Individualized PEEP titration guided by intratidal compliance profile analysis improves regional ventilation – a randomized controlled trial

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Abstract

Background Application of positive end-expiratory pressure (PEEP) improves lung aeration and reduces mechanical stress during mechanical ventilation. Although numerous approaches for PEEP titration have been proposed, there is no accepted strategy to titrate optimal PEEP. By analyzing the intratidal compliance profiles, PEEP may be titrated patient-individually. Methods After obtaining informed consent, we measured respiratory system mechanics and regional ventilation in 60 consecutive patients undergoing elective surgery, randomly allocated to the control group (PEEP = 5 cmH 2 O) or the intervention group receiving individually titrated PEEP, guided by intratidal compliance profile analysis. Primary endpoint was the nonlinear intratidal compliance. We further investigated respiratory and hemodynamic variables, regional ventilation and compliance profiles. Results Compliance was comparable between control [63.2 (14.0) mL·cmH 2 O -1] and intervention group [67.8 (15.9) mL·cmH 2 O -1 , p = 0.271]. Besides PEEP [control: 5.0 (0.0), intervention: 5.8 (1.1) cmH 2 O] respiratory and hemodynamic variables were comparable between the two groups. The compliance profile analysis showed no significant differences between the two groups. Relative thoracic electrical impedance was better maintained in the intervention group (89.3 (19.4) %) than in the control group (78.3 (23.6) %, p < 0.001). No significant differences in dorsal to ventral ventilation distribution was found between the two groups. Conclusions Individualized PEEP titration according to bedside compliance profile analysis improves regional ventilation without affecting respiratory and hemodynamic variables negatively and may be a promising approach to patient-individual ventilation setting.

Background

During mechanical ventilation, it is widely accepted that the application of low tidal volume and low driving pressure [i.e. the difference between plateau pressure (P_{Plat}) and (positive) end-expiratory pressure (PEEP)] protect the lung from destructive effects of alveolar overdistension [1–4].

In combination with low tidal volumes, application of adequate PEEP and the performance of recruitment maneuvers was shown to improve postoperative pulmonary function, arterial oxygenation and to reduce health care utilization [2, 5]. Many techniques were developed to determine adequate PEEP [6–9]. One of these techniques, first described in 1979 for patients with severe lung injury [10], is based on setting the PEEP slightly above the lower inflection point of the inspiratory limb of the static pressure-volume (PV) curve [6, 11, 12]. Other techniques focus on the respiratory system compliance (C_{RS}). For example, PEEP can be titrated to reach the maximum quasi-static compliance, calculated by dividing V_T by the driving pressure [9, 13, 14]. However, a single value compliance cannot reflect the non-linearity of intratidal respiratory system mechanics during the breathing cycle [15, 16] and therefore always a maneuver is required to identify the PEEP for maximal compliance. To cope with the non-linearity of the intratidal C_{RS} under the dynamic conditions of mechanical ventilation, the gliding-SLICE method [17, 18] was introduced, enhancing the classical SLICE method [19, 20]. In brief, the pressure-volume curve is subdivided in several volume steps and the volume dependent compliance is calculated on the base of data points within a certain volume range ('slice') around the current step via multiple linear regression analysis (Fig. 1). The resulting compliance-volume curve can then be classified as follows: An increasing compliance profile is interpreted to indicate intratidal recruitment/de-recruitment, suggesting an increase of PEEP. A decreasing compliance profile indicates overdistension, suggesting a decrease of PEEP. A horizontal compliance profile is assumed preferable as it does not indicate either of both unwished conditions. According to these three basic compliance profiles, combinations may be observed [18] (Fig. 1). A previously described Decision Support System with a Graphical User Interface (GUI) implements the gliding-SLICE method into a user-friendly tool to recommend a bedside patient-individual PEEP titration during mandatory ventilation [21]. Using exemplary data from patients ventilated in the volume- and pressure-controlled mode, a theoretical study demonstrated that the Decision Support System allows to estimate the intratidal compliance-profiles and that the recommended PEEP adjustments directed to ventilation with horizontal compliance profiles [21].

We hypothesized that individualized PEEP titration based on the analysis of the intratidal compliance profile improves respiratory system mechanics and regional ventilation during perioperative mandatory ventilation. Therefore we determined dynamic C_{RS}, frequency of compliance profiles, regional ventilation, and respiratory and hemodynamic variables in 60 mandatory ventilated consecutive patients undergoing otorhinolaryngeal surgery.

Methods

Ethics, consent and permission

The study was approved by the Ethics Committee of the University Medical Centre of Freiburg (vote # 268/15) on 29th June 2015 and registered at the German Register for Clinical Trials (DRKS00008924). This study adheres to CONSORT guidelines.

Study design and patient population

After obtaining written informed consent from all individual participants included in the study, we studied respiratory mechanics, hemodynamic variables and regional ventilation in 60 consecutive patients with American Society of Anesthesiologists (ASA) physical status I-III, undergoing otorhinolaryngeal surgery at the Medical Center of the University of Freiburg, Germany. The study was performed as a prospective parallel arm, randomized, controlled trial with an allocation ratio of 1:1. Randomization was carried out in blocks of 30 by a computer generated allocation sequence. Participiants were enrolled and assigned to the interventions by a study related anesthetist. Exclusion criteria were ASA physical status > III, age < 18 years, pregnancy, emergency procedure, cardiac pacemaker and other active implants, obesity (BMI ≥ 30 $kg \cdot m^{-2}$) history of pulmonary disease, laparoscopic surgery or refusal of participation.

Procedure

After primary recruitment and preoperative evaluation, the patients received routine monitoring (electrocardiography, SpO_2, noninvasive blood pressure measurement; Infinity Delta XL, Dräger Medical, Lübeck, Germany). After preoxygenation to an expiratory fraction of oxygen of 0.8, anesthesia was induced and maintained as total intravenous anesthesia with a continuous infusion of propofol (Propofol 1%, Fresenius Kabi, Bad Homburg, Germany; target controlled infusion, effect site target concentration for induction: 6-8 $\mu g \cdot mL^{-1}$, target concentration for maintenance: 3-5 $\mu g \cdot mL^{-1}$, Agilia, Schnider Model; Fresenius Kabi) and remifentanil (TEVA GmbH, Ulm, Germany; induction: 1-2 $\mu g \cdot kg^{-1}$, maintenance: 0.15-0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Tracheal intubation was facilitated with 0.15 $mg \cdot kg^{-1}$ predicted body weight (PBW) [22] cisatracurium (Fresenius Kabi). Potential hypotension (defined as mean arterial pressure < 65 mmHg) was treated with a continuous infusion of norepinephrine (0.03-0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). For tracheal intubation, we used tracheal tubes with low pressure cuffs (internal diameter of 7.0-7.5 mm for women and 8.0 mm for men; Mallinckrodt Hallo-Contour; Covidien, Neustadt an der Donau, Germany). All patients were ventilated in the volume-controlled mode with a tidal volume (V_T) of 7 $mL \cdot kg^{-1}$ PBW. Ventilation frequency was set to maintain an end-tidal carbon dioxide partial pressure between 35 and 40 mmHg. The initial PEEP was set to 5 cmH_2O, according to our local standard. Following baseline measurements, the randomization was disclosed. In the control group, this PEEP was maintained for the whole procedure, in the intervention group, the PEEP was adjusted dynamically according to the recommendations resulting from the intratidal compliance profile analysis (see below).

Gliding-SLICE

For intratidal compliance analysis via the gliding-SLICE method, we chose a number of 21 equidistant slices as a tradeoff between calculation effort and reasonable resolution. The resulting intratidal compliance curves were classified into six different compliance profiles, as described earlier [20, 23, 24]. In brief, a second order polynomial was fit into the compliance-volume curve, and the resulting segment of a parabola was assumed to represent the compliance-volume curve in a filtered form. If the segment showed an increase of more than 20% of the compliance maximum, the profile was classified as containing an increasing part. A segment decreasing by more than 20% of the compliance maximum was classified as containing a decreasing part. A segment containing the angular point of the parabola was classified as containing the horizontal part. A compliance profile with less than 20% change was classified as horizontal (Fig. 1) [21, 25]. The Decision Support Systems suggested a PEEP increase of 2 cmH_2O in case of a merely increasing compliance profile, 1 cmH_2O in case of an increasing compliance profile with horizontal component, a PEEP decrease of 2 cmH_2O in case of a merely decreasing compliance profile and 1 cmH_2O in case of a decreasing compliance profile with horizontal component. A merely horizontal compliance profile resulted in the suggestion to maintain PEEP as it is.

Electrical impedance tomography

Regional ventilation was measured via electrical impedance tomography (EIT, PulmoVista 500, Dräger Medical) every 10 minutes for a duration of 2 minutes. EIT recordings were offline evaluated using software developed in Matlab (MATLAB R2014a, The Mathworks Inc., Natick, MA, USA). As a first step, the relevant lung areas were determined for each patient by applying the lung area estimation method [26, 27] to the raw EIT data. Subsequently, the obtained lung area was then applied to all recorded raw EIT frames. After this preprocessing, functional impedance images were generated. This was done by subtracting the frames corresponding to the start of inspiration from the frames corresponding to the end of inspiration. Thus, these functional images represent the distribution of the tidal volume for each breath. The images were divided into ventral and dorsal parts to generate a representation of the tidal variation in these regions of interest [28]. Then, mean electrical impedance (EI_{Th}) was calculated for each EIT measurement and normalized to baseline measurements. Further, we compared the distribution of impedance for equal large ventral and dorsal lung area.

End points and data collection

The intratidal nonlinear compliance was the primary endpoint of this study. Secondary endpoints were frequencies of compliance profiles, mean thoracic electrical impedance (EI_{Th}) the ventilation distribution (separated into ventral and dorsal lung areas), the respiratory system variables [peak inspiratory pressure (PIP), P_{Plat}, mean tracheal pressure (P_{mean}), PEEP] and hemodynamic variables [systolic blood pressure (BP_{sys}), diastolic blood pressure (BP_{dias}), heart rate and mean arterial pressure (MAP)].

Sample size calculation and statistical evaluation

In regard to the trial design (unpaired test conditions) and an assumed standardized effect size of the primary endpoint of 0.8, 50 patients were required to reach a test power of 0.8 with a desired level of significance of 0.05. To compensate for potential incomplete data sets, a total of 60 patients were recruited.

Data are presented as mean (SD). Differences between the two groups were assessed with unpaired Students t-test, respectively. Statistical significance was considered for $p < 0.05$. Preceding, Shapiro-Wilk tests were used to confirm that the assumed normal distribution cannot be rejected. For not normally distributed data, differences between the two groups were assessed with Mann-Whitney U tests.

Results

Patients were recruited from November, 5th 2015 to January, 29th 2016. In total, 60 patients were included. 12 patients had to be excluded due to incomplete data sets (Fig. 2). During the study protocol, no adverse or serious events occurred. Age, gender, ASA physical status, PBW, actual body weight (ABW) and BMI were comparable between the two groups (Table 1).

PEEP was higher in the intervention group compared to the control group [control: 5.0 (0.2) cmH_2O, intervention: 5.8 (1.1) cmH_2O, $p < 0.001$; range control: 5.0-5.0 cmH_2O, range intervention: 3.9-8.5 cmH_2O]. In total, a PEEP adaption was performed in 12 patients in the intervention group. These individualized PEEP titrations according to the gliding-SLICE method had no significant effect on the other measured respiratory system or hemodynamic variables (Table 2). The frequencies of the compliance profiles showed no significant difference between the two groups (Table 3).

During the course of ventilation, EI_{Th} decreased more in the control group than in the intervention group [difference in EI_{Th} between baseline measurements and intervention period for control group: 78.3 (23.6) % and intervention group: 89.3 (19.4) %, $p < 0.001$] (Fig. 3). No significant difference in impedance distribution was found between the two groups (Fig. 4).

Discussion

In this study, we compared the effects of an individualized PEEP titration according to bedside analysis of the intratidal profile of the dynamic C_{RS}. The main findings are that only small PEEP adaptations are required to transfer increasing to horizontal compliance profiles and that the individualized PEEP titration improved regional ventilation without affecting impedance distribution and respiratory or hemodynamic variables negatively.

Respiratory and hemodynamic variables

Besides PEEP, none of the respiratory and hemodynamic variables differed between the two investigated patient groups. PEEP is generally associated with recruitment and one might expect that C_{RS} increases with increasing PEEP. However, in agreement with earlier studies [15, 29] C_{RS} remained unchanged besides PEEP related changes in regional ventilation. Compared to lungs with severe lung-injury and impaired respiratory system mechanics, healthy lungs are in a well recruited state, thus compliance may barely depend on lung volume. In particular, in our study, patients showed respiratory system mechanics that were mostly characterized by a horizontal compliance profile and consequently PEEP adaptations were performed less frequent than we had expected. It follows that the observed improvement in regional ventilation may have increased C_{RS}, if the studied patient collective would have included more patients with impaired respiratory system mechanics and/or surgical procedures associated with an increased risk for alterations of respiratory functions (e.g. laparoscopic surgery, patient positioning, obesity). Since this is the first study in which we applied individualized PEEP titration according to the compliance profile analysis, we did not include patients at risk for impaired respiratory system performance. One might speculate further that the comparably high alveolar recruitment in the studied patients was the reason that we did not find significant differences in C_{RS}.

By increasing the intrathoracic pressure, PEEP was shown to affect the cardiac performance by altering the left ventricular preload, afterload and cardiac contractility [30]. Previous studies found that in case of increasing intratidal compliance profiles, a small increase in PEEP directed to ventilation with horizontal compliance [15, 29]. Since the overall increase of PEEP in our intervention group was comparably low, it is not surprising that our individualized PEEP titration had no effect on the measured hemodynamic variables. With regard to the unaffected respiratory and hemodynamic variables, it is even more remarkable that our ventilation strategy improved regional ventilation, anyway.

Regional ventilation

Even in patients without impaired respiratory function, induction of general anesthesia and consecutive mechanical ventilation bear the risk for atelectrauma [31]. Studies that focus on perioperative lung-protective ventilation strategies in patients without severe lung-injury showed that the rate of postoperative pulmonary complications was lower when the ventilation strategy included low tidal volume, high PEEP and repetitive recruitment maneuvers [2, 5]. The application of low PEEP levels was shown to promote tidal small airway closure and consecutive atelectasis [32]. As a non-invasive, radiation-free method, EIT can be used to monitor regional ventilation and the formation of atelectasis [33]. In contrast to other studies that showed that the EIT can be used to titrate PEEP individually [34, 35], we used the EIT as an external measurement and could demonstrate that an individualized PEEP titration guided by the intratidal compliance profile analysis improved lung ventilation. Our PEEP titration strategy is based on analyses of the intratidal compliance profiles utilizing only data which are available from standard monitoring. In contrast, previously described techniques for titrating PEEP (decremental PEEP trial [36], dead space fraction [37], indices of regional ventilation [34, 35, 38], esophageal pressure [39] or other imaging techniques [40]) require additional equipment, involve additional burden for the patient or may *per se* not be available at the bedside. The techniques based on the determination of best PEEP from static respiratory system variables, such as the static PV curve, did not contribute to the dynamic intratidal changes in respiratory system mechanics [41], required sedation and often muscle relaxation [6]. Moreover they required a prolonged maneuver during which the patient is not sufficiently ventilated. During a decremental PEEP trial, adequate ventilation is warranted however, to identify the PEEP for maximum C_{RS}, the optimal PEEP must necessarily be exceeded during the maneuver. Thus, both PEEP titration methods bear the risk for overdistension and cannot be applied continuously. By contrast, PEEP titration based on the intratidal compliance profile does not require a maneuver, may be applied on a breath by breath analysis and is applicable for consecutive PEEP adjustment.

Limitations

We did not perform invasive blood pressure measurement to evaluate hemodynamic performances with a higher temporal resolution and arterial blood gas analyses. Placing an arterial line is not part of our standard treatment in the patients conducted in the present study. We felt that the risks of an arterial line placement would not outweigh the potential benefits of such measurement. Since the intention of our study was to investigate the impact of comparable new patient-individual PEEP titration strategy in non-injured respiratory system, we did not include patients at high risk to the formation of atelectasis. Thus, further studies are required to investigate the potential impact of PEEP titration based on bedside analysis of non-linear intratidal compliance on the respiratory system mechanics in patients prone to an impaired respiratory function.

Conclusions

This is the first study to investigate regional ventilation during PEEP titration guided by intratidal compliance profile analysis in patients. The bedside analysis of non-linear intratidal mechanics of the respiratory system using the gliding-SLICE method improved regional ventilation without affecting respiratory system or hemodynamic variables negatively. It follows that this study may be considered as an impulse for bedside intratidal compliance profile analysis as part of lung-protective ventilation strategies in perioperatively ventilated patients.

Abbreviations

ABW, actual body weight

ASA, American Society of Anesthesiologists

BMI, body mass index

C_{RS}, compliance of the respiratory system

C_{stat}, quasi-static compliance of the respiratory system

EIT, electrical impedance tomography

EI_{Th}, mean thoracic electrical impedance

FeO_2, expiratory oxygen concentration

FiO_2, inspiratory oxygen concentration

I:E, ratio of inspiratory time to expiratory time

MAP, mean arterial pressure

PBW, predicted body weight

PEEP, positive end-expiratory pressure

PIP, peak inspiratory pressure

P_{mean}, mean airway pressure

P_{Plat}, plateau pressure

BP_{dias}, diastolic blood pressure

BP_{sys}, systolic blood pressure

SpO_2, peripheral oxygen saturation (pulse oximetry)

VF, ventilation frequency

V_T, tidal volume

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the University Medical Centre of Freiburg (Engelbergstr. 21, 79106 Freiburg, Germany, Ethical Committee N° 268/15) on 29th June 2015 (Chairperson Prof. Dr. R. Korinthenberg). Written informed consent was obtained from all participants.

Consent for publication

Not applicable

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on request. Please note that EIT data files require large memory. A separate data transfer service will be used to transfer EIT data files.

Competing interests

J.W., J.G., J.S., S. L.-Z., S. B. and S.W declare no conflicts of interest. S.S. has a consulting contract with Gründler GmbH, Freudenstadt (no relationship to this study).

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Author's contributions

Planning the study: S. S., S. W.

Conduction of the study: J. G., S. W.

Data analysis: J. W., S. L.-Z., S. B., S. S., S. W.

Drafting the article: J.W., J. S., S. S., S. W.

Revising the article for important intellectual content: All authors.

All authors have read and approved the manuscript.

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Tables

Table 1: Patients characteristics (n = 48).

Parameter	Control (n = 23)	Intervention (n = 25)
Age (yr)	50.1 (17.0)	45.0 (16.0)
Gender (n), female/male	12/11	6/21
ASA I/II/III (n)	10/12/1	8/17/0
PBW (kg)	47.4 (2.6)	48.3 (2.6)
ABW (kg)	73.7 (13.7)	79.6 (14.5)
BMI ($kg \cdot m^{-2}$)	24.5 (3.3)	26.5 (5.2)

ASA, physical status according to the American Association of Anesthesiologists; PBW, predicted body weight; ABW, actual body weight; BMI, body mass index.

Table 2: Respiratory and hemodynamic variables.

Variable	Control (*n = 23*)	Intervention (*n = 25*)	p-value
V_T (mL)	541.9 (71.9)	552.6 (61.9)	0.565
V_T PBW ($mL \cdot kg^{-1}$)	7.4 (0.9)	7.1 (0.9)	0.300
VF ($\cdot min^{-1}$)	11.8 (1.3)	11.7 (1.7)	0.843
PIP (cmH_2O)	16.6 (2.7)	17.1 (3.1)	0.722
P_{Plat} (cmH_2O)	14.0 (2.3)	14.3 (2.4)	0.656
P_{mean} (cmH_2O)	8.6 (0.9)	8.3 (0.9)	0.400
PEEP (cmH_2O)	5.0 (0.0)	5.8 (1.1)	< 0.001
ΔP (cmH_2O)	8.9 (2.3)	8.5 (2.0)	0.695
C_{RS} ($mL \cdot cmH_2O^{-1}$)	63.2 (14.0)	67.8 (15.9)	0.508
FiO_2	60.6 (1.6)	60.4 (1.5)	0.802
SpO_2	99.1 (0.8)	98.8 (0.9)	0.177
$PetCO_2$ (mmHg)	37.4 (1.5)	38.9 (4.6)	0.296
Heart rate ($\cdot min^{-1}$)	54.9 (7.8)	55.4 (9.0)	0.796
BP_{sys} (mmHg)	101.1 (10.2)	100.4 (11.6)	0.236
BP_{dias} (mmHg)	62.8 (12.5)	61.7 (12.3)	0.667
MAP (mmHg)	75.6 (11.0)	74.6 (11.1)	0.296
Duration of anesthesia (min)	83.2 (33.3)	87.5 (28.7)	0.378

V_T, tidal volume; V_T PBW, tidal volume per predicted body weight; VF, ventilation frequency; PIP, peak inspiratory pressure; P_{Plat}, plateau pressure; P_{mean}, mean airway pressure; PEEP, positive end-expiratory pressure; ΔP, driving pressure; C_{RS}, respiratory system compliance; FiO_2, fraction of inspired oxygen; SpO_2, peripheral oxygen saturation; $PetCO_2$, end-tidal carbon dioxide partial pressure; BP_{sys}, systolic blood pressure; BP_{dias}, diastolic blood pressure; MAP, mean arterial pressure.

Table 3: Frequencies of compliance profiles.

Compliance profile	Control (*n = 23*)	Intervention (*n = 25*)	p-value
Horizontal (min)	70.9 (32.3)	86.0 (28.7)	0.117
Increasing (min)	6.0 (14.4)	5.5 (3.6)	0.948
Decreasing (min)	0.0	0.0	1.000
Mixed (min)	0.0	0.0	1.000

Increasing compliance profile = increasing + increasing-horizontal compliance profile, decreasing compliance profile = decreasing + decreasing-horizontal compliance profile. Differences between the two groups were assessed with Mann-Whitney U tests.

Figures

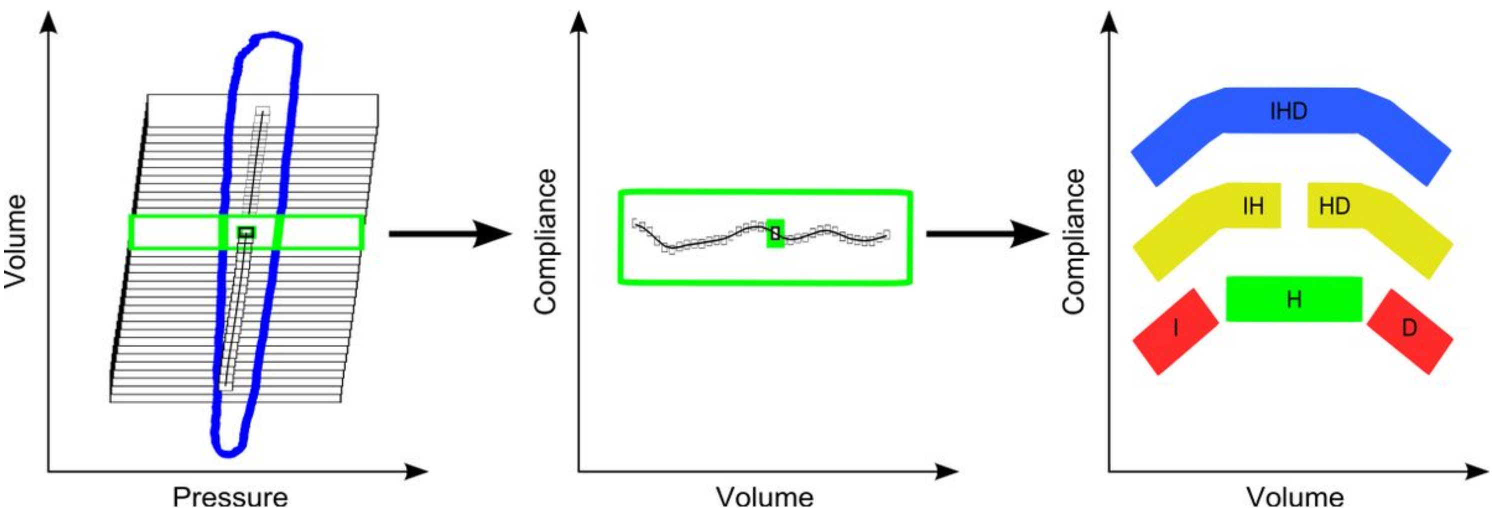

Figure 1

Intratidal compliance profile analysis during a single breathing cycle according to the gliding-SLICE method[24]. The tidal pressure-volume curve is divided into 21 equidistant slices. For each slice, the compliance profile is determined based on multiple linear regression analysis and matched to the respective tidal volume. The resulting intratidal compliance curves were classified into six different compliance profiles (H = horizontal compliance profile, I/IH = increasing compliance profile, D/HD = decreasing compliance profile, IHD = mixed compliance profiles).

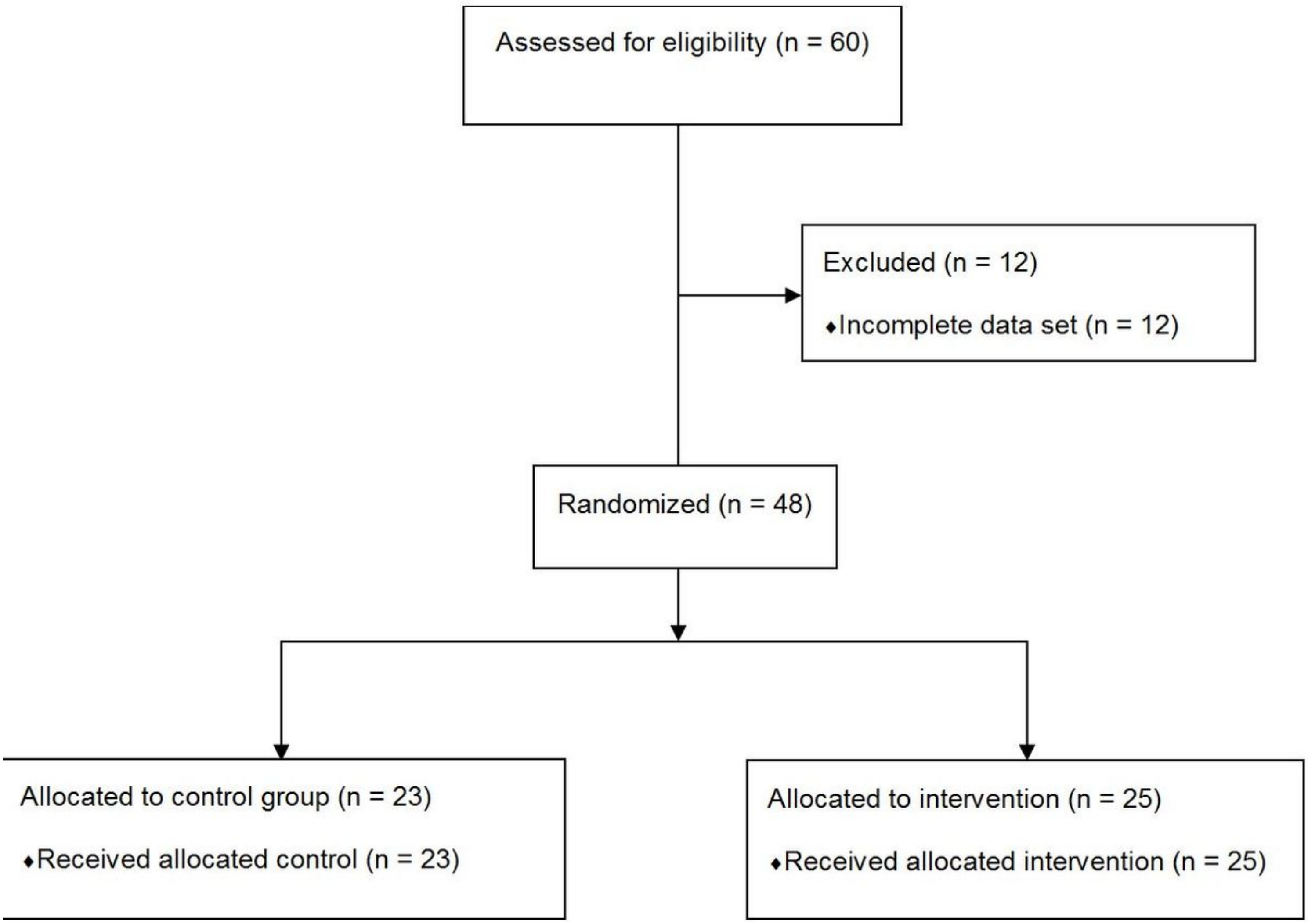

Figure 2

Flow diagram of the study population.

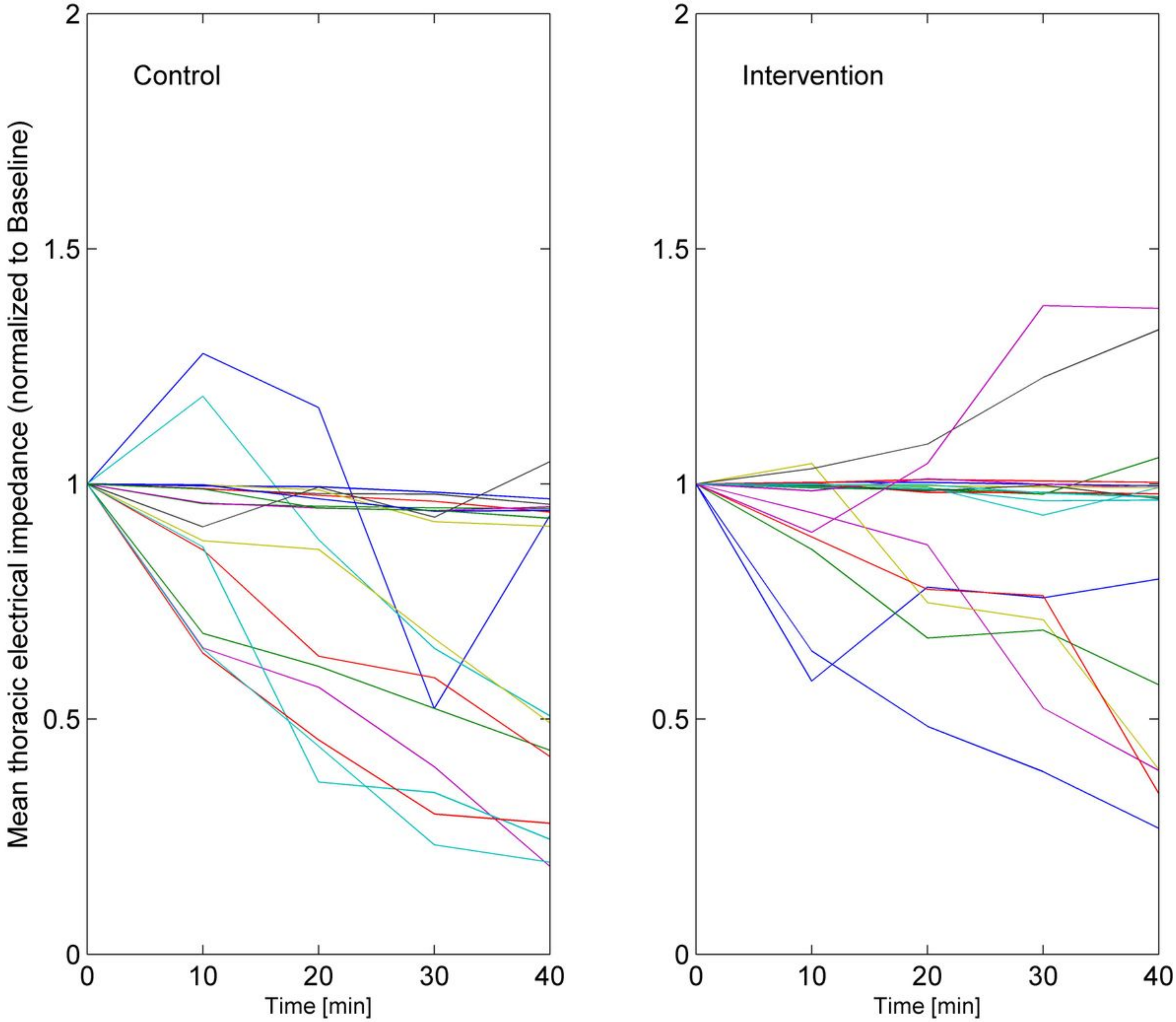

Figure 3

Course of mean thoracic electrical impedance (EITh) of all patients in the control and intervention group.

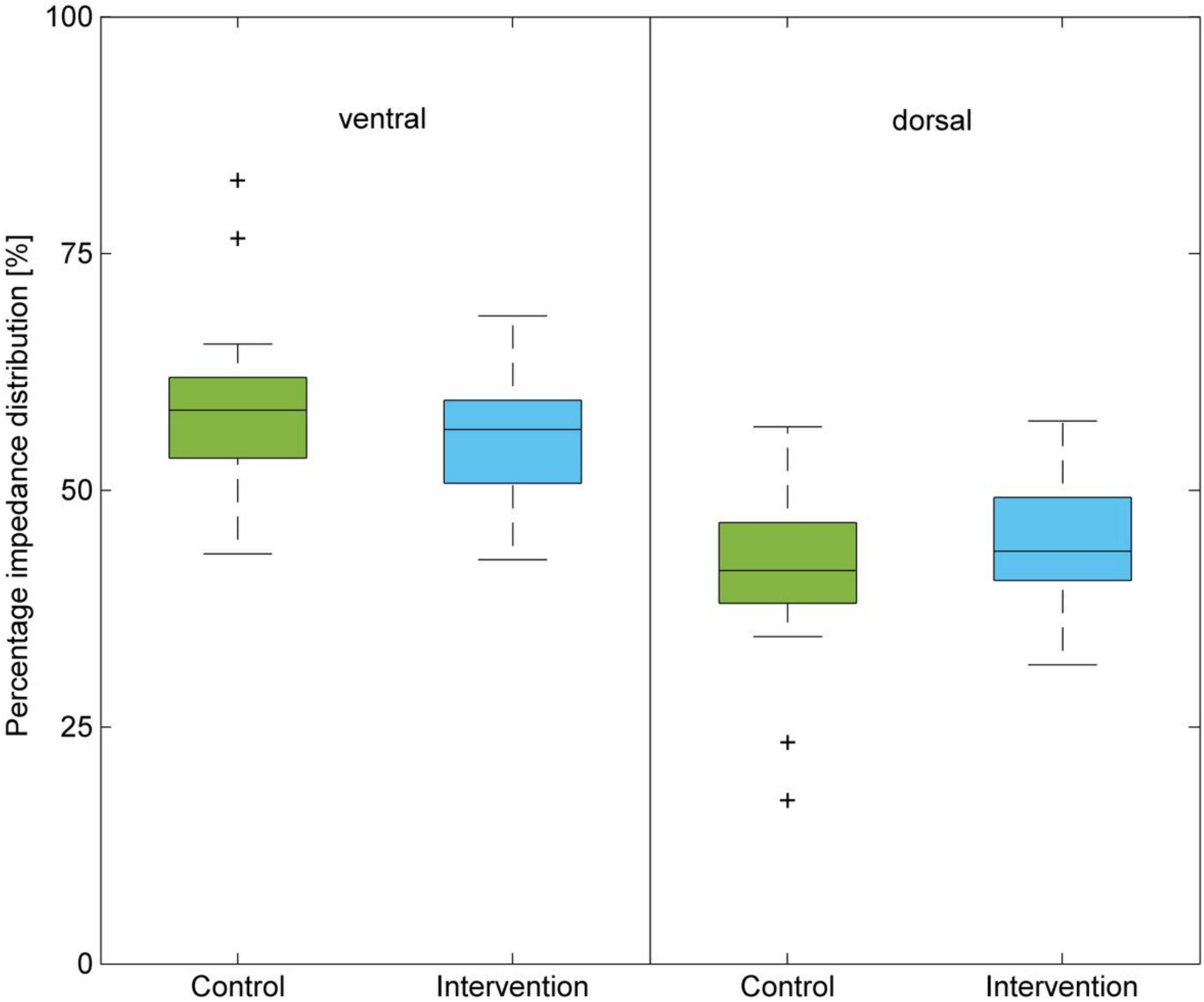

Figure 4

Impedance distribution (ventral and dorsal) for the control and intervention group. There was no significant difference in impedance distribution between the two groups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.doc