CRF will be handed over to the principal
17 investigator immediately after collection of data. The principal
18 investigator keeps the study documents in a study folder not
19 accessible to third parties. **(page 9)**
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23 In the intervention group, baseline measurements are followed by the
24 standardized setup and adjustment of EIT, where a belt with 16
25 integrated electrodes is attached circularly to the thorax. This is
26 followed by the optimization of the respirator settings by means of EIT
27 using a defined algorithm, according the recommendations of the
28 Translational EIT Development Study Group (TREND) (see below,
29 figure 2). The EIT algorithm focuses on homogenisation of lung
30 ventilation described by the fast-response parameter ROI (region of
31 interest) to titrate protective PEEP and tidal volume combinations. The
32 next step is nebulization and inhalation of salbutamol for 15 minutes.
33 Subsequently, ventilator settings are reset to baseline as before EIT
34 adjustment. After a period of 30 minutes, a new data collection after
35 salbutamol administration including EIT measurement is done and an
36 arterial blood gas analysis is performed (figure 1). Data is documented
37 in the CRF. **(page 9-10)**
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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



1
2 Outcomes 12 The primary objective is to assess if additional use of EIT can
3 increase the effectiveness of inhaled salbutamol, and therefore
4 decrease the airway resistance 30 minutes after salbutamol inhalation
5 more effective than without usage of EIT. **(page 10)**
6
7

8 The secondary objectives will be to compare the EIT-intervention
9 group and the control group regarding: Before and 30 minutes after
10 salbutamol inhalation [Changes made in ventilator settings under EIT,
11 tidal volume, compliance, resistance, arterial oxygen partial pressure
12 (paO₂), Horowitz index, arterial carbon dioxide partial pressure
13 (paCO₂), peripheral and arterial oxygen saturation, upper and lower
14 inflection point of the pressure-volume curve, EIT parameters: Region
15 of Interest (ROI), changes of end expiratory lung volume (Delta-EELV)
16 and changes of end expiratory lung impedance (Delta-EELI), heart
17 rate, blood pressure]; duration of mechanical ventilation; length of stay
18 on ICU and hospital, readmission rate on ICU; 30-days mortality.
19 **(pages 10-11)**
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24 Additionally, after pseudonymization a large body of clinical and
25 demographic data will be entered into a database for later analysis,
26 including pre-existing morbidities, Simplified Acute Physiology Score II
27 (SAPSII), Sepsis-related Organ Failure Assessment Score (SOFA),
28 body mass index (BMI), necessity for renal replacement therapy,
29 ventilator settings, PaO₂/FiO₂ ratio (Horowitz index), vital parameters,
30 medications and dosage of vasoactive drugs and blood chemistry
31 values. **(page 7)**
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Participant
timeline

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

TIMEPOINT	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
	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 (<i>for EIT group only</i>)			X		X	
Duration of mechanical ventilation, length of stay on ICU/in hospital, readmission rate on ICU						X
30-days mortality						X

1
2 Sample size 14 A total of 80 mechanically ventilated patients will be included in the
3 study, with 40 patients in the intervention group and 40 patients in the
4 control group. With a total cohort size of $n=80$, a power of $> 95\%$
5 (alpha error $p = 0.05$, beta error < 0.05) will be reached, referring to
6 the data from a reference work (table 1) by Malliotakis et al.
7 Calculations from these values indicate that 76 participants (38 per
8 group) are required to achieve a power of 95% with an alpha error of
9 5%. (**pages 7-8**)
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Variable	R_{int}	R_{rs}
$n_{Baseline}$	10	10
n_{30min}	10	10
Mean_{Baseline} \pm SD	18.4 \pm 4.0 [cmH ₂ O//sec]	26.5 \pm 4.1 [cmH ₂ O//sec]
Mean_{30min} \pm SD	15.5 \pm 3.6 [cmH ₂ O//sec]	23.1 \pm 3.6 [cmH ₂ O//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

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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//s), respectively

Recruitment 15 We will ensure patient recruitment by screening patients on ICU daily. Eligible patients will be approached by the principal investigator 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.

- 1
2 Implementation 16c A physician who is independent to this trial will generate allocation
3 sequence. Enrolment and assignment will be done by the principal
4 investigator and/or eligible physicians.
5
- 6 Blinding 17a No blinding will be performed.
7 (masking)
8
9 17b NA
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11 **Methods: Data collection, management, and analysis**

- 12
- 13 Data collection 18a The documentation of the data will be pseudonymized and computer-
14 methods assisted from our patient data management system (PDMS) (Dräger
15 ICM, Dräger Medical, Lübeck, Germany) in a central offline database.
16 **(page 11)**
17
18 18b All above mentioned parameters will be collected during the patients
19 stay in hospital until discharge, death or 30th day of stay on ICU. In
20 case of discharge from ICU, follow-up to evaluate 30-days survival will
21 be performed by visit on normal ward or a phone call by one of the
22 investigators. **(page 11)**
23
24 Data 19 All collected data will solely be provided in pseudonymized form for
25 management further study analyzation. Access to the pseudonymization key, which
26 is password protected, is only available to the principal investigator of
27 this study. **(page 11)**
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- 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 \pm 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

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- 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

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- 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)**

1			
2	Protocol	25	Principal investigator will communicate all important modifications to
3	amendments		study personnel.
4			
5	Consent or assent	26a	Informed consent will be obtained by principal investigator and/or
6			eligible physicians.
7			
8		26b	NA
9			
10	Confidentiality	27	All records, subjects' identities and data management will remain
11			confidential with the General Data Protection Regulation (GDPR) of
12			the European Parliament and the Council of the European Union.
13			(page 11)
14			
15	Declaration	of 28	None to declare (page 19)
16	interests		
17			
18	Access to data	29	The data of the described study will be available from the Dryad
19			repository after publication. (page 19)
20			
21	Ancillary	and 30	No arrangements have been made for compensation to those who
22	post-trial care		suffer harm from trial participation. This has been stated in the
23			informed consent.
24			
25	Dissemination	31a	A manuscript with the results of the study will be published in a peer-
26	policy		reviewed journal. (page 12)
27			
28		31b	NA
29			
30		31c	A publication of this study protocol in BMJ Open is submitted.
31			
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34	Appendices		
35			
36	Informed consent	32	An informed consent form is available in German language can be
37	materials		obtained from the authors.
38			
39	Biological	33	NA
40	specimens		
41			

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Diagnostics, Pharmacology and therapeutics, Respiratory medicine
Keywords:	optimization of ventilation, inhalation, nebulization, region of interest, end expiratory lung volume, end expiratory lung impedance

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Manuscripts

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4 1 **Evaluation of inhaled salbutamol effectiveness under**
5
6 2 **supportive use of electrical impedance tomography in**
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8 3 **ventilated ICU patients: study protocol for a randomized**
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10 4 **controlled clinical trial**
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31 13 **Running head:** EIT-guided ventilator optimization for salbutamol inhalation
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38 17 **Word count:** 2874 (Introduction: 466; Methods/Design: 1750; Discussion: 658)
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30 **Abstract**

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

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

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

51 **Trial registration:** German trial register (DRKS.de); ID: DRKS00014706; registered on
52 14th May 2018

56 **Article Summary**

57 ***Strengths and limitations of this study***

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

71
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74 **Keywords: EIT, optimization of ventilation, inhalation, nebulization, region of**
75 **interest, end expiratory lung volume, end expiratory lung impedance**

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82 Introduction

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

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

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3 107 The inhalative administration of drugs is an established, non-invasive and painless
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5 108 application form, which is used in treatment of obstructive airways diseases. An
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8 109 important advantage is that significant higher local concentrations of the drug at the site
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10 110 of action are achieved without significant systemic exposure ^{13 14}. Several studies could
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12 111 not show a benefit of inhaled medication ¹⁵⁻¹⁷. Unfortunately, these studies could not
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14 112 address the crucial issue whether the medication was distributed effectively in critical ill
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16
17 113 ventilated patients. To the present day, there is no established non-invasive real-time
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19 114 monitoring to measure or visualize the effectiveness or distribution of nebulized drugs
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21 115 in ventilated patients at bedside ¹⁴.

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25 116 Based on this issue, our study wants to elucidate the extent to which the effectiveness
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27 117 of inhaled drugs, e.g. β 2 sympathomimetics, can be optimized by the additional use of
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29 118 EIT for adjusting ventilator settings. Accordingly, we want to test the hypothesis
30
31 119 whether EIT can increase the effectiveness of inhaled salbutamol.

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133 **Methods and analysis**

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

139

140 **Study population and general data acquisition**

141 This study was reviewed and approved by the Ethics Committee of the Medical Faculty
142 of Ruhr-University Bochum (17-6306) and registered in the German Clinical Trial
143 Register (DRKS00014706). It will be conducted in accordance with the Declaration of
144 Helsinki and German laws and regulations. All patients will be admitted to the intensive
145 care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum and will be
146 recruited from June 2018 to June 2019. We will perform EIT measurements with
147 PulmoVista™ (Dräger Medical, Lübeck, Germany) and a size adjusted chest belt with
148 16 electrodes. The diagnosis of acute or chronic airway obstruction will include clinical
149 examination and expiration-flow analyzation. Patients at the age of 18 years or more,
150 diagnosed with an acute airway obstruction or known chronic obstructive pulmonary
151 disease under mechanical ventilation for less than 48 hours and providing written
152 informed consent or a positive vote of an independent consultant are eligible for
153 inclusion. Exclusion criteria are: pregnancy or lactation, severe obesity (body mass
154 index > 35), missing medical indication and/or contraindication for inhaled salbutamol
155 administration, Horowitz index ≥ 400 , prior phase of long-term ventilation > 14 days, a
156 study-independent medical indication for salbutamol nebulization in obstructive
157 pulmonary disease and/or an acute obstructive condition and procedure of withdrawing
158 life-sustaining therapy. Furthermore, patients with the following pre-existing conditions

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3 159 and operations will be excluded: patients with chest trauma or surgery (e.g.
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5 160 pneumectomy), pneumonia, ARDS with or without ECMO therapy, neuromuscular
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7 161 diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic events, active
8
9 162 implants (e.g. pacemakers, ICD) or thoracic skin lesions and wound dressings.
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11
12 163 Patients will be treated generally with a multimodal concept, which includes analgesia
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14 164 and sedation, fluid administration, lung-protective mechanical ventilation,
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16 165 anticoagulation, as well as hemodynamic, antibiotic and diagnostic management as
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18 166 recommended by guidelines, standard operating procedures or evidence based best
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20 167 practice. Additionally, after pseudonymization a large body of clinical and demographic
21
22 168 data will be entered into a database for later analysis, including pre-existing morbidities,
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24 169 Simplified Acute Physiology Score II (SAPSII), Sepsis-related Organ Failure
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26 170 Assessment Score (SOFA), body mass index (BMI), necessity for renal replacement
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28 171 therapy, ventilator settings, PaO₂/FiO₂ ratio (Horowitz index), vital parameters,
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30 172 medications and dosage of vasoactive drugs and blood chemistry values.
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174 **Patient and public involvement**

40 175 Patients were not involved in the development of the research question, outcome
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42 176 measures or study design.
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178 **Sample size calculation**

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49 179 A total of 80 mechanically ventilated patients will be included in the study, with 40
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51 180 patients in the intervention group and 40 patients in the control group. With a total
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53 181 cohort size of n=80, a power of > 95% (alpha error p = 0.05, beta error < 0.05) will be
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55 182 reached, referring to the data from a reference work (table 1) by Malliotakis et al. ¹⁸.
56
57 183 Calculations from these values indicate that 76 participants (38 per group) are required
58
59 184 to achieve a power of 95% with an alpha error of 5%. To compensate a potential
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185 insufficiency of our a-priori sample size calculation, due to the lack of comparable
 186 studies, we will also perform a post-hoc power analysis to evaluate our beta-error.
 187 Additionally, all results will be presented with an effect size estimation described as
 188 standardized mean difference.

189

190 **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

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

194

195

196 Study design

197 The total study duration is planned for 18 months. It will take 12 months for recruitment
 198 of patients and collection of data, last 6 months are scheduled for analyzation. For each
 199 patient an individual study duration is assigned of one day. In the control group, 1.75
 200 hours are scheduled per patient. These include study education and randomization (30
 201 mins), data collection before inhalation (30 mins), drug nebulization and inhalation (15
 202 mins) and measurements after inhalation (30 mins; figure 1). In the interventional
 203 group, study explanation and randomization (30 mins), data collection before inhalation
 204 (30 mins), the installation and adjustment of EIT (30 mins), the optimization of ventilator

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3 205 settings (15 mins), drug nebulization and inhalation (15 mins), resetting ventilator
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5 206 settings to baseline and measurements 30 minutes after inhalation add up to a total
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7 207 duration of 2.5 hours (figure 1).
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11 209 **Randomization**

12 210 Block-balanced randomization, in a 1:1 ratio, will be computer-generated by StatsDirect
13
14 211 (StatsDirect Ltd., Cambridge, United Kingdom) with random block sizes between $n = 10$
15
16 212 and $n = 20$, additionally using random permutations of treatments within each block.
17
18 213 Investigators will be blinded to the allocation according to the randomization list until the
19
20 214 study patient has been included.
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27 216 **Interventional procedure**

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29 217 EIT and control group undergo an arterial blood gas analysis and corresponding airway
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31 218 measurements to determine baseline parameters before salbutamol inhalation (figure
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33 219 1; Supplemental material 1+2). Therefore, 1.25 mg / 2.5 mL salbutamol (Sultanol[®],
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35 220 Glaxo Smith Kline plc., Brentford, United Kingdom) is applied with a vibrating mesh
36
37 221 nebulizer (Solo[®], Aerogen, Galway, Ireland).
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44 223 In the control group, baseline measurement is followed by ultrasound nebulization and
45
46 224 inhalation with salbutamol for 15 minutes, following measurements and arterial blood
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48 225 gas analysis 30 minutes after inhalation (figure 1). In addition, all study-relevant data
49
50 226 are documented pseudonymised in the case report form (CRF) to ensure a
51
52 227 standardized operating (Supplemental material 2). This CRF will be handed over to the
53
54 228 principal investigator immediately after collection of data. The principal investigator
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56 229 keeps the study documents in a study folder not accessible to third parties.
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3 231 In the intervention group, baseline measurements are followed by the standardized
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5 232 setup and adjustment of EIT, where a belt with 16 integrated electrodes is attached
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7 233 circularly to the thorax (Supplemental material 3). This is followed by the optimization of
8
9 234 the respirator settings by means of EIT using a defined algorithm (figure 2), according
10
11 235 the recommendations of the Translational EIT Development Study Group (TREND) ⁵.
12
13 236 The EIT algorithm focuses on homogenisation of lung ventilation described by the fast-
14
15 237 response parameter ROI (region of interest) to titrate protective PEEP and tidal volume
16
17 238 combinations (figure 2). The next step is nebulization and inhalation of salbutamol for
18
19 239 15 minutes. Subsequently, ventilator settings are reset to baseline as before EIT
20
21 240 adjustment. After a period of 30 minutes, a new data collection after salbutamol
22
23 241 administration including EIT measurement is done and an arterial blood gas analysis is
24
25 242 performed (figure 1). Data is documented in the CRF (Supplemental material 1).
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33 244 **Objectives**

34
35 245 The primary objective is to assess if additional use of EIT can increase the
36
37 246 effectiveness of inhaled salbutamol, and therefore decrease the airway resistance 30
38
39 247 minutes after salbutamol inhalation more effective than without usage of EIT. The
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41 248 secondary objectives will be to compare the EIT-intervention group and the control
42
43 249 group regarding:
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45

- 46 250 • Before and 30 minutes after salbutamol inhalation:
 - 47 251 ○ Changes made in ventilator settings under EIT,
 - 48 252 ○ tidal volume, compliance, resistance, arterial oxygen partial pressure
 - 49 253 (p_aO_2), Horowitz index, arterial carbon dioxide partial pressure (p_aCO_2),
 - 50 254 peripheral and arterial oxygen saturation,
 - 51 255 ○ upper and lower inflection point of the pressure-volume curve,
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3 256 ○ EIT parameters: Region of Interest (ROI), changes of end expiratory lung
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5 257 volume (Delta-EELV) and changes of end expiratory lung impedance
6
7 258 (Delta-EELI),
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10 259 ○ heart rate, blood pressure
11
12 260 • duration of mechanical ventilation,
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14 261 • length of stay on ICU and hospital, readmission rate on ICU.
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17 262 • 30-days mortality
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21 264 **Data collection**

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24 265 The documentation of the data will be pseudonymized and computer-assisted from our
25
26 266 patient data management system (PDMS) (Dräger ICM, Dräger Medical, Lübeck,
27
28 267 Germany) in a central offline database. Therefore, all collected data will solely be
29
30 268 provided in pseudonymized form for further study analyzation. Access to the
31
32 269 pseudonymization key, which is password protected, is only available to the principal
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34 270 investigator of this study. All above mentioned parameters will be collected during the
35
36 271 patients stay in hospital until discharge, death or 30th day of stay on ICU. In case of
37
38 272 discharge from ICU, follow-up to evaluate 30-days survival will be performed by visit on
39
40 273 normal ward or a phone call by one of the investigators. Data entered in the central
41
42 274 offline database will be monitored by an independent clinical research associate and
43
44 275 checked for consistency and missing values. All records, subjects' identities and data
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46 276 management will remain confidential with the General Data Protection Regulation
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48 277 (GDPR) of the European Parliament and the Council of the European Union.
49
50 278 Furthermore, this protocol was designed following the recommendations for
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52 279 interventional trials (SPIRIT; figure 3; Supplemental material 4).
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282 **Statistical analysis**

283 Since this is a study designed to demonstrate superiority of the primary endpoint
284 (change in airway resistance 30 minutes after salbutamol inhalation), whether an
285 additional use of EIT increases the effectiveness of inhaled salbutamol, we will perform
286 an intention-to-treat and additionally a per-protocol analysis as recommended by the
287 CONSORT guidelines¹⁹. The per-protocol population will be defined as randomized
288 patients without major protocol deviations, such as non-considerations of exclusion
289 criteria or missing data for the primary endpoint. Baseline characteristics of all patients
290 will be described per group. Qualitative data will be described as frequencies and
291 percentages. Continuous variables are presented as means \pm standard deviation in
292 case of normal distribution and as median and interquartile range (25th; 75th
293 percentile) in case of non-normally distributed variables. Continuous variables will be
294 compared using parametric Student's t-test or non-parametric Mann-Whitney-U-Test.
295 Categorical variables will be characterized by numbers with percentages and will be
296 compared using the Chi-square test or a Fisher's exact test. Superiority will be
297 assumed, if the 95% confidence interval for the difference between the means excludes
298 zero or p-values are statistically significantly different at an a priori alpha error of less
299 than 0.05.

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

303

304 **Ethics and dissemination**

305 A manuscript with the results of the study will be published in a peer-reviewed journal.

306 The study has received the following approvals: Ethics Committee of the Medical

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3 307 Faculty of Ruhr-University Bochum (17-6306). On completion of the trial, and after
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5 308 publication of the primary manuscript, data will be made available in a free accessible
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8 309 online repository.
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330 Discussion

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

334 The administration of inhaled drugs is routinely used in intensive care units, due to the
335 advantage of delivering high drug concentrations to the airway, along with rapid onset
336 of action and fewer systemic side effects. However, it is believed that the beneficial
337 effects of inhaled drugs are smaller in patients on mechanical ventilation than in those
338 breathing spontaneously. In this regard, a previous study could demonstrate that only
339 2.9% of the administered drug dose reached the distal airway in ventilated patients,
340 compared to 11.9% in patients without artificial airway ¹⁶. A recently published review,
341 regarding inhalative drug therapy in mechanical ventilation, stated that ventilator
342 settings play an crucial role in inhaled drug delivery ¹⁴. A tidal volume of at least 500
343 mL, increased inspiratory time and a low inspiratory flow are general recommendations
344 in order to optimize drug distribution in the lungs ^{14 20 21}. Nevertheless, attention should
345 be paid to serious adverse effects of high (> 500 mL) tidal volumes, especially in
346 patients with acute or chronic airway obstructions. In these patients high tidal volumes
347 can lead to dynamic hyperinflation or can cause a severe barotrauma ¹⁴. Furthermore,
348 no clinical studies exist showing the beneficial effects of any particular ventilation mode
349 on inhaled drug delivery ^{20 21}. Therefore, a new diagnostic and guiding tool for adequate
350 optimization of ventilator settings prior to nebulization of inhalative drugs would be
351 desirable. Hence, fast, non-invasive and reliable assessment at bedside in critical ill
352 and ventilated patients is one of the cornerstones for modern intensive care monitoring.
353 EIT, although with some constrains, may be a promising solution. EIT images are valid
354 measurements of the regional distribution of ventilation and changes in lung volume in
355 real-time. This dynamic evaluation makes EIT a promising tool for guided optimization

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3 356 of ventilator parameters on an individualized base. Several studies in the last years
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5 357 have already demonstrated that EIT-guided respirator optimization results in significant
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7 358 improved respiratory mechanics and improved gas exchange ^{1 4 7 22}. However, a global
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10 359 standard based on a broad base of evidence was one of the most discussed topics in
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12 360 Respiratory Medicine over the last years. Therefore, the plausibility of EIT
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14 361 measurements highly depends on the correct belt position, proper impedance
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17 362 visualization, correct analysis and data interpretation ²³.

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19 363 The crucial step forward was the publication of recommendations of the TREND
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21 364 (Translational EIT Development Study) group ⁵. These recommendations highlight the
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23 365 need for a consensus about examinations, consistent terminology and generally
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25 366 accepted approaches to EIT images and analysis. Based on this highly appreciated
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27 367 consensus statement we are now able to compare, understand and reproduce study
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29 368 findings from among different research groups and provide a standardized use in
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31 369 clinical routine.

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35 370 A further limitation is that EIT captures only ventral-to-dorsal ventilation distribution.
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37 371 However, Bikker et al. also reported different ventilation distribution between cranial
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39 372 and caudal lung levels during decremental PEEP trials ²⁴, concluding that existing EIT
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41 373 systems will not be able to cover the optimal PEEP titration for the whole lung.

42
43 374 Despite the possible limitations of EIT, this device can provide a remarkable advance in
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45 375 the field of individualized and guided mechanical ventilation adjustments. Therefore,
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47 376 this study can shed light on the extent to which the additional use of EIT for optimizing
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49 377 the ventilator settings can increase the effectiveness of inhaled salbutamol.

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54 379 **Outlook**

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56 380 EIT could help to visualize and verify an effective nebulization that could provide a safe,
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58 381 efficient and individualized way of inhalative drug application, e.g. by increasing the

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3 382 effective dose reaching distal airway. Therefore, these results are also of great interest
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5 383 beyond salbutamol nebulization, e.g. for safe usage of inhalative antibiotics in critical ill
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8 384 and ventilated patients.
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12 386 ***Trial status***

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14 387 The first patients were randomized in June 2018. The inclusion of participants is
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16
17 388 ongoing and is expected to continue until June 2019.
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56 471 during a decremental positive end-expiratory lung pressure trial. *Crit Care*
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475 **List of abbreviations**

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6	ARDS	Acute respiratory distress syndrome
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8	BMI	Body mass index
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10	CRF	Case report form
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12	delta-EELI	Change of end expiratory lung impedance
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14	delta-EELV	Change of end expiratory lung volume
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17	DRKS	Deutsches Register für klinische Studien
18		
19	ECMO	Extracorporeal membrane oxygenation
20		
21	EIT	Electrical impedance tomography
22		
23		
24	GDPR	General data protection regulation
25		
26	ICD	Implantable cardioverter defibrillator
27		
28	ICU	Intensive care unit
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30		
31	NYHA	New York Heart Association
32		
33	p _a CO ₂	Partial pressure of arterial carbon dioxide
34		
35	p _a O ₂	Partial pressure of arterial oxygen
36		
37		
38	PDMS	Patient data management systems
39		
40	PEEP	Positive end-expiratory pressure
41		
42	R	Resistance
43		
44		
45	ROI	Region of interest
46		
47	SAPSII	Simplified acute physiology score II
48		
49	SD	Standard deviation
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51	SOFA score	Sepsis-related organ failure assessment score
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53	Spirit	Standard Protocol Items - Recommendations for Interventional
54		
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56	TREND group	Translational EIT Development Study group
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3 477 **Declarations**
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8 479 **Ethics approval and consent to participate**
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10 480 This study was reviewed and approved by the Ethics Committee of the Medical Faculty
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12 481 of the Ruhr-Universität Bochum (no. 17-6306) and written informed consent or a
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14 482 positive vote of an independent consultant are eligible for inclusion.
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19 484 **Consent for publication**
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22 485 Not applicable
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26 487 **Availability of data and material**
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29 488 The data of the described study will be available from the Dryad repository after
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31 489 publication.
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35 491 **Conflict of interests**
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37
38 492 None to declare
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41
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44
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46
47 496 University Bochum (Ref. No. IN-1214264), just for financial support for publication
48
49 497 costs. This will have no impact on our study design or collection, analysis and
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51 498 interpretation of our data.
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56 500 **Author Statement**
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59 501 Dr. med. Tim Rahmel: Main author of this manuscript, written and revising the
60
502 manuscript

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2
3 503 Alexandra Koniusch: Supporting methodical description and participated in the design
4
5 504 of this study
6
7 505 Dr. med. Günther Oprea: Supporting data collection, participated in the design of this
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9 506 study, and revising the manuscript
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11
12 507 Martin Schwertner: Supporting data collection, participated in the design of this study,
13
14 508 and revising the manuscript
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16
17 509 Prof. Dr. med. Michael Adamzik: Supporting data collection, participated in the design
18
19 510 of this study and revising the manuscript
20
21
22 511 Dr. med. Hartmuth Nowak: Supporting data collection, participated in the design of this
23
24 512 study, written and revising the manuscript
25
26 513 All authors read and approved the final manuscript.
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516 Not applicable

517

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526 44892 Bochum, Germany

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3 **529 Legends**
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6 **530 Figure 1:** Flowchart of interventional procedures on intervention and control group with
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8 **531** duration of each step and performed measurements (EIT = electrical impedance
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10 **532** tomography, ICU = intensive care unit)
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13 **533**
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15 **534 Figure 2:** Flowchart of EIT-guided optimization of ventilator settings (ROI = region of
16
17 **535** interest, Pmax = maximum airway pressure, P_{insp} = inspiratory pressure, PEEP =
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19 **536** positive end expiratory pressure)
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22 **537**
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24 **538 Figure 3:** Schedule of enrolment, interventions and assessments – SPIRIT Figure
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26 **539** (SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials, EIT =
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28 **540** electrical impedance tomography, ICU = intensive care unit)
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31 **541**
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34 **542 Supplemental material**
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36 **543 Supplemental material 1:** Case report form of intervention group
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38 **544 Supplemental material 2:** Case report form of control group
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40 **545 Supplemental material 3:** Additional information - EIT algorithm
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42 **546 Supplemental material 4:** Spirit checklist
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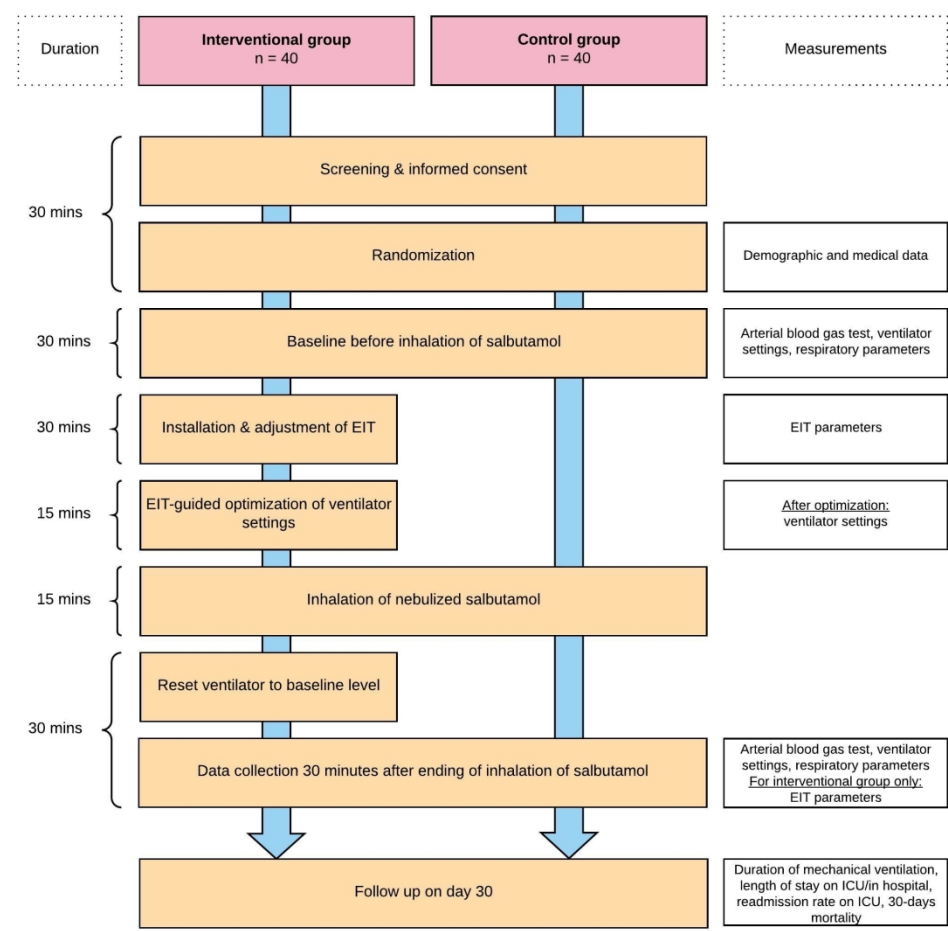


Figure 1: Flowchart of interventional procedures on intervention and control group with duration of each step and performed measurements (EIT = electrical impedance tomography, ICU = intensive care unit)

184x181mm (300 x 300 DPI)

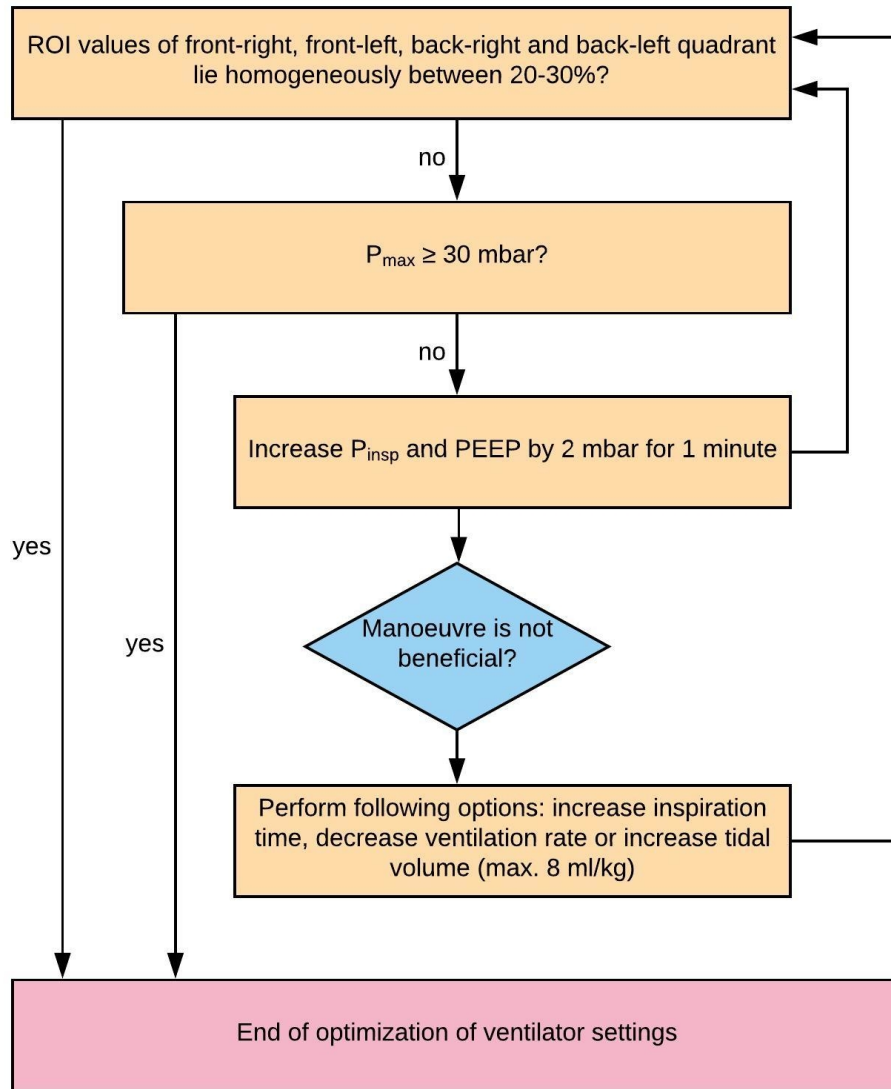


Figure 2: Flowchart of EIT-guided optimization of ventilator settings (ROI = region of interest, P_{max} = maximum airway pressure, P_{insp} = inspiratory pressure, PEEP = positive end expiratory pressure)

114x136mm (300 x 300 DPI)

TIMEPOINT	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
	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	<input type="checkbox"/>	<input type="checkbox"/>
• Known obstructive airway disease or acute airway obstruction and	<input type="checkbox"/>	<input type="checkbox"/>
• Medical indication for salbutamol inhalation	<input type="checkbox"/>	<input type="checkbox"/>
• Mechanical ventilated patient (<48h) and Horowitz index (p_aO_2/F_iO_2) < 400	<input type="checkbox"/>	<input type="checkbox"/>
• Written informed consent or positive vote of an independent consultant	<input type="checkbox"/>	<input type="checkbox"/>

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	<input type="checkbox"/>	<input type="checkbox"/>
• Lack of medical indication and/or contraindications to administration of salbutamol	<input type="checkbox"/>	<input type="checkbox"/>
• Age < 18 years	<input type="checkbox"/>	<input type="checkbox"/>
• 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)	<input type="checkbox"/>	<input type="checkbox"/>
• Severe obesity (BMI > 35)	<input type="checkbox"/>	<input type="checkbox"/>
• Prior phase of long-term ventilation > 14 days	<input type="checkbox"/>	<input type="checkbox"/>
• Do-not-resuscitate order	<input type="checkbox"/>	<input type="checkbox"/>
• Pregnancy or lactation	<input type="checkbox"/>	<input type="checkbox"/>

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

male female

Height |_|_|_| cm **weight** |_|_|_|. |_| kg **BMI** |_|_|. |_| kg/m²

• **Blood pressure** |_|_|_| / |_|_| **heart rate** |_|_|_| bpm

body temperature |_|_|. |_| °C

• Pregnancy excluded

• Note participation in the medical record! carried out

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- **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 (paO₂) (____), Horowitz index (____), arterial carbon dioxide partial pressure (paCO₂) (____), 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-expiratory lung volume (Delta-EELV) (____) and changes of end-expiratory 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 (paO₂) (____), Horowitz index (____), arterial carbon dioxide partial pressure (paCO₂) (____), 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-expiratory lung volume (Delta-EELV) (____) and changes of end-expiratory 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	<input type="checkbox"/>	<input type="checkbox"/>
• Known obstructive airway disease or acute airway obstruction and	<input type="checkbox"/>	<input type="checkbox"/>
• Medical indication for salbutamol inhalation		
• Mechanical ventilated patient (<48h) and Horowitz index (p_aO_2/F_iO_2) < 400	<input type="checkbox"/>	<input type="checkbox"/>
• Written informed consent or positive vote of an independent consultant	<input type="checkbox"/>	<input type="checkbox"/>

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	<input type="checkbox"/>	<input type="checkbox"/>
• Lack of medical indication and/or contraindications to administration of salbutamol	<input type="checkbox"/>	<input type="checkbox"/>
• Age < 18 years	<input type="checkbox"/>	<input type="checkbox"/>
• 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)	<input type="checkbox"/>	<input type="checkbox"/>
• Severe obesity (BMI > 35)	<input type="checkbox"/>	<input type="checkbox"/>
• Prior phase of long-term ventilation > 14 days	<input type="checkbox"/>	<input type="checkbox"/>
• Do-not-resuscitate order	<input type="checkbox"/>	<input type="checkbox"/>
• Pregnancy or lactation	<input type="checkbox"/>	<input type="checkbox"/>

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

male female

Height |_|_|_| cm **weight** |_|_|_|. |_| kg **BMI** |_|_|. |_| kg/m²

• **Blood pressure** |_|_|_| / |_|_| **heart rate** |_|_|_| bpm

body temperature |_|_|. |_| °C

• Pregnancy excluded

• Note participation in the medical record! carried out

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3 • **Procedure in the control group**
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- 5 ○ Study education including randomization (30 min)
- 6 ▪ Measurement of SOFA-Score (____), PCT (____), CRP (____), antibiotics
7 (____), vital parameters (____), catecholamines (____), sedation (____)
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- 10 ○ Data collection before inhalation (30 min)
- 11 ▪ Measurement of airway resistance before salbutamol inhalation (____)
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- 13 ▪ Measurement of tidal volume (____), lung compliance (____), arterial oxygen
14 partial pressure (paO₂) (____), Horowitz index (____), arterial carbon dioxide
15 partial pressure (paCO₂) (____), peripheral oxygen saturation (____), arterial
16 oxygen saturation (____), upper (____) and lower (____) inflectionpoint of the
17 pressure-volume-curve
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- 19 ▪ Arterial blood sampling
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- 22 ○ Salbutamol nebulization and inhalation (15 min)
- 23
- 24 ○ Data collection after inhalation (30 min)
- 25 ▪ Measurement of airway resistance after salbutamol inhalation (____)
- 26
- 27 ▪ Measurement of tidal volume (____), lung compliance (____), arterial oxygen
28 partial pressure (paO₂) (____), Horowitz index (____), arterial carbon dioxide
29 partial pressure (paCO₂) (____), peripheral oxygen saturation (____), arterial
30 oxygen saturation (____), upper (____) and lower (____) inflectionpoint of the
31 pressure-volume-curve
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- 33 ▪ Arterial blood sampling
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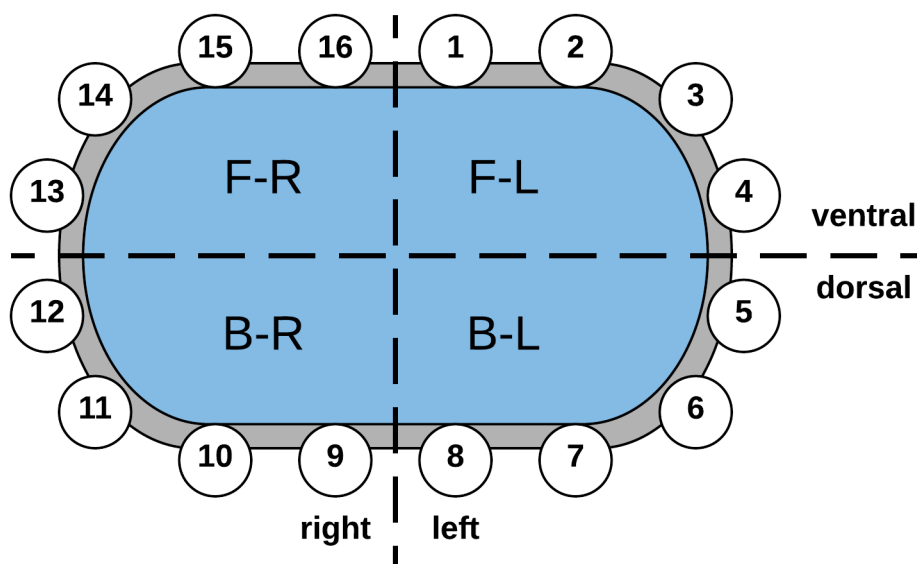
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Signature of the examiner _____

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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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.	<input type="checkbox"/>

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.	<input type="checkbox"/>
2.	Delta-EELV (changes of end expiratory lung volume): Choose "Views" in right upper corner of the screen and tap on "End expiratory trend".	<input type="checkbox"/>
3.	Delta-EELI (changes of end expiratory lung impedance): Choose "Views" in right upper corner of the screen and tap on "Delta-EELI".	<input type="checkbox"/>



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 14 th May 2018 (page 6)
Protocol version	3	10 th 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)

- 1
2 Roles and 5a Dr. med. Tim Rahmel, Department of Anaesthesiology, Intensive Care
3 responsibilities and Pain Medicine, University Hospital Knappschaftskrankenhaus
4 Bochum, Bochum, Germany: Principal investigator, main author of
5 this manuscript, written and revising the manuscript
6
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10 participated in the design of this study
11
12 Dr. med. Günther Oprea, Department of Anaesthesiology, Intensive
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14 Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting
15 data collection, participated in the design of this study, and revising
16 the manuscript
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18 Martin Schwertner, Department of Anaesthesiology, Intensive Care
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21 in the design of this study, and revising the manuscript
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26 data collection, participated in the design of this study and revising the
27 manuscript
28
29 Dr. med. Hartmuth Nowak, Department of Anaesthesiology, Intensive
30 Care and Pain Medicine, University Hospital
31 Knappschaftskrankenhaus Bochum, Bochum, Germany: Co-Principal
32 investigator, supporting data collection, participated in the design of
33 this study, written and revising the manuscript (**pages 19-20**)
34
35
36 5b NA
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38 5c Support is granted by the DFG Open Access Publication Funds of the
39 Ruhr-University Bochum (Ref. No. IN-1214264), just for financial
40 support for publication costs. This will have no impact on our study
41 design or collection, analysis and interpretation of our data. (**page 19**)
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44 5d NA
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Introduction

1
2 Background and 6a The inhalative administration of drugs is a non-invasive application
3 rationale form that is regularly used in the treatment of ventilated patients in
4 critical care setting. However, assessment of effectiveness or
5 distribution of nebulized drugs is one of the lacking cornerstones of
6 modern intensive care monitoring as several studies could not show a
7 benefit of inhaled medication. Unfortunately, these studies could not
8 address the crucial issue whether the medication was distributed
9 effectively in critical ill ventilated patients. To the present day, there is
10 no established non-invasive real-time monitoring to measure or
11 visualize the effectiveness or distribution of nebulized drugs in
12 ventilated patients at bedside. Electrical impedance tomography (EIT)
13 may provide a promising new monitoring and guiding tool for an
14 adequate optimization of mechanical ventilation in critically ill patients.
15 EIT makes use of changes in thoracic impedance, which in turn result
16 in different concentrations of free ions due to changes in air content of
17 the lung tissue. Therefore, EIT may assist in defining mechanical
18 ventilation settings, assess distribution of tidal volume and evaluation
19 of associated pathologies at bedside. Prior studies demonstrated that
20 equivalent diagnostic findings between EIT and thoracic computed
21 tomography could be achieved in critically ill patients in terms of
22 regional ventilation in different thoracic regions, and also offered a
23 valid examiner-independent test reproducibility of the results. **(pages**
24 **4-5)**

31 6b As no non-invasive real-time monitoring for visualization of nebulized
32 drugs in ventilated patients at bedside is established to the present
33 day, comparator will be standard of care with no EIT-optimized
34 application of salbutamol. **(pages 4-5)**

37 Objectives 7 Our study wants to elucidate the extent to which the effectiveness of
38 inhaled drugs, e.g. β 2 sympathomimetics, can be optimized by the
39 additional use of EIT for adjusting ventilator settings. Accordingly, we
40 want to test the hypothesis whether EIT can increase the
41 effectiveness of inhaled salbutamol. **(page 5)**

44 Trial design 8 This study is a randomized, open-label superiority trial, comparing two
45 groups of mechanically ventilated patients with an acute or chronic
46 bronchial airway obstruction according the effectiveness of inhaled
47 salbutamol with (intervention) or without (control) additional use of EIT
48 for optimizing the ventilator settings. **(page 6)**

52 **Methods: Participants, interventions, and outcomes**

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

1
2 Eligibility criteria 10 Patients at the age of 18 years or more, diagnosed with an acute
3 airway obstruction or known chronic obstructive pulmonary disease
4 under mechanical ventilation for less than 48 hours and providing
5 written informed consent or a positive vote of an independent
6 consultant are eligible for inclusion. **(page 6)**
7

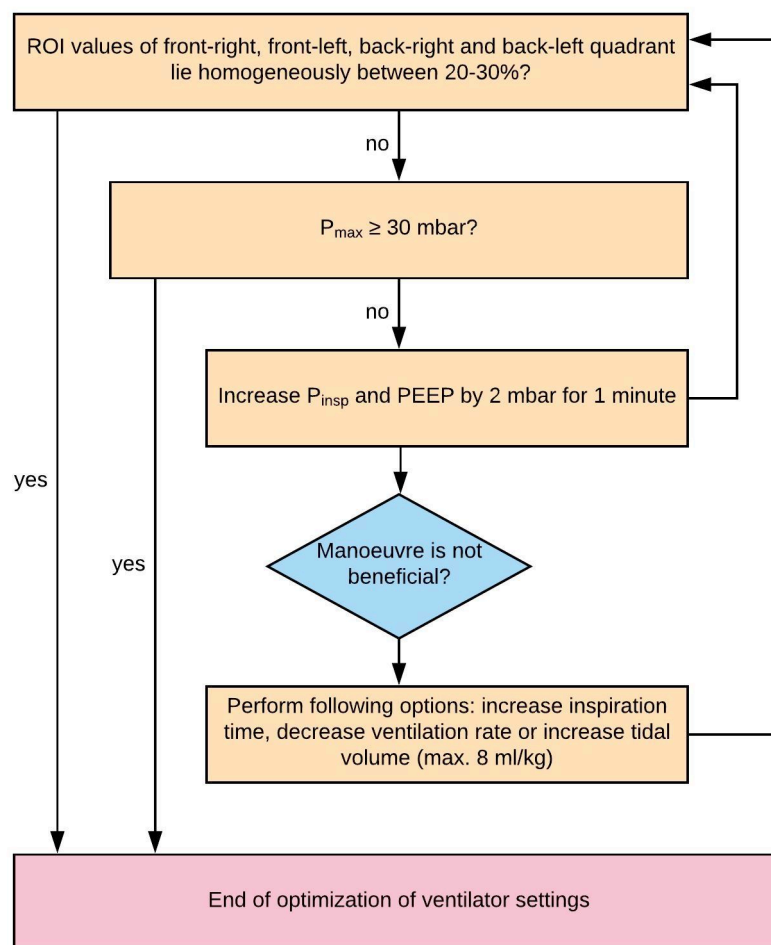
8
9 Exclusion criteria are: pregnancy or lactation, severe obesity (body
10 mass index > 35), missing medical indication and/or contraindication
11 for inhaled salbutamol administration, Horowitz index ≥ 400 , prior
12 phase of long-term ventilation > 14 days, a study-independent medical
13 indication for salbutamol nebulization in obstructive pulmonary
14 disease and/or an acute obstructive condition and procedure of
15 withdrawing life-sustaining therapy. Furthermore, patients with the
16 following pre-existing conditions and operations will be excluded:
17 patients with chest trauma or surgery (e.g. pneumectomy),
18 pneumonia, ARDS with or without ECMO therapy, neuromuscular
19 diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic
20 events, active implants (e.g. pacemakers, ICD) or thoracic skin lesions
21 and wound dressings. **(page 6-7)**
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2 Interventions 11a EIT and control group undergo an arterial blood gas analysis and
3 corresponding airway measurements to determine baseline
4 parameters before salbutamol inhalation. Therefore, 1.25 mg / 2.5 mL
5 salbutamol (Sultanol®, Glaxo Smith Kline plc., Brentford, United
6 Kingdom) is applied with a vibrating mesh nebulizer (Solo®, Aerogen,
7 Galway, Ireland). **(page 9)**
8
9

10
11 In the control group, baseline measurement is followed by ultrasound
12 nebulization and inhalation with salbutamol for 15 minutes, following
13 measurements and arterial blood gas analysis 30 minutes after
14 inhalation. In addition, all study-relevant data are documented
15 pseudonymised in the case report form (CRF) to ensure a
16 standardized operating. This CRF will be handed over to the principal
17 investigator immediately after collection of data. The principal
18 investigator keeps the study documents in a study folder not
19 accessible to third parties. **(page 9)**
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23 In the intervention group, baseline measurements are followed by the
24 standardized setup and adjustment of EIT, where a belt with 16
25 integrated electrodes is attached circularly to the thorax. This is
26 followed by the optimization of the respirator settings by means of EIT
27 using a defined algorithm, according the recommendations of the
28 Translational EIT Development Study Group (TREND) (see below,
29 figure 2). The EIT algorithm focuses on homogenisation of lung
30 ventilation described by the fast-response parameter ROI (region of
31 interest) to titrate protective PEEP and tidal volume combinations. The
32 next step is nebulization and inhalation of salbutamol for 15 minutes.
33 Subsequently, ventilator settings are reset to baseline as before EIT
34 adjustment. After a period of 30 minutes, a new data collection after
35 salbutamol administration including EIT measurement is done and an
36 arterial blood gas analysis is performed (figure 1). Data is documented
37 in the CRF. **(page 9-10)**
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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

1
2 Outcomes 12 The primary objective is to assess if additional use of EIT can
3 increase the effectiveness of inhaled salbutamol, and therefore
4 decrease the airway resistance 30 minutes after salbutamol inhalation
5 more effective than without usage of EIT. **(page 10)**
6
7

8 The secondary objectives will be to compare the EIT-intervention
9 group and the control group regarding: Before and 30 minutes after
10 salbutamol inhalation [Changes made in ventilator settings under EIT,
11 tidal volume, compliance, resistance, arterial oxygen partial pressure
12 (paO₂), Horowitz index, arterial carbon dioxide partial pressure
13 (paCO₂), peripheral and arterial oxygen saturation, upper and lower
14 inflection point of the pressure-volume curve, EIT parameters: Region
15 of Interest (ROI), changes of end expiratory lung volume (Delta-EELV)
16 and changes of end expiratory lung impedance (Delta-EELI), heart
17 rate, blood pressure]; duration of mechanical ventilation; length of stay
18 on ICU and hospital, readmission rate on ICU; 30-days mortality.
19
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21
22 **(pages 10-11)**
23

24 Additionally, after pseudonymization a large body of clinical and
25 demographic data will be entered into a database for later analysis,
26 including pre-existing morbidities, Simplified Acute Physiology Score II
27 (SAPSII), Sepsis-related Organ Failure Assessment Score (SOFA),
28 body mass index (BMI), necessity for renal replacement therapy,
29 ventilator settings, PaO₂/FiO₂ ratio (Horowitz index), vital parameters,
30 medications and dosage of vasoactive drugs and blood chemistry
31 values. **(page 7)**
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Participant
timeline

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

TIMEPOINT	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
	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 (<i>for EIT group only</i>)			X		X	
Duration of mechanical ventilation, length of stay on ICU/in hospital, readmission rate on ICU						X
30-days mortality						X

1
2 Sample size 14 A total of 80 mechanically ventilated patients will be included in the
3 study, with 40 patients in the intervention group and 40 patients in the
4 control group. With a total cohort size of n=80, a power of > 95%
5 (alpha error p = 0.05, beta error < 0.05) will be reached, referring to
6 the data from a reference work (table 1) by Malliotakis et al.
7 Calculations from these values indicate that 76 participants (38 per
8 group) are required to achieve a power of 95% with an alpha error of
9 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//sec]	26.5±4.1 [cmH2O//sec]
Mean _{30min} ± SD	15.5±3.6 [cmH2O//sec]	23.1±3.6 [cmH2O//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//s), respectively

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

Methods: Assignment of interventions (for controlled trials)

Allocation:

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

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

1
2 Implementation 16c A physician who is independent to this trial will generate allocation
3 sequence. Enrolment and assignment will be done by the principal
4 investigator and/or eligible physicians.
5

6 Blinding 17a No blinding will be performed.
7 (masking)

8
9 17b NA
10

11 **Methods: Data collection, management, and analysis**

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13 Data collection 18a The documentation of the data will be pseudonymized and computer-
14 methods assisted from our patient data management system (PDMS) (Dräger
15 ICM, Dräger Medical, Lübeck, Germany) in a central offline database.
16 **(page 11)**
17

18
19 18b All above mentioned parameters will be collected during the patients
20 stay in hospital until discharge, death or 30th day of stay on ICU. In
21 case of discharge from ICU, follow-up to evaluate 30-days survival will
22 be performed by visit on normal ward or a phone call by one of the
23 investigators. **(page 11)**
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25
26 Data 19 All collected data will solely be provided in pseudonymized form for
27 management further study analyzation. Access to the pseudonymization key, which
28 is password protected, is only available to the principal investigator of
29 this study. **(page 11)**
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- 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 \pm 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

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- 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

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- 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)**

1			
2	Protocol	25	Principal investigator will communicate all important modifications to
3	amendments		study personnel.
4			
5	Consent or assent	26a	Informed consent will be obtained by principal investigator and/or
6			eligible physicians.
7			
8		26b	NA
9			
10	Confidentiality	27	All records, subjects' identities and data management will remain
11			confidential with the General Data Protection Regulation (GDPR) of
12			the European Parliament and the Council of the European Union.
13			(page 11)
14			
15	Declaration	of 28	None to declare (page 19)
16	interests		
17			
18			
19	Access to data	29	The data of the described study will be available from the Dryad
20			repository after publication. (page 19)
21			
22	Ancillary	and 30	No arrangements have been made for compensation to those who
23	post-trial care		suffer harm from trial participation. This has been stated in the
24			informed consent.
25			
26	Dissemination	31a	A manuscript with the results of the study will be published in a peer-
27	policy		reviewed journal. (page 12)
28			
29		31b	NA
30			
31		31c	A publication of this study protocol in BMJ Open is submitted.
32			
33			
34	Appendices		
35			
36	Informed consent	32	An informed consent form is available in German language can be
37	materials		obtained from the authors.
38			
39	Biological	33	NA
40	specimens		
41			

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026038.R3
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Date Submitted by the Author:	25-Jan-2019
Complete List of Authors:	Rahmel, Tim; Universitätsklinikum Knappschafts Krankenhaus Bochum, Koniusch, Alexandra; Universitätsklinikum Knappschafts Krankenhaus Bochum Schwertner, Martin; Universitätsklinikum Knappschafts Krankenhaus Bochum Oprea, Günther; Universitätsklinikum Knappschafts Krankenhaus Bochum Adamzik, Michael; Universitätsklinikum Knappschafts Krankenhaus Bochum Nowak, Hartmuth; Universitätsklinikum Knappschafts Krankenhaus Bochum
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Diagnostics, Pharmacology and therapeutics, Respiratory medicine
Keywords:	optimization of ventilation, inhalation, nebulization, region of interest, end expiratory lung volume, end expiratory lung impedance

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Manuscripts

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4 1 **Evaluation of inhaled salbutamol effectiveness under**
5
6 2 **supportive use of electrical impedance tomography in**
7
8 3 **ventilated ICU patients: study protocol for a randomized**
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10 4 **controlled clinical trial**
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12

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31 13 **Running head:** EIT-guided ventilator optimization for salbutamol inhalation
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33 14
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35 15
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37

38 17 **Word count:** 2874 (Introduction: 466; Methods/Design: 1750; Discussion: 658)
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40 18
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30 **Abstract**

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

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

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

51 **Trial registration:** German trial register (DRKS.de); ID: DRKS00014706; registered on
52 14th May 2018

56 **Article Summary**

57 ***Strengths and limitations of this study***

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

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

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82 Introduction

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

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

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3 107 The inhalative administration of drugs is an established, non-invasive and painless
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5 108 application form, which is used in treatment of obstructive airways diseases. An
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8 109 important advantage is that significant higher local concentrations of the drug at the site
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10 110 of action are achieved without significant systemic exposure ^{13 14}. Several studies could
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12 111 not show a benefit of inhaled medication ¹⁵⁻¹⁷. Unfortunately, these studies could not
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14 112 address the crucial issue whether the medication was distributed effectively in critical ill
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17 113 ventilated patients. To the present day, there is no established non-invasive real-time
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19 114 monitoring to measure or visualize the effectiveness or distribution of nebulized drugs
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21 115 in ventilated patients at bedside ¹⁴.

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25 116 Based on this issue, our study wants to elucidate the extent to which the effectiveness
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27 117 of inhaled drugs, e.g. β 2 sympathomimetics, can be optimized by the additional use of
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29 118 EIT for adjusting ventilator settings. Accordingly, we want to test the hypothesis
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31 119 whether EIT can increase the effectiveness of inhaled salbutamol.

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133 **Methods and analysis**

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

139

140 **Study population and general data acquisition**

141 This study was reviewed and approved by the Ethics Committee of the Medical Faculty
142 of Ruhr-University Bochum (17-6306) and registered in the German Clinical Trial
143 Register (DRKS00014706). It will be conducted in accordance with the Declaration of
144 Helsinki and German laws and regulations. All patients will be admitted to the intensive
145 care unit (ICU) of University Hospital Knappschaftskrankenhaus Bochum and will be
146 recruited from June 2018 to June 2019. We will perform EIT measurements with
147 PulmoVista™ (Dräger Medical, Lübeck, Germany) and a size adjusted chest belt with
148 16 electrodes. The diagnosis of acute or chronic airway obstruction will include clinical
149 examination and expiration-flow analyzation. Patients at the age of 18 years or more,
150 diagnosed with an acute airway obstruction or known chronic obstructive pulmonary
151 disease under mechanical ventilation for less than 48 hours and providing written
152 informed consent or a positive vote of an independent consultant are eligible for
153 inclusion. Exclusion criteria are: pregnancy or lactation, severe obesity (body mass
154 index > 35), missing medical indication and/or contraindication for inhaled salbutamol
155 administration, Horowitz index ≥ 400 , prior phase of long-term ventilation > 14 days, a
156 study-independent medical indication for salbutamol nebulization in obstructive
157 pulmonary disease and/or an acute obstructive condition and procedure of withdrawing
158 life-sustaining therapy. Furthermore, patients with the following pre-existing conditions

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3 159 and operations will be excluded: patients with chest trauma or surgery (e.g.
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5 160 pneumectomy), pneumonia, ARDS with or without ECMO therapy, neuromuscular
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7 161 diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic events, active
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10 162 implants (e.g. pacemakers, ICD) or thoracic skin lesions and wound dressings.
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12 163 Patients will be treated generally with a multimodal concept, which includes analgesia
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14 164 and sedation, fluid administration, lung-protective mechanical ventilation,
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16 165 anticoagulation, as well as hemodynamic, antibiotic and diagnostic management as
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18 166 recommended by guidelines, standard operating procedures or evidence based best
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20 167 practice. Additionally, after pseudonymization a large body of clinical and demographic
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22 168 data will be entered into a database for later analysis, including pre-existing morbidities,
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24 169 Simplified Acute Physiology Score II (SAPSII), Sepsis-related Organ Failure
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26 170 Assessment Score (SOFA), body mass index (BMI), necessity for renal replacement
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28 171 therapy, ventilator settings, PaO₂/FiO₂ ratio (Horowitz index), vital parameters,
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30 172 medications and dosage of vasoactive drugs and blood chemistry values.
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174 **Patient and public involvement**

40 175 Patients were not involved in the development of the research question, outcome
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42 176 measures or study design.
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178 **Sample size calculation**

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49 179 A total of 80 mechanically ventilated patients will be included in the study, with 40
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51 180 patients in the intervention group and 40 patients in the control group. With a total
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53 181 cohort size of n=80, a power of > 95% (alpha error p = 0.05, beta error < 0.05) will be
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55 182 reached, referring to the data about the salbutamol treatment effect from a reference
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57 183 work (table 1) by Malliotakis et al. ¹⁸, and according to our estimation of a clinically
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59 184 meaningful effect size. Calculations from these values indicate that 76 participants (38
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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 [cmH ₂ O/l/sec]	26.5±4.1 [cmH ₂ O/l/sec]
Mean _{30min} ± SD	15.5±3.6 [cmH ₂ O/l/sec]	23.1±3.6 [cmH ₂ O/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 work¹⁸; 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

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3 205 (30 mins), the installation and adjustment of EIT (30 mins), the optimization of ventilator
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5 206 settings (15 mins), drug nebulization and inhalation (15 mins), resetting ventilator
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7 207 settings to baseline and measurements 30 minutes after inhalation add up to a total
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9 208 duration of 2.5 hours (figure 1).
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14 210 **Randomization**
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16 211 Block-balanced randomization, in a 1:1 ratio, will be computer-generated by StatsDirect
17 212 (StatsDirect Ltd., Cambridge, United Kingdom) with random block sizes between $n = 10$
18 213 and $n = 20$, additionally using random permutations of treatments within each block.
19 214 Investigators will be blinded to the allocation according to the randomization list until the
20 215 study patient has been included.
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30 217 **Interventional procedure**

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32 218 EIT and control group undergo an arterial blood gas analysis and corresponding airway
33 219 measurements to determine baseline parameters before salbutamol inhalation (figure
34 220 1; Supplemental material 1+2). Therefore, 1.25 mg / 2.5 mL salbutamol (Sultanol®,
35 221 Glaxo Smith Kline plc., Brentford, United Kingdom) is applied with a vibrating mesh
36 222 nebulizer (Solo®, Aerogen, Galway, Ireland).
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46 224 In the control group, baseline measurement is followed by ultrasound nebulization and
47 225 inhalation with salbutamol for 15 minutes, following measurements and arterial blood
48 226 gas analysis 30 minutes after inhalation (figure 1). In addition, all study-relevant data
49 227 are documented pseudonymised in the case report form (CRF) to ensure a
50 228 standardized operating (Supplemental material 2). This CRF will be handed over to the
51 229 principal investigator immediately after collection of data. The principal investigator
52 230 keeps the study documents in a study folder not accessible to third parties.
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232 In the intervention group, baseline measurements are followed by the standardized
233 setup and adjustment of EIT, where a belt with 16 integrated electrodes is attached
234 circularly to the thorax (Supplemental material 3). This is followed by the optimization of
235 the respirator settings by means of EIT using a defined algorithm (figure 2), according
236 the recommendations of the Translational EIT Development Study Group (TREND)⁵.
237 The EIT algorithm focuses on homogenisation of lung ventilation described by the fast-
238 response parameter ROI (region of interest) to titrate protective PEEP and tidal volume
239 combinations (figure 2). The next step is nebulization and inhalation of salbutamol for
240 15 minutes. Subsequently, ventilator settings are reset to baseline as before EIT
241 adjustment. After a period of 30 minutes, a new data collection after salbutamol
242 administration including EIT measurement is done and an arterial blood gas analysis is
243 performed (figure 1). Data is documented in the CRF (Supplemental material 1).

244

245 Objectives

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

- 251 • Before and 30 minutes after salbutamol inhalation:
 - 252 ○ Changes made in ventilator settings under EIT,
 - 253 ○ tidal volume, compliance, resistance, arterial oxygen partial pressure
254 (p_aO_2), Horowitz index, arterial carbon dioxide partial pressure (p_aCO_2),
255 peripheral and arterial oxygen saturation,
 - 256 ○ upper and lower inflection point of the pressure-volume curve,

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3 257 ○ EIT parameters: Region of Interest (ROI), changes of end expiratory lung
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5 258 volume (Delta-EELV) and changes of end expiratory lung impedance
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7 (Delta-EELI),
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10 260 ○ heart rate, blood pressure
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12 261 • duration of mechanical ventilation,
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14 262 • length of stay on ICU and hospital, readmission rate on ICU.
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17 263 • 30-days mortality
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21 265 **Data collection**

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24 266 The documentation of the data will be pseudonymized and computer-assisted from our
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26 267 patient data management system (PDMS) (Dräger ICM, Dräger Medical, Lübeck,
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28 268 Germany) in a central offline database. Therefore, all collected data will solely be
29
30 269 provided in pseudonymized form for further study analyzation. Access to the
31
32 270 pseudonymization key, which is password protected, is only available to the principal
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34 271 investigator of this study. All above mentioned parameters will be collected during the
35
36 272 patients stay in hospital until discharge, death or 30th day of stay on ICU. In case of
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38 273 discharge from ICU, follow-up to evaluate 30-days survival will be performed by visit on
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40 274 normal ward or a phone call by one of the investigators. Data entered in the central
41
42 275 offline database will be monitored by an independent clinical research associate and
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44 276 checked for consistency and missing values. All records, subjects' identities and data
45
46 277 management will remain confidential with the General Data Protection Regulation
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48 278 (GDPR) of the European Parliament and the Council of the European Union.
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50 279 Furthermore, this protocol was designed following the recommendations for
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52 280 interventional trials (SPIRIT; figure 3; Supplemental material 4).
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283 **Statistical analysis**

284 Since this is a study designed to demonstrate superiority of the primary endpoint
285 (change in airway resistance 30 minutes after salbutamol inhalation), whether an
286 additional use of EIT increases the effectiveness of inhaled salbutamol, we will perform
287 an intention-to-treat and additionally a per-protocol analysis as recommended by the
288 CONSORT guidelines¹⁹. The per-protocol population will be defined as randomized
289 patients without major protocol deviations, such as non-considerations of exclusion
290 criteria or missing data for the primary endpoint. Baseline characteristics of all patients
291 will be described per group. Qualitative data will be described as frequencies and
292 percentages. Continuous variables are presented as means \pm standard deviation in
293 case of normal distribution and as median and interquartile range (25th; 75th
294 percentile) in case of non-normally distributed variables. Continuous variables will be
295 compared using parametric Student's t-test or non-parametric Mann-Whitney-U-Test.
296 Categorical variables will be characterized by numbers with percentages and will be
297 compared using the Chi-square test or a Fisher's exact test. Superiority will be
298 assumed, if the 95% confidence interval for the difference between the means excludes
299 zero or p-values are statistically significantly different at an a priori alpha error of less
300 than 0.05.

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

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305 **Ethics and dissemination**

306 A manuscript with the results of the study will be published in a peer-reviewed journal.

307 The study has received the following approvals: Ethics Committee of the Medical

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3 308 Faculty of Ruhr-University Bochum (17-6306). On completion of the trial, and after
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5 309 publication of the primary manuscript, data will be made available in a free accessible
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8 310 online repository.
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331 Discussion

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

335 The administration of inhaled drugs is routinely used in intensive care units, due to the
336 advantage of delivering high drug concentrations to the airway, along with rapid onset
337 of action and fewer systemic side effects. However, it is believed that the beneficial
338 effects of inhaled drugs are smaller in patients on mechanical ventilation than in those
339 breathing spontaneously. In this regard, a previous study could demonstrate that only
340 2.9% of the administered drug dose reached the distal airway in ventilated patients,
341 compared to 11.9% in patients without artificial airway ¹⁶. A recently published review,
342 regarding inhalative drug therapy in mechanical ventilation, stated that ventilator
343 settings play an crucial role in inhaled drug delivery ¹⁴. A tidal volume of at least 500
344 mL, increased inspiratory time and a low inspiratory flow are general recommendations
345 in order to optimize drug distribution in the lungs ^{14 20 21}. Nevertheless, attention should
346 be paid to serious adverse effects of high (> 500 mL) tidal volumes, especially in
347 patients with acute or chronic airway obstructions. In these patients high tidal volumes
348 can lead to dynamic hyperinflation or can cause a severe barotrauma ¹⁴. Furthermore,
349 no clinical studies exist showing the beneficial effects of any particular ventilation mode
350 on inhaled drug delivery ^{20 21}. Therefore, a new diagnostic and guiding tool for adequate
351 optimization of ventilator settings prior to nebulization of inhalative drugs would be
352 desirable. Hence, fast, non-invasive and reliable assessment at bedside in critical ill
353 and ventilated patients is one of the cornerstones for modern intensive care monitoring.
354 EIT, although with some constrains, may be a promising solution. EIT images are valid
355 measurements of the regional distribution of ventilation and changes in lung volume in
356 real-time. This dynamic evaluation makes EIT a promising tool for guided optimization

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3 357 of ventilator parameters on an individualized base. Several studies in the last years
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5 358 have already demonstrated that EIT-guided respirator optimization results in significant
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7 359 improved respiratory mechanics and improved gas exchange ^{1 4 7 22}. However, a global
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10 360 standard based on a broad base of evidence was one of the most discussed topics in
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12 361 Respiratory Medicine over the last years. Therefore, the plausibility of EIT
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14 362 measurements highly depends on the correct belt position, proper impedance
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16 363 visualization, correct analysis and data interpretation ²³.

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19 364 The crucial step forward was the publication of recommendations of the TREND
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21 365 (Translational EIT Development Study) group ⁵. These recommendations highlight the
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23 366 need for a consensus about examinations, consistent terminology and generally
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25 367 accepted approaches to EIT images and analysis. Based on this highly appreciated
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27 368 consensus statement we are now able to compare, understand and reproduce study
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29 369 findings from among different research groups and provide a standardized use in
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31 370 clinical routine.

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35 371 A further limitation is that EIT captures only ventral-to-dorsal ventilation distribution.
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37 372 However, Bikker et al. also reported different ventilation distribution between cranial
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39 373 and caudal lung levels during decremental PEEP trials ²⁴, concluding that existing EIT
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41 374 systems will not be able to cover the optimal PEEP titration for the whole lung.

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44 375 Despite the possible limitations of EIT, this device can provide a remarkable advance in
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46 376 the field of individualized and guided mechanical ventilation adjustments. Therefore,
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48 377 this study can shed light on the extent to which the additional use of EIT for optimizing
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50 378 the ventilator settings can increase the effectiveness of inhaled salbutamol.

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55 380 **Outlook**

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58 381 EIT could help to visualize and verify an effective nebulization that could provide a safe,
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60 382 efficient and individualized way of inhalative drug application, e.g. by increasing the

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3 383 effective dose reaching distal airway. Therefore, these results are also of great interest
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5 384 beyond salbutamol nebulization, e.g. for safe usage of inhalative antibiotics in critical ill
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8 385 and ventilated patients.
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12 387 ***Trial status***

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14 388 The first patients were randomized in June 2018. The inclusion of participants is
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17 389 ongoing and is expected to continue until June 2019.
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476 **List of abbreviations**

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6	ARDS	Acute respiratory distress syndrome
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8	BMI	Body mass index
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10	CRF	Case report form
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12	delta-EELI	Change of end expiratory lung impedance
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14	delta-EELV	Change of end expiratory lung volume
15		
16		
17	DRKS	Deutsches Register für klinische Studien
18		
19	ECMO	Extracorporeal membrane oxygenation
20		
21	EIT	Electrical impedance tomography
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23		
24	GDPR	General data protection regulation
25		
26	ICD	Implantable cardioverter defibrillator
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28	ICU	Intensive care unit
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31	NYHA	New York Heart Association
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33	p _a CO ₂	Partial pressure of arterial carbon dioxide
34		
35	p _a O ₂	Partial pressure of arterial oxygen
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37		
38	PDMS	Patient data management systems
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40	PEEP	Positive end-expiratory pressure
41		
42	R	Resistance
43		
44		
45	ROI	Region of interest
46		
47	SAPSII	Simplified acute physiology score II
48		
49	SD	Standard deviation
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51	SOFA score	Sepsis-related organ failure assessment score
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53	Spirit	Standard Protocol Items - Recommendations for Interventional
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56	TREND group	Translational EIT Development Study group
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3 478 **Declarations**
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8 480 **Ethics approval and consent to participate**
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10 481 This study was reviewed and approved by the Ethics Committee of the Medical Faculty
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12 482 of the Ruhr-Universität Bochum (no. 17-6306) and written informed consent or a
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14 483 positive vote of an independent consultant are eligible for inclusion.
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19 485 **Consent for publication**
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22 486 Not applicable
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26 488 **Availability of data and material**
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29 489 The data of the described study will be available from the Dryad repository after
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31 490 publication.
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35 492 **Conflict of interests**
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37
38 493 None to declare
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41
42 495 **Funding**
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44
45 496 We acknowledge support by the DFG Open Access Publication Funds of the Ruhr-
46
47 497 University Bochum (Ref. No. IN-1214264), just for financial support for publication
48
49 498 costs. This will have no impact on our study design or collection, analysis and
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51 499 interpretation of our data.
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56 501 **Author Statement**
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59 502 Dr. med. Tim Rahmel: Main author of this manuscript, written and revising the
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503 manuscript

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3 504 Alexandra Koniusch: Supporting methodical description and participated in the design
4
5 505 of this study
6
7 506 Dr. med. Günther Oprea: Supporting data collection, participated in the design of this
8
9 507 study, and revising the manuscript
10
11
12 508 Martin Schwertner: Supporting data collection, participated in the design of this study,
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16
17 510 Prof. Dr. med. Michael Adamzik: Supporting data collection, participated in the design
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19 511 of this study and revising the manuscript
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21 512 Dr. med. Hartmuth Nowak: Supporting data collection, participated in the design of this
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23 513 study, written and revising the manuscript
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25
26 514 All authors read and approved the final manuscript.
27
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29
30

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32
33 517 Not applicable
34
35
36
37

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530 **Legends**

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

534
535 **Figure 2:** Flowchart of EIT-guided optimization of ventilator settings (ROI = region of
536 interest, Pmax = maximum airway pressure, P_{insp} = inspiratory pressure, PEEP =
537 positive end expiratory pressure)

538
539 **Figure 3:** Schedule of enrolment, interventions and assessments – SPIRIT Figure
540 (SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials, EIT =
541 electrical impedance tomography, ICU = intensive care unit)

543 **Supplemental material**

544 **Supplemental material 1:** Case report form of intervention group

545 **Supplemental material 2:** Case report form of control group

546 **Supplemental material 3:** Additional information - EIT algorithm

547 **Supplemental material 4:** Spirit checklist

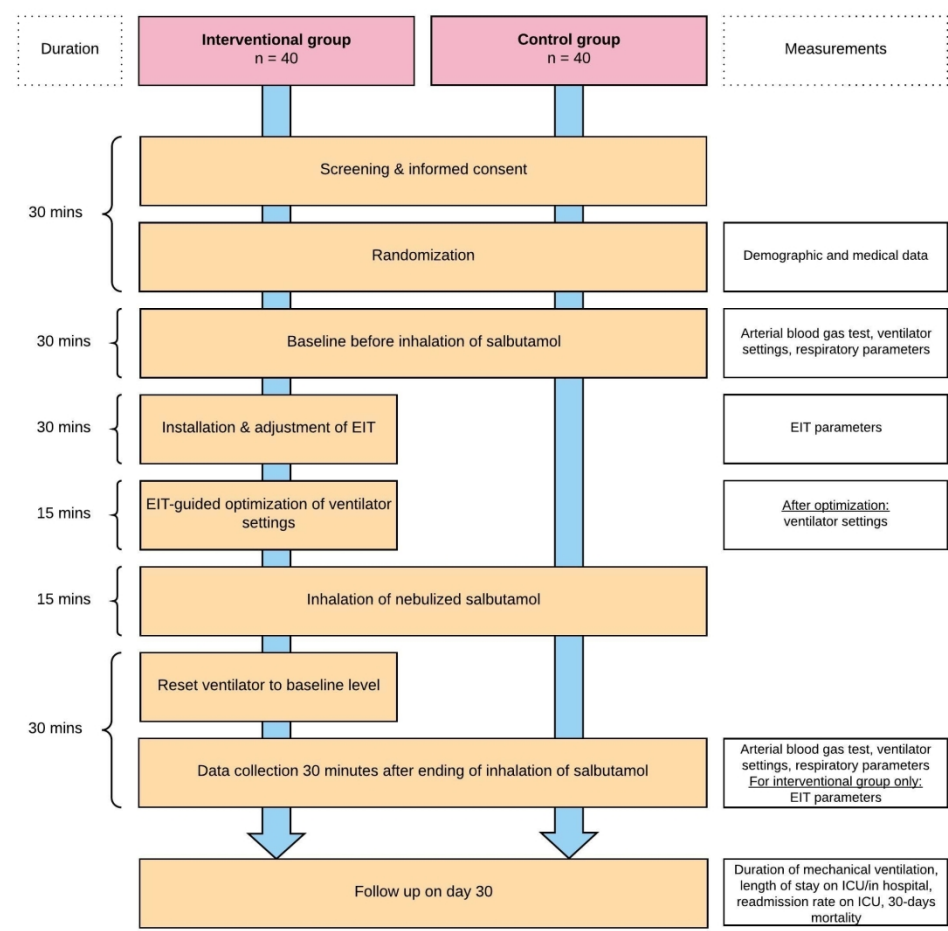


Figure 1: Flowchart of interventional procedures on intervention and control group with duration of each step and performed measurements (EIT = electrical impedance tomography, ICU = intensive care unit)

184x181mm (300 x 300 DPI)

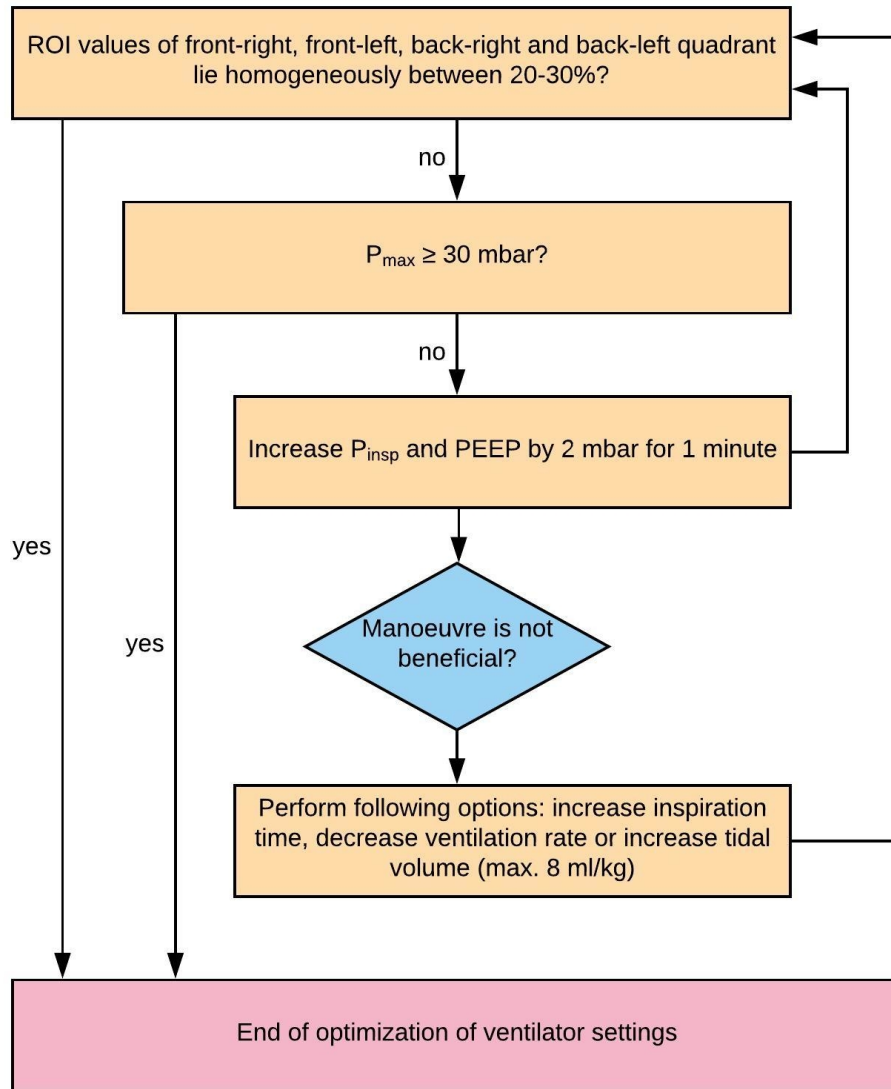


Figure 2: Flowchart of EIT-guided optimization of ventilator settings (ROI = region of interest, P_{max} = maximum airway pressure, P_{insp} = inspiratory pressure, PEEP = positive end expiratory pressure)

114x136mm (300 x 300 DPI)

TIMEPOINT	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
	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	<input type="checkbox"/>	<input type="checkbox"/>
• Known obstructive airway disease or acute airway obstruction and	<input type="checkbox"/>	<input type="checkbox"/>
• Medical indication for salbutamol inhalation		
• Mechanical ventilated patient (<48h) and Horowitz index (p_aO_2/F_iO_2) < 400	<input type="checkbox"/>	<input type="checkbox"/>
• Written informed consent or positive vote of an independent consultant	<input type="checkbox"/>	<input type="checkbox"/>

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	<input type="checkbox"/>	<input type="checkbox"/>
• Lack of medical indication and/or contraindications to administration of salbutamol	<input type="checkbox"/>	<input type="checkbox"/>
• Age < 18 years	<input type="checkbox"/>	<input type="checkbox"/>
• 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)	<input type="checkbox"/>	<input type="checkbox"/>
• Severe obesity (BMI > 35)	<input type="checkbox"/>	<input type="checkbox"/>
• Prior phase of long-term ventilation > 14 days	<input type="checkbox"/>	<input type="checkbox"/>
• Do-not-resuscitate order	<input type="checkbox"/>	<input type="checkbox"/>
• Pregnancy or lactation	<input type="checkbox"/>	<input type="checkbox"/>

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

male female

Height |_|_|_| cm **weight** |_|_|_|. |_| kg **BMI** |_|_|. |_| kg/m²

• **Blood pressure** |_|_|_| / |_|_| **heart rate** |_|_|_| bpm

body temperature |_|_|. |_| °C

• Pregnancy excluded

• Note participation in the medical record! carried out

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- **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 (paO₂) (____), Horowitz index (____), arterial carbon dioxide partial pressure (paCO₂) (____), 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-expiratory lung volume (Delta-EELV) (____) and changes of end-expiratory 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 (paO₂) (____), Horowitz index (____), arterial carbon dioxide partial pressure (paCO₂) (____), 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-expiratory lung volume (Delta-EELV) (____) and changes of end-expiratory 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	<input type="checkbox"/>	<input type="checkbox"/>
• Known obstructive airway disease or acute airway obstruction and	<input type="checkbox"/>	<input type="checkbox"/>
• Medical indication for salbutamol inhalation		
• Mechanical ventilated patient (<48h) and Horowitz index (p_aO_2/F_iO_2) < 400	<input type="checkbox"/>	<input type="checkbox"/>
• Written informed consent or positive vote of an independent consultant	<input type="checkbox"/>	<input type="checkbox"/>

Exclusion criteria	Yes	No
• Refusal of the patient or lack of consent	<input type="checkbox"/>	<input type="checkbox"/>
• Lack of medical indication and/or contraindications to administration of salbutamol	<input type="checkbox"/>	<input type="checkbox"/>
• Age < 18 years	<input type="checkbox"/>	<input type="checkbox"/>
• 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)	<input type="checkbox"/>	<input type="checkbox"/>
• Severe obesity (BMI > 35)	<input type="checkbox"/>	<input type="checkbox"/>
• Prior phase of long-term ventilation > 14 days	<input type="checkbox"/>	<input type="checkbox"/>
• Do-not-resuscitate order	<input type="checkbox"/>	<input type="checkbox"/>
• Pregnancy or lactation	<input type="checkbox"/>	<input type="checkbox"/>

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

male female

Height |_|_|_| cm **weight** |_|_|_|.|_| kg **BMI** |_|_|.|_| kg/m²

• **Blood pressure** |_|_|_| / |_|_| **heart rate** |_|_|_| bpm

body temperature |_|_|.|_| °C

• Pregnancy excluded

• Note participation in the medical record! carried out

1
2
3 • **Procedure in the control group**
4

- 5 ○ Study education including randomization (30 min)
- 6 ▪ Measurement of SOFA-Score (____), PCT (____), CRP (____), antibiotics
7 (____), vital parameters (____), catecholamines (____), sedation (____)
- 8
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- 10 ○ Data collection before inhalation (30 min)
- 11 ▪ Measurement of airway resistance before salbutamol inhalation (____)
- 12
- 13 ▪ Measurement of tidal volume (____), lung compliance (____), arterial oxygen
14 partial pressure (paO₂) (____), Horowitz index (____), arterial carbon dioxide
15 partial pressure (paCO₂) (____), peripheral oxygen saturation (____), arterial
16 oxygen saturation (____), upper (____) and lower (____) inflectionpoint of the
17 pressure-volume-curve
- 18
- 19
- 20 ▪ Arterial blood sampling
- 21
- 22 ○ Salbutamol nebulization and inhalation (15 min)
- 23
- 24 ○ Data collection after inhalation (30 min)
- 25 ▪ Measurement of airway resistance after salbutamol inhalation (____)
- 26
- 27 ▪ Measurement of tidal volume (____), lung compliance (____), arterial oxygen
28 partial pressure (paO₂) (____), Horowitz index (____), arterial carbon dioxide
29 partial pressure (paCO₂) (____), peripheral oxygen saturation (____), arterial
30 oxygen saturation (____), upper (____) and lower (____) inflectionpoint of the
31 pressure-volume-curve
- 32
- 33 ▪ Arterial blood sampling
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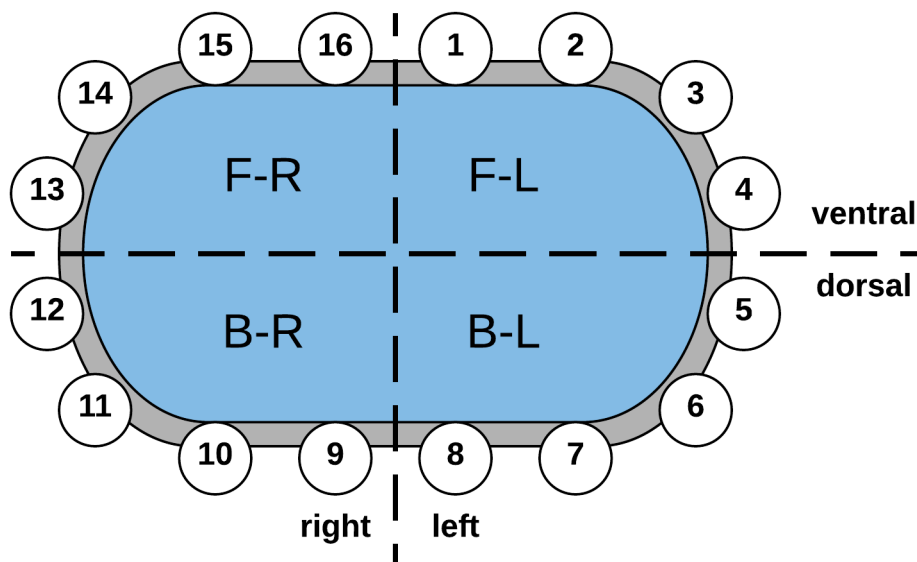
Date |__|__|. |__|__| 201__

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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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).	<input type="checkbox"/>
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.	<input type="checkbox"/>
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.	<input type="checkbox"/>

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.	<input type="checkbox"/>
2.	Delta-EELV (changes of end expiratory lung volume): Choose "Views" in right upper corner of the screen and tap on "End expiratory trend".	<input type="checkbox"/>
3.	Delta-EELI (changes of end expiratory lung impedance): Choose "Views" in right upper corner of the screen and tap on "Delta-EELI".	<input type="checkbox"/>



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 14 th May 2018 (page 6)
Protocol version	3	10 th 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)

- 1
2 Roles and 5a Dr. med. Tim Rahmel, Department of Anaesthesiology, Intensive Care
3 responsibilities and Pain Medicine, University Hospital Knappschaftskrankenhaus
4 Bochum, Bochum, Germany: Principal investigator, main author of
5 this manuscript, written and revising the manuscript
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7 Alexandra Koniusch, Department of Anaesthesiology, Intensive Care
8 and Pain Medicine, University Hospital Knappschaftskrankenhaus
9 Bochum, Bochum, Germany: Supporting methodical description and
10 participated in the design of this study
11
12 Dr. med. Günther Oprea, Department of Anaesthesiology, Intensive
13 Care and Pain Medicine, University Hospital
14 Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting
15 data collection, participated in the design of this study, and revising
16 the manuscript
17
18 Martin Schwertner, Department of Anaesthesiology, Intensive Care
19 and Pain Medicine, University Hospital Knappschaftskrankenhaus
20 Bochum, Bochum, Germany: Supporting data collection, participated
21 in the design of this study, and revising the manuscript
22
23 Prof. Dr. med. Michael Adamzik, Department of Anaesthesiology,
24 Intensive Care and Pain Medicine, University Hospital
25 Knappschaftskrankenhaus Bochum, Bochum, Germany: Supporting
26 data collection, participated in the design of this study and revising the
27 manuscript
28
29 Dr. med. Hartmuth Nowak, Department of Anaesthesiology, Intensive
30 Care and Pain Medicine, University Hospital
31 Knappschaftskrankenhaus Bochum, Bochum, Germany: Co-Principal
32 investigator, supporting data collection, participated in the design of
33 this study, written and revising the manuscript (**pages 19-20**)
34
35
36 5b NA
37
38 5c Support is granted by the DFG Open Access Publication Funds of the
39 Ruhr-University Bochum (Ref. No. IN-1214264), just for financial
40 support for publication costs. This will have no impact on our study
41 design or collection, analysis and interpretation of our data. (**page 19**)
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Introduction

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2 Background and 6a The inhalative administration of drugs is a non-invasive application
3 rationale form that is regularly used in the treatment of ventilated patients in
4 critical care setting. However, assessment of effectiveness or
5 distribution of nebulized drugs is one of the lacking cornerstones of
6 modern intensive care monitoring as several studies could not show a
7 benefit of inhaled medication. Unfortunately, these studies could not
8 address the crucial issue whether the medication was distributed
9 effectively in critical ill ventilated patients. To the present day, there is
10 no established non-invasive real-time monitoring to measure or
11 visualize the effectiveness or distribution of nebulized drugs in
12 ventilated patients at bedside. Electrical impedance tomography (EIT)
13 may provide a promising new monitoring and guiding tool for an
14 adequate optimization of mechanical ventilation in critically ill patients.
15 EIT makes use of changes in thoracic impedance, which in turn result
16 in different concentrations of free ions due to changes in air content of
17 the lung tissue. Therefore, EIT may assist in defining mechanical
18 ventilation settings, assess distribution of tidal volume and evaluation
19 of associated pathologies at bedside. Prior studies demonstrated that
20 equivalent diagnostic findings between EIT and thoracic computed
21 tomography could be achieved in critically ill patients in terms of
22 regional ventilation in different thoracic regions, and also offered a
23 valid examiner-independent test reproducibility of the results. **(pages**
24 **4-5)**

31 6b As no non-invasive real-time monitoring for visualization of nebulized
32 drugs in ventilated patients at bedside is established to the present
33 day, comparator will be standard of care with no EIT-optimized
34 application of salbutamol. **(pages 4-5)**

37 Objectives 7 Our study wants to elucidate the extent to which the effectiveness of
38 inhaled drugs, e.g. β 2 sympathomimetics, can be optimized by the
39 additional use of EIT for adjusting ventilator settings. Accordingly, we
40 want to test the hypothesis whether EIT can increase the
41 effectiveness of inhaled salbutamol. **(page 5)**

44 Trial design 8 This study is a randomized, open-label superiority trial, comparing two
45 groups of mechanically ventilated patients with an acute or chronic
46 bronchial airway obstruction according the effectiveness of inhaled
47 salbutamol with (intervention) or without (control) additional use of EIT
48 for optimizing the ventilator settings. **(page 6)**

52 **Methods: Participants, interventions, and outcomes**

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

1
2 Eligibility criteria 10 Patients at the age of 18 years or more, diagnosed with an acute
3 airway obstruction or known chronic obstructive pulmonary disease
4 under mechanical ventilation for less than 48 hours and providing
5 written informed consent or a positive vote of an independent
6 consultant are eligible for inclusion. **(page 6)**
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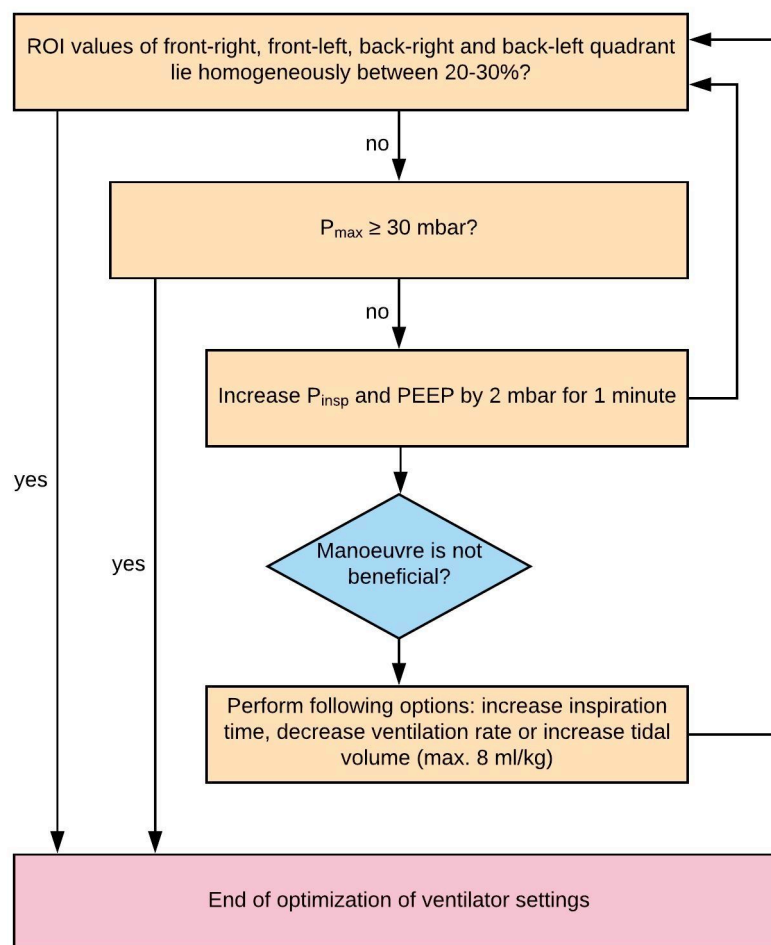
8
9 Exclusion criteria are: pregnancy or lactation, severe obesity (body
10 mass index > 35), missing medical indication and/or contraindication
11 for inhaled salbutamol administration, Horowitz index ≥ 400 , prior
12 phase of long-term ventilation > 14 days, a study-independent medical
13 indication for salbutamol nebulization in obstructive pulmonary
14 disease and/or an acute obstructive condition and procedure of
15 withdrawing life-sustaining therapy. Furthermore, patients with the
16 following pre-existing conditions and operations will be excluded:
17 patients with chest trauma or surgery (e.g. pneumectomy),
18 pneumonia, ARDS with or without ECMO therapy, neuromuscular
19 diseases, severe cardiac diseases (e.g. NYHA III-IV), acute ischemic
20 events, active implants (e.g. pacemakers, ICD) or thoracic skin lesions
21 and wound dressings. **(page 6-7)**
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2 Interventions 11a EIT and control group undergo an arterial blood gas analysis and
3 corresponding airway measurements to determine baseline
4 parameters before salbutamol inhalation. Therefore, 1.25 mg / 2.5 mL
5 salbutamol (Sultanol®, Glaxo Smith Kline plc., Brentford, United
6 Kingdom) is applied with a vibrating mesh nebulizer (Solo®, Aerogen,
7 Galway, Ireland). **(page 9)**
8
9

10
11 In the control group, baseline measurement is followed by ultrasound
12 nebulization and inhalation with salbutamol for 15 minutes, following
13 measurements and arterial blood gas analysis 30 minutes after
14 inhalation. In addition, all study-relevant data are documented
15 pseudonymised in the case report form (CRF) to ensure a
16 standardized operating. This CRF will be handed over to the principal
17 investigator immediately after collection of data. The principal
18 investigator keeps the study documents in a study folder not
19 accessible to third parties. **(page 9)**
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23 In the intervention group, baseline measurements are followed by the
24 standardized setup and adjustment of EIT, where a belt with 16
25 integrated electrodes is attached circularly to the thorax. This is
26 followed by the optimization of the respirator settings by means of EIT
27 using a defined algorithm, according the recommendations of the
28 Translational EIT Development Study Group (TREND) (see below,
29 figure 2). The EIT algorithm focuses on homogenisation of lung
30 ventilation described by the fast-response parameter ROI (region of
31 interest) to titrate protective PEEP and tidal volume combinations. The
32 next step is nebulization and inhalation of salbutamol for 15 minutes.
33 Subsequently, ventilator settings are reset to baseline as before EIT
34 adjustment. After a period of 30 minutes, a new data collection after
35 salbutamol administration including EIT measurement is done and an
36 arterial blood gas analysis is performed (figure 1). Data is documented
37 in the CRF. **(page 9-10)**
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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

1
2 Outcomes 12 The primary objective is to assess if additional use of EIT can
3 increase the effectiveness of inhaled salbutamol, and therefore
4 decrease the airway resistance 30 minutes after salbutamol inhalation
5 more effective than without usage of EIT. **(page 10)**
6
7

8 The secondary objectives will be to compare the EIT-intervention
9 group and the control group regarding: Before and 30 minutes after
10 salbutamol inhalation [Changes made in ventilator settings under EIT,
11 tidal volume, compliance, resistance, arterial oxygen partial pressure
12 (paO₂), Horowitz index, arterial carbon dioxide partial pressure
13 (paCO₂), peripheral and arterial oxygen saturation, upper and lower
14 inflection point of the pressure-volume curve, EIT parameters: Region
15 of Interest (ROI), changes of end expiratory lung volume (Delta-EELV)
16 and changes of end expiratory lung impedance (Delta-EELI), heart
17 rate, blood pressure]; duration of mechanical ventilation; length of stay
18 on ICU and hospital, readmission rate on ICU; 30-days mortality.
19 **(pages 10-11)**
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24 Additionally, after pseudonymization a large body of clinical and
25 demographic data will be entered into a database for later analysis,
26 including pre-existing morbidities, Simplified Acute Physiology Score II
27 (SAPSII), Sepsis-related Organ Failure Assessment Score (SOFA),
28 body mass index (BMI), necessity for renal replacement therapy,
29 ventilator settings, PaO₂/FiO₂ ratio (Horowitz index), vital parameters,
30 medications and dosage of vasoactive drugs and blood chemistry
31 values. **(page 7)**
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Participant
timeline

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

TIMEPOINT	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close out
	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 (<i>for EIT group only</i>)			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//sec]	26.5±4.1 [cmH2O//sec]
Mean _{30min} ± SD	15.5±3.6 [cmH2O//sec]	23.1±3.6 [cmH2O//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//s), respectively

Recruitment 15 We will ensure patient recruitment by screening patients on ICU daily. Eligible patients will be approached by the principal investigator 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.

1
2 Implementation 16c A physician who is independent to this trial will generate allocation
3 sequence. Enrolment and assignment will be done by the principal
4 investigator and/or eligible physicians.
5

6 Blinding 17a No blinding will be performed.
7 (masking)

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9 17b NA
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11 **Methods: Data collection, management, and analysis**

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13 Data collection 18a The documentation of the data will be pseudonymized and computer-
14 methods assisted from our patient data management system (PDMS) (Dräger
15 ICM, Dräger Medical, Lübeck, Germany) in a central offline database.
16 **(page 11)**
17

18
19 18b All above mentioned parameters will be collected during the patients
20 stay in hospital until discharge, death or 30th day of stay on ICU. In
21 case of discharge from ICU, follow-up to evaluate 30-days survival will
22 be performed by visit on normal ward or a phone call by one of the
23 investigators. **(page 11)**
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26 Data 19 All collected data will solely be provided in pseudonymized form for
27 management further study analyzation. Access to the pseudonymization key, which
28 is password protected, is only available to the principal investigator of
29 this study. **(page 11)**
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Review only

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- 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 \pm 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

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- 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

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- 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)**

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2	Protocol	25	Principal investigator will communicate all important modifications to
3	amendments		study personnel.
4			
5	Consent or assent	26a	Informed consent will be obtained by principal investigator and/or
6			eligible physicians.
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8		26b	NA
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10	Confidentiality	27	All records, subjects' identities and data management will remain
11			confidential with the General Data Protection Regulation (GDPR) of
12			the European Parliament and the Council of the European Union.
13			(page 11)
14			
15	Declaration	of 28	None to declare (page 19)
16	interests		
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18			
19	Access to data	29	The data of the described study will be available from the Dryad
20			repository after publication. (page 19)
21			
22	Ancillary	and 30	No arrangements have been made for compensation to those who
23	post-trial care		suffer harm from trial participation. This has been stated in the
24			informed consent.
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27	Dissemination	31a	A manuscript with the results of the study will be published in a peer-
28	policy		reviewed journal. (page 12)
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30		31b	NA
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32		31c	A publication of this study protocol in BMJ Open is submitted.
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34	Appendices		
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36	Informed consent	32	An informed consent form is available in German language can be
37	materials		obtained from the authors.
38			
39	Biological	33	NA
40	specimens		
41			

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.