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Electrical Impedance Tomography during the Extubation Phase in Very Preterm Born Infants

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Keywords
Electrical impedance tomography · Extubation · Ventilation · Preterm neonate

Abstract

Introduction: Although many preterm born infants require invasive mechanical ventilation, it is also associated with detrimental effects. Early extubation should be pursued, but extubation failure is yet common. The critical transition to noninvasive ventilation is characterized by respiratory physiological changes, warranting noninvasive monitoring. We aimed to determine whether electrical impedance tomography (EIT) could provide insights into the respiratory mechanics of neonates around extubation, and if findings were different between successful and failed extubation. ***Methods:*** Single-center observational study where EIT and transcutaneous CO_2 measurements were performed in preterm born infants <32 weeks gestational age. Measurements were performed from 24 h before up to 48 h after extubation. EIT parameters extracted from the hour before and after extubation were analyzed to evaluate the short-term physiological changes. ***Results:*** Twenty-one patients were included and 6 (29%) were reintubated. End-expiratory lung impedance and tidal impedance variation were stable around extubation ($p = 0.86$ and $p = 0.47$, respectively). Compared to successfully extubated patients, reintubated patients showed more lung inhomogeneity (GI index) after extubation (0.75 vs. 0.84, $p = 0.03$). The percentage of nondependent silent spaces decreased after extubation in successfully extubated patients ($p < 0.001$). Body position and ventilator mode influenced these findings. ***Conclusion:*** EIT measurements in preterm neonates provide valuable insight into the respiratory physiology during the transition from invasive to noninvasive ventilation, with significant differences in ventilation distribution and lung homogeneity between successfully extubated and reintubated patients. EIT has the potential to guide personalized respiratory support by assessing ventilation distribution and quantifying inhomogeneity, aiding in the optimization of ventilation settings.

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Introduction

Many preterm infants need invasive mechanical ventilation after birth, due to their underdeveloped lungs [1]. Despite being life-saving, invasive ventilation is also accompanied by adverse effects, such as increased risk of bronchopulmonary dysplasia (BPD) and ventilator-associated pneumonia [2]. Therefore, it is recommended to extubate these patients as expeditiously as possible [3]. To facilitate early extubation, neonates are supported with noninvasive ventilation after extubation [4]. This transition is a critical phase, with a high risk (30–50%) of extubation failure [5–7]. The transition period is characterized by respiratory physiological changes.

Electrical impedance tomography (EIT) is a noninvasive imaging technology, providing continuous and real-time information on the air distribution within the lungs [8, 9]. It is a useful bedside technique for closely monitoring and assessing the impact of interventions, such as ventilator mode and body position, on an infant's respiratory physiology during the critical extubation phase [10, 11]. EIT has been used in research in preterm neonates but is not yet part of routine clinical care [12]. Previous studies found a drop in end-expiratory lung impedance (EELI) surrounding the moment of extubation, implying a loss of lung aeration, which was regained during noninvasive ventilation [11, 13, 14].

The present physiological study was conducted to determine whether EIT monitoring around extubation could provide insights into the respiratory mechanics of the preterm born neonate. We analyzed EIT parameters during the transition from invasive to noninvasive respiratory support and examined if findings were different between patients with extubation success and failure.

Methods

Study Design and Population

This observational study was conducted in the Neonatal Intensive Care Unit (level III/IV) of Erasmus MC Sophia, Rotterdam, The Netherlands. Patients were enrolled with a gestational age between 24 and 32 weeks, invasively ventilated for at least 24 h and considered ready for extubation within the coming days. The protocol was approved by the Local Ethics Review Committee (MEC-2019-0478). Written informed consent was obtained from both parents. Exclusion criteria were contraindications for an EIT measurement, unstable clinical condition or transferal to another hospital before extubation.

Study Protocol

Continuous EIT monitoring was performed with the Sentec EIT system (LuMon™; Sentec AG, Therwil, Switzerland), the belt was applied between the 4th and 6th intercostal space [15]. Contact agent was applied to the belt before the start of the measurement and when insufficient skin-to-belt contact was observed. EIT measurements were conducted in the period from up to 24 h prior to extubation up to 48 h after extubation. Extubation failure was defined as reintubation within 48 h after extubation. Upon reviewing the data, the reliability of such long-term EIT recordings was considered insufficient for further analysis (see Discussion: limitations); we, therefore, focused on the short-term effect of extubation (i.e., EIT recordings of 60 min before and after extubation). See online supplementary 1 (for all online suppl. material, see https://doi.org/10.1159/000544811) for the inclusion time-line and EIT setup. Continuous transcutaneous CO_2 was obtained using a dedicated sensor (SenTec OxiVenT™, Sentec AG).

Preprocessing and Analysis

Data preprocessing and analysis were performed in Matlab R2021a (Mathworks, Natick, MA, USA). We designed and applied an EIT preprocessing method, as described in previous work [16], to remove outliers, artefacts and noise components and select stable tidal breathing periods. Stable EIT periods were selected in the period from 20 to 60 min before and after extubation. Since multiple events such as patient care and bronchial suctioning affect the EIT signal, and because most of these events occurred in the first 20 min before and after extubation, we discarded this period from the analysis. Data were analyzed on a breath-by-breath basis and the following parameters were computed:

- End-expiratory lung impedance (EELI) as the baseline EIT signal.
- Tidal impedance variation (i.e., delta impedance, dZ)
- Dependent and nondependent silent spaces (DSS, NSS): reflecting poorly or non-ventilated lung. Pixels within the lung contour (as per manufacturer's software) showing impedance changes <10% of the maximum impedance change were quantified as silent space. Pixels below or above the center of ventilation were considered DSS or NSS, respectively [17].
- Functional lung space: 100% minus the percentage of pixels defined as silent space.
- EIT-based respiratory rate (RR_{EIT}), calculated by the EIT device.
- Minute volume (MV_{EIT}): dZ in (AU) multiplied with RR_{EIT}

- Global inhomogeneity (GI) index, homogeneity of the ventilation distribution calculated as the sum of the absolute difference between the dZ per pixel and the median dZ, divided by the sum of all impedance values [18]:

$$GI = \frac{\sum_{x,y\in lung} \left| dZ_{xy} - Median\left(dZ_{lung}\right) \right|}{\sum_{x,y\in lung} dZ_{xy}}$$

Only pixels within the predefined lung contour were included for this calculation. A GI of zero represents a perfect homogeneous ventilation distribution; a larger GI indicates more inhomogeneous tidal volume distribution.

Breath-by-breath parameters were averaged before statistical analysis. Clinical data on sex, gestational age, birth weight, APGAR score, surfactant use, antenatal steroids, mechanical ventilation, and pulmonary condition was obtained from the electronic patient file.

Statistical Analysis

Statistical analyses were performed using R version 2022.07.2 (R-studio). Descriptive data are presented as mean ± standard deviation; distribution of normality was checked through the Shapiro-Wilk test. Non-normal distributed data were presented as median with interquartile ranges. A paired *t* test was used to test for significant difference in the continuous parameters before and after extubation. Non-normally distributed data were analyzed using a Wilcoxon signed-rank test. A Fisher's exact test was used to determine significant differences in the categorical baseline parameters. Subgroup analyses were performed to test whether changes in EIT parameters were different between patients with successful or failed extubation. This was analyzed with linear mixed-effect models with fixed effects of measurement step and group-by-step interaction and random effect of the subject; estimated means were compared after Tukey correction. As this was an observational study, body position and ventilation mode were not standardized but may affect changes in EIT parameters. To explore the separate effects of body position and ventilation mode, we applied additional linear mixed-effects models. For all analyses, p value <0.05 was considered statistically significant.

Results

Twenty-one patients were enrolled; their baseline characteristics and ventilator settings during invasive ventilation and noninvasive ventilation post-extubation are presented in Table 1. An illustrative example of EIT during the extubation phase is provided in Figure 1. The patient was on synchronized intermitted mandatory ventilation and extubated to continuous positive airway pressure.

EIT Parameters before and after Extubation

EIT parameters before and after extubation for the whole group are presented in Table 2. EELI values and dZ showed no significant difference before and after extubation ($p = 0.86$ and $p = 0.47$, respectively). The NSS decreased ($p < 0.001$), while the DSS increased after extubation ($p < 0.001$).

Successful Extubation and Reintubation

Six patients (29%) were reintubated within 48 h after extubation, mostly due to an increased number of incidents (desaturation, bradycardia, and apnea) after extubation. At baseline, the birthweight was significantly lower (702 vs. 1,056 g), and the total ventilation duration (56 vs. 21 days) was significantly higher for the reintubated patients ($p < 0.05$ for both). There was a trend toward a longer invasive mechanical ventilation duration before the EIT measurements (15 days, $p = 0.07$). Ventilator settings, 1 h before and after extubation, were similar for the successful extubation and reintubation group.

Differences between patients who were reintubated ($n = 6$) and patients that were successfully extubated ($n = 15$) are presented in Figure 2. The change in EELI and dZ was not significant between the groups nor between before and after extubation. MV_{EIT} changed significantly in patients that were successfully extubated ($p = 0.02$ for interaction effect of group by measurement step) resulting in lower values after extubation as compared to the reintubation group ($p = 0.018$). The GI was significantly higher after extubation ($p = 0.03$) in reintubated patients. NSS decreased in successfully extubated patients after extubation ($p < 0.001$). DSS increased significantly in both groups after extubation (successful extubation $p = 0.006$, reintubation $p = 0.015$).

Explorative Analysis

Body position and ventilation mode were not standardized between patients and influenced EIT parameters. After extubation, 10 patients were placed in prone position (of which 3 patients failed extubation) and 11 patients were in supine position (of which 3 patients failed extubation); all patients were in supine position before extubation. Minute ventilation

Table 1. Baseline characteristics in the overall population and for the successful extubated patients and reintubated patients

	Total population (n = 21)	Successful extubation (n = 15)	Reintubation (n = 6)	p value
Male/female	M = 13, F = 8	M = 11, F = 4	M = 2, F = 4	0.14
Gestational age, weeks	26 [24.6; 27.7]	26.4 [24.9; 28.9]	25.4 [24.7; 26.2]	0.22
Birth weight, g	955.29 (320.6)	1,056 (314.4)	701.7 (162.0)	0.01
Postmenstrual age, weeks	30.6 [28.3; 33.3]	30.6 [28.8; 33.15]	29.5 [28; 35]	0.88
Age at extubation, days	24 [9; 35]	23 [6; 34]	32 [20.8; 64.2]	0.20
Weight at extubation, g	1,280 [890; 1,510]	1,309 [1,022.5; 1,492.5]	872.5 [772.5; 1,756.3]	0.21
Patients who received exogenous surfactant, n (%)	18 (86%)	12 (80%)	6 (100%)	0.53
Days of invasive mechanical ventilation total, days	29 [14; 41]	21 [4.5; 31]	55.5 [36.5; 80.5]	0.004
Days of invasive mechanical ventilation before measurements, days	17 [5; 28]	14 [4.5; 23.5]	29 [18.8; 44.5]	0.07
APGAR score	8 [7; 8]	8 [7; 8]	7 [6.3; 7.8]	0.36
Patients who completed course of antenatal steroids, n (%)	10 (47%)	9 (60%)	1 (17%)	0.15
Ventilator settings before extubation				
FiO_2, %	25 [22; 29]	23 [21; 25.5]	28.5 [25.8; 29]	0.08
Conventional ventilation (SIMV/SIPPV) (n = 17)				
PEEP, cmH_2O	7 [6; 7]	7 [6; 7]	7 [7; 7]	0.19
Ppeak, cmH_2O	16 [14; 16]	15.5 [13.75; 16]	16 [16; 18]	0.09
Pmean, cmH_2O	9.7 (2.1)	9.1 (1.6)	11 (2.7)	0.19
Respiratory rate, bpm	43.2 (8.6)	44.1 (8.1)	41 (10.2)	0.69
HFO (n = 4)				
CDP	11.8 (1.6)	11.7 (2.0)	11.9	1
Transcutaneous CO_2, mm Hg[a]	48.9 [42.6; 52.9]	45.7 [42.2; 50.5]	54.1 [48.4; 65.2]	0.21
Ventilator settings after extubation				
FiO_2, %	32.9 (7.7)	30.1 (6.6)	39.8 (5.9)	0.32
PEEP, cmH_2O	7.2 (1.1)	6.9 (1.1)	7.8 (0.8)	0.19
Ppeak, cmH_2O	14 [14; 15]	14 [13.8; 15]	14 [14; 16]	0.19
Pmean, cmH_2O	8.6 [7.6; 9.6]	8.5 [7.0; 9.7]	9.2 [8.5; 9.6]	0.20
Respiratory rate, bpm	40 [40; 60]	42 [40; 69]	40 [40; 48]	0.38
Transcutaneous CO_2, mm Hg[a]	50.6 [41.7; 55.1]	43.9 [41.2; 53.3]	54.5 [52.5; 124.2]	0.21

Including the ventilator settings before and after extubation. FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; Ppeak, peak pressure; Pmean, mean pressure; HFO, high frequency oscillation; CDP, continuous distending pressure. [a]Not measured in all patients.

decreased significantly after extubation in patients in prone position ($p = 0.016$). The NSS decreased (supine $p = 0.02$, prone $p < 0.001$) and the DSS increased (supine $p = 0.02$, prone $p < 0.001$) after extubation, see online supplementary 2.

The ventilation mode prior to extubation was different among the study participants, see Table 1. dZ ($p = 0.04$) and MV_{EIT} ($p = 0.002$) were higher in patients on conventional ventilation compared to HFO ventilation before extubation. Patients on HFO ventilation had more NSS before extubation ($p = 0.006$) and a higher GI index before and after extubation ($p = 0.007$ and $p = 0.03$, respectively). The functional lung space was significantly higher at both timepoints for patients on conventional ventilation ($p = 0.04$ and $p = 0.01$, respectively), see online supplementary 3.

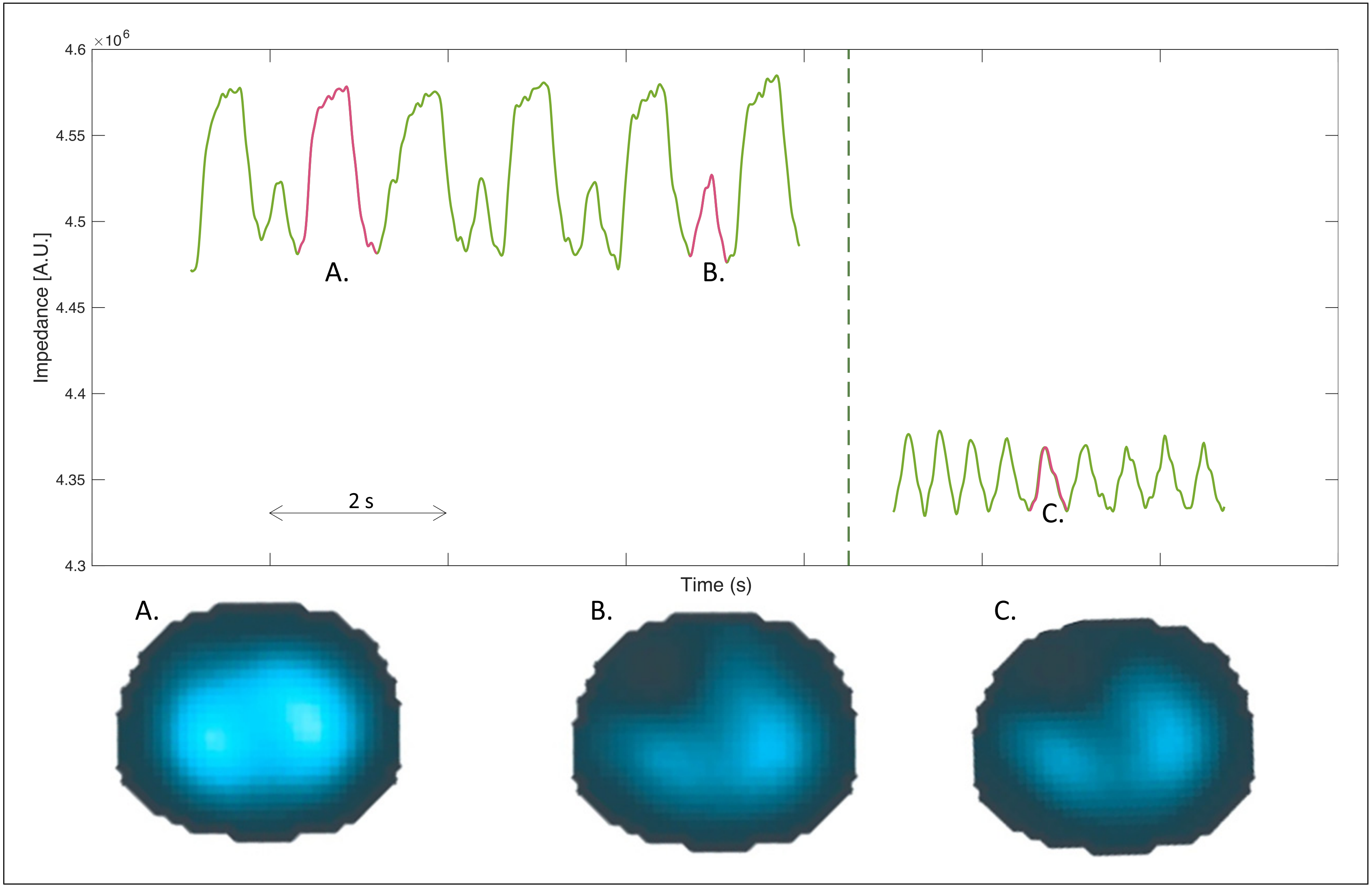

Fig. 1. Global impedance signal of a patient on SIMV ventilation before extubation and CPAP after extubation. The horizontal line indicates the moment of extubation. Breath A: supported breath by mechanical ventilation with homogeneous ventilation over all lung field. Breath B: unsupported spontaneous breath during SIMV, with decreased ventilation in the right ventral lung. Breath C: spontaneous breathing after extubation during CPAP, with a similar ventilation pattern as breath B. This patient required reintubation due to stridor and dyspnea.

Table 2. EIT parameters before and after extubation in the full patient group (n = 21)

	Before extubation	After extubation	p value
EELI, %	100	99	0.86
dZ, %	100	80	0.47
MV_{EIT}, A.U./min	2.5E06±8.7E05	2.2E06±6.7E05	0.16
RR_{EIT}, BPM	56.6±12.4	58.3±13.8	0.60
NSS, %	26.7±7.5	18.1±8.1	<0.001
DSS, %	8.4 [6.4; 12.6]	17.2±6.3	<0.001
FLS, %	63.2±7.1	64.7±9.6	0.44
GI	0.8±0.1	0.8±0.1	0.20
COVx (pixel number)	16.7±1.2	16.7±0.1	0.98
COVy (pixel number)	17.5±0.8	17.4±0.7	0.54

Discussion

This observational study shows that EIT parameters provide insight in the respiratory physiology during the transition from invasive to noninvasive mechanical ventilation. The main findings of the study are: (1) EIT parameters changed significantly after extubation. Whereas dZ and EELI remained stable, the NSS dropped and DSS increased after extubation. This indicates stable tidal volumes and functional residual capacity (FRC), with a changed ventilated area after extubation. (2) EIT parameters showed significant differences between patients with extubation success and failure. There was more lung inhomogeneity (i.e., higher GI) after extubation in patients that were reintubated. MV_{EIT}, GI, and NSS decreased after extubation in patients that were successfully extubated. DSS increased after extubation in both groups. The mode of ventilation and body position affected the changes in respiratory physiology.

Related Works

We found comparable EELI values before and after extubation, indicating stable end-expiratory lung volumes (EELVs). This stability suggests that the noninvasive support provided post-extubation offers sufficient aeration. Our results differ from previous literature. Plastina et al. [13] observed a drop in EELI during tube fixation tape removal pre-extubation, EELI was regained during noninvasive ventilation and increased further in prone position. Similarly, van der Burg et al. [14] found increased EELV post-extubation, which was further enhanced in prone position. In contrast, our study found consistent EELI levels pre- and post-extubation, regardless of body position. These differences may be due to the severity of disease in our cohort and the ventilation mode before extubation. In our study, only patients at high risk of reintubation were placed in prone position, whereas in van der Burg's work [14], all patients were placed in prone position. In addition, van der Burg et al. [14] normalized EELV for body weight, which was not done in the current work.

In addition to previous studies [11, 13, 14], we observed a decrease of the NSS after extubation. This observation suggests overdistended lungs during invasive ventilation. The trend of NSS was always decreasing after extubation, independent of the ventilation mode or position. A significant difference was found between HFO and conventional ventilation before extubation, with more NSS in patients on HFO, indicating more overdistention. The DSS increased after extubation, indicating derecruitment. Significantly, more DSS was found after extubation in patients extubated from HFO. DSS and NSS represent the EIT pixels not significantly contributing to the ventilation, with the pixel location based on the center of ventilation. This means that with adjusted body positions, NSS and DSS prior to versus after extubation do not necessarily represent the same pixels [19]. In supine position, pixels on the ventral side of the patient are considered NSS. In prone position, the ventral side is regarded as DSS. Hence, within-patient changes in silent spaces should be interpreted with caution.

The GI was higher after extubation in patients requiring reintubation. A higher GI implies more regional difference in lung mechanics, which could be caused by atelectasis, overdistension, inflammation, or a ventilation-perfusion mismatch. Earlier studies in adult patient found higher GI values in patients failing the spontaneous breathing trail

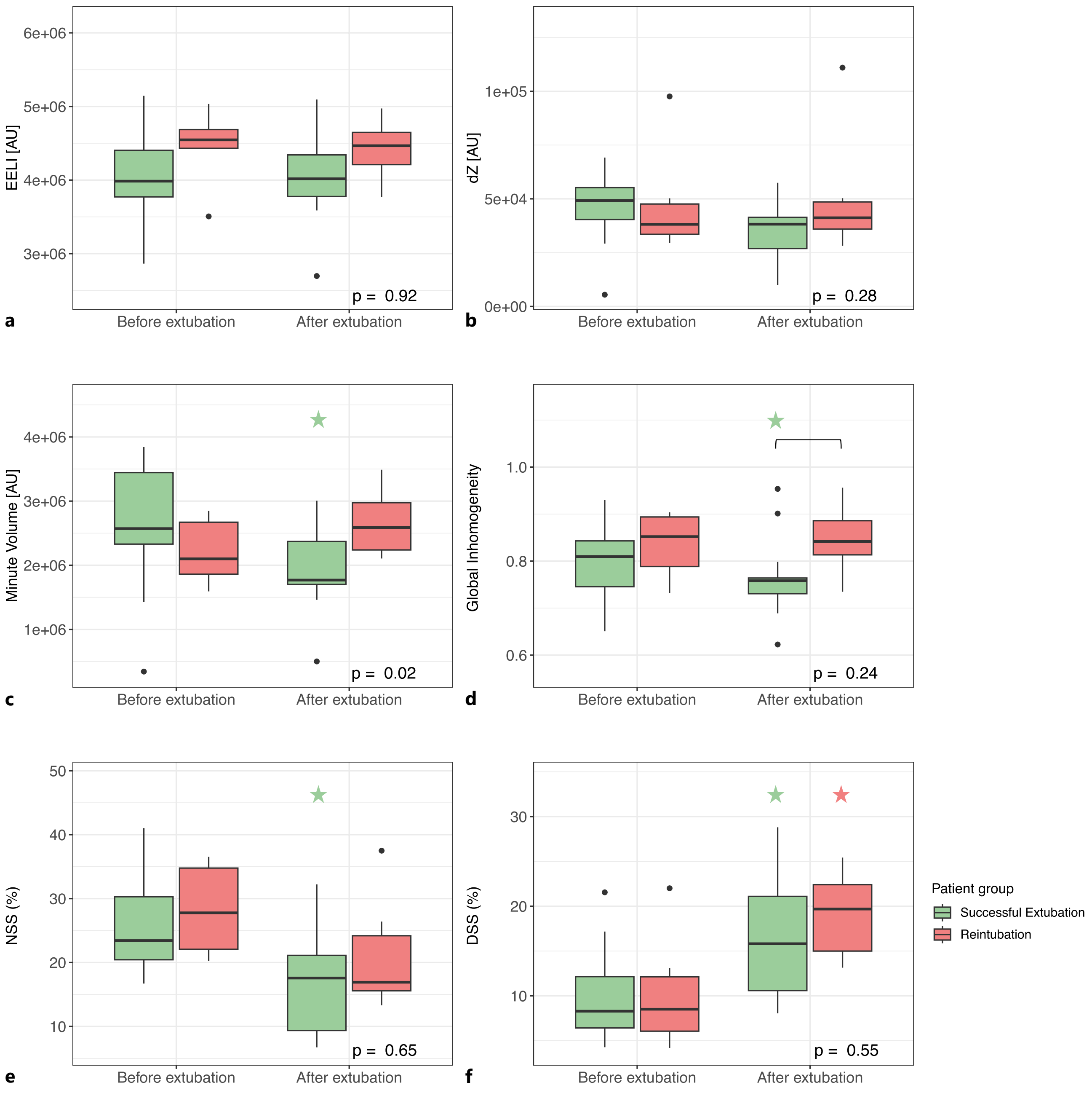

Fig. 2. a EELI level before and after extubation. **b** dZ before and after extubation. **c** MV_{EIT} before and after extubation. **d** GI before and after extubation. **e** NSS before and after extubation. **f** DSS before and after extubation. The group with successfully extubated patients is colored green, the group with reintubated patients is colored red. Significant differences from baseline within a group are indicated with a green star for patients with successful extubation and with a red star for reintubated patients. Significant difference at a time point between the groups is indicated with a horizontal bar. *p* values in the figures are for interaction effect of group by measurement step.

(SBT) and extubation [16, 20]. The role of GI and other EIT parameters predicting extubation failure in neonates requires further study.

Clinical Utility of EIT in Preterm Neonates

Determining the tidal volume in patients undergoing noninvasive ventilation is challenging due to leaks, and establishing the FRC is this context is impossible [12, 21]. EIT during invasive ventilation allows to compute the correlation of (tidal) impedance changes with known (tidal) volume changes [22]. Hereby, EIT is the only non-invasive imaging technique that enables to monitor these parameters' trends after extubation [23]. Considering the multitude of factors that hamper the evaluation of long-term/multiday EIT recordings [9], focus should be on evaluating short-term physiological changes. The patient in Figure 1 illustrates the utility of EIT in monitoring individual responses to ventilation changes. Notably, the ventilation distribution observed during breath B foreshadowed the post-extubation pattern seen in breath C, indicating potential issues that led to reintubation. While EIT-derived cohort trends may be not always be obvious, EIT offers advantages in assessing/managing individual patient responses, thereby allowing personalized ventilation. Standardized EIT acquisition and computation of parameters is needed to evaluate and validate which EIT parameters yield the best performance in guiding ventilator settings/strategies [9, 24].

Whereas on the adult ICU the SBT is standard-of-care, this is seldom performed in neonates. A recent meta-analysis showed that the SBT in premature infants can accurately predict extubation success but not failure [25]. Given the high reintubation rate in preterm neonates, there is need for better prediction of extubation failure. Incorporating EIT in weaning protocols to evaluate the ventilation distribution of spontaneous breaths may enhance the ability to predict extubation failure. Considering that spontaneous breaths may better mimic the lung mechanics and work of breathing after extubation. Figure 1 demonstrates that the ventilation distribution during a spontaneous breath indeed closely mirrored the distribution after extubation. Future research could explore spontaneous breathing pre-extubation as predictors of extubation failure.

Strengths and Limitations

This was the first study aiming to perform long-term continuous EIT in preterm born neonates. The measurements were performed with the LuMon EIT device, providing novel parameters (i.e., silent spaces) that were not previously investigated around extubation. We present group trends and individual patient observations, showing the potential of EIT as a tool that could guide personalized mechanical ventilation.

Our study had several limitations and we experienced multiple constraints during the EIT measurements. The original goal of our study was to measure EIT around extubation for up to 72 h. As the reliability of the EIT signal is limited for comparisons over long time periods due to the multitude of factors that can influence signal quality (for instance, but not limited to: skin-to-belt contact, patient movements, belt displacements), we only included data from the first hour before and after extubation.

This study was purely observational; therefore, the effects of ventilator mode and body position were not investigated in a structured manner. Our findings reflect clinical choices and the clinical course.

Conclusion

EIT measurements in preterm born neonates provide insight on the respiratory physiology in the transition from invasive to noninvasive mechanical ventilation. After extubation, EIT parameters indicate stable tidal volumes and FRC, with changes in the ventilation distribution. Significant differences were observed between successfully extubated and reintubated patients, with greater lung inhomogeneity in reintubated patients. EIT could support decisions in how to optimize respiratory support according to the individual patient needs, facilitating personalized treatment.

Statement of Ethics

This study protocol was reviewed and approved by the Research Ethics Committee (METC) of the Erasmus MC, Approval No. MEC-2019-0478. Written informed consent to participate in the study was obtained from the parents of the participant.

Conflict of Interest Statement

All declared interests are not related to the submitted work. A.H.J. has received research funding (paid to the institution) from ZonMw, Pulmotech B.V., Liberate Medical, the Netherlands eScience center and Health~Holland. H.E. has received unrestricted research grants from ZonMW (The Netherlands), Fisher and Paykel Healthcare (Auckland, New Zealand), Roche Diagnostics International Ltd. (Basel, Switzerland), and Ventinova Medical B.V. (Eindhoven, The Netherlands) and speakers' fee from Getinge (Sweden). The remaining authors declare that they have no relevant competing interests.

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Author Contributions

Concept and design: J.J.W., T.G.G., I.K.M.R., D.G., and A.A.K. Data acquisition: J.J.W. Data analysis: J.J.W., A.H.J., and T.G.G. Data interpretation: all authors. Manuscript drafting: J.J.W., A.H.J., and H.E. Manuscript revising for intellectual contact and final approval: all authors.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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