

***Changes in respiratory patterns from Pressure Control
Ventilation to Neurally Adjusted Ventilatory Assist
assessed by Electrical Impedance Tomography***

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Data Availability Statement

The data supporting this study's findings are not publicly available because they contain information that could compromise the privacy of research participants. However, the data is available by request, subject to approval [RB].

Ethical statement:

The study protocol was reviewed and approved by the Northern Ostrobothnia Health Care District Research Ethics Committee, approval number (EETTMK:35/2017), and written informed consent was obtained from a parent before any study-related procedures. This was an observational study with all treatment decisions being made by clinicians according to clinical needs. The standard clinical practice of the NICU at Oulu University Hospital involved weaning premature infants from mechanical ventilation using NAVA. Therefore, no additional Edi-catheters were used during this study.

Funding Sources

The CRADL study, coordinated by Professor Richard Bayford, was supported by the European Union's Horizon 2020 Research and Innovation Programme under grant agreement 668259 and by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contact number 15.0342-1. MD Rahtu received a personal research grant from the Alma and K.A. Snellman Foundation, Oulu, Finland and the Finnish Cultural Foundation. The Finnish Foundation for Pediatric Research supported Dr.

Kallio. The funders had no role in this study's design, data collection and analysis, or reporting.

Keywords: EIT, NAVA, mechanical ventilation, premature infant, ventilation distribution

Meetings: The preliminary data was presented as an oral presentation during the poster session at the 14th European Conference on Pediatric and Neonatal Ventilation (EPNV) in April 2018.

Running head: Respiratory patterns from PCV to NAVA assessed by EIT

Abstract

Introduction: Neurally Adjusted Ventilatory Assist (NAVA) is increasingly used as ventilatory support for preterm infants. Changes in ventilation distribution and respiratory patterns during the transition from patient-triggered time-cycled Pressure Controlled Ventilation (PCV) to NAVA have not yet been studied. This study aimed to evaluate the impact of ventilation mode (PCV and NAVA, respectively) on ventilation distribution and breathing patterns in preterm infants with Electrical Impedance Tomography.

Methods: This study included 16 premature infants at Oulu University Hospital who participated in the observational CRADL project and were on NAVA. EIT data was retrospectively assessed by choosing a 1-minute stable recording before and after the change from one to the other mode. The primary endpoint was changes in global and regional ventilation parameters (ΔZ), and the secondary endpoints were Centers of Ventilation (CoVs), the amount of silent spaces, and the duration of inspiratory and respiratory cycle times.

Results: A larger variation in the global tidal impedance variation ($P < 0.05$) and the respiratory cycle time ($P < 0.05$) was observed on NAVA than on PCV. Sighs, which were determined as a breath impedance change twice the size of an average breath on PCV, were more frequent during NAVA than PCV (5.1% vs 0.8%, respectively). Mean global or regional impedance variations or silent spaces did not differ between PCV and NAVA.

Conclusion: NAVA allowed more variable breathing patterns during invasive respiratory support than patient-triggered PCV. However, variability in the respiratory cycle did not lead to systematic changes in ventilation distribution or silent spaces.

Introduction

Neurally Adjusted Ventilatory Assist (NAVA) is a ventilation mode that adjusts positive inspiratory pressures (PIP) in response to the infant's respiratory pattern ¹. The electrical activity of the diaphragm (Edi) reflects the neural respiratory demand, which the ventilator uses to proportionally assist each individual breath ^{1,2}. NAVA enables variations in respiratory rate, inspiration time, PIP and tidal volume ³, resulting in greater variability in these parameters compared to conventional modes of mechanical ventilation (MV) ^{4,5}. NAVA enhances patient-ventilator synchrony ^{6,7}, leading to improved dynamic compliance and increased patient comfort. Better patient-ventilator synchrony results in improved oxygenation ^{6,8} and enables ventilation with lower PIP and mean airway pressures ⁶⁻⁹, consequently reducing the need for sedatives ^{6,10}. Despite these immediate benefits, long-term advantages remain unconfirmed ^{9,11,12}.

NAVA enables infants to recruit their lungs by allowing them to take larger sighs ^{5,13}. Previously, it has been shown that premature infants' neural feedback mechanisms are mature enough to achieve respiratory muscle unloading to prevent excessive tidal volumes while on NAVA ³. However, large sighs that briefly result in very large tidal volumes and

overdistension¹³, might potentially increase the risk for ventilator-induced lung injury (VILI) and air leak, especially in situations where breathing effort is driven by non-physiological pulmonary needs such as heat, pain, or in case of severe lung disease and uneven ventilation distribution, such as meconium aspiration syndrome¹³. These concerns and clinical observations have raised questions about the potential risk of overdistention during NAVA.

Electrical impedance tomography (EIT) is a bedside imaging modality for monitoring regional lung ventilation and aeration¹⁴. It provides real-time distribution of tidal impedance variation (ΔZ) and end-expiratory lung impedance on a breath-by-breath basis, reflecting the distribution of tidal and end-expiratory lung volumes, respectively¹⁵. The principle of EIT is based on measuring changes in the electrical conductivity of tissues in response to small alternating electrical currents¹⁶. It is radiation-free and has been validated as safe and feasible for preterm infants¹⁵⁻¹⁷. EIT has the potential to identify recruitable alveolar collapse and overdistention¹⁵, as well as some adverse effects of MV, such as air leaks^{13,18-20} or endotracheal tube malposition²¹, in addition to enhancing our understanding of respiratory physiology under various conditions¹³.

NAVA has demonstrated immediate benefits of being a lung-protective ventilation mode, yet its recommendations as a standard ventilation mode for premature infants remain a topic of ongoing debate^{3,12,22,23}. EIT provides a direct view of lung mechanics and respiratory patterns, yet changes in ventilation distribution and respiratory patterns during the

163 transition from patient-triggered time-cycled PCV to NAVA have not been
164 studied. This study aimed to enhance our understanding of lung
165 physiology during NAVA compared to the conventional MV.

Materials and Methods

Subjects were selected from the participants in the Continuous Regional Analysis Device for Neonate Lung (CRADL) project (ClinicalTrials.gov identifier: NCT2962505) ¹⁷. Premature infants born after 28 weeks of gestation were eligible for CRADL. This research focused on premature infants requiring invasive ventilation for RDS at Oulu University Hospital, supported by both PCV and NAVA during the 72-hour EIT recording period. This was an observational study with all treatment decisions being made by clinicians according to clinical needs. The standard clinical practice of the NICU at Oulu University Hospital involved weaning premature infants from mechanical ventilation using NAVA. Therefore, no additional Edi-catheters were used during this study. The study protocol was reviewed and approved by the Northern Ostrobothnia Health Care District Research Ethics Committee, approval number (EETTMK:35/2017), and written informed consent was obtained from a parent before any study-related procedures.

Clinical information of the patients was collected from the Centricity Critical Care Clinisoft monitoring database and the local patient management system, ESKO. All patients received MV using a Servo-i ventilator (Getinge AB, Gothenburg, Sweden). Following the local treatment regime at the time of the CRADL trial, all infants were first on flow-triggered, time-cycled PCV, and then the ventilation mode was changed to NAVA. In comparing the ventilation modes, infants served as their own control. Ventilator settings followed lung protective principles,

and the observed tidal volumes were under 7ml/kg on both ventilation modes (data not shown, available on request). Clinicians adjusted the settings according to clinical needs without any study-related protocol. All infants had received surfactant treatment prior to the selected recording periods.

EIT recordings were performed with the Sentec BB² device (SenTecAG, Landquart, Switzerland) and 32-electrode-built-in textile belts (SenTecAG, Landquart, Switzerland) ²⁴. These belts were placed on the neonates' chests at nipple level at the study inclusion. Ultrasound gel (Aquasonic100, Parker Laboratory, USA) was applied to improve the contact between the electrodes and the skin. Clinicians were blinded to EIT images through a specially designed graphical user interface. It enabled the marking of clinical interventions within the EIT recordings, including the timing of changes in ventilation mode or adjustments in patient positioning. In addition, video recordings were used to validate patient positioning at each point in time.

The EIT data were analysed using IBEX software provided by the EIT device manufacturer. The change of the ventilation mode was identified within the EIT recordings, and a 1-minute stable signal, where all breaths were correctly detected, was selected during PCV and NAVA. A margin was left before and after the change to ensure the reliability of the data. Patients' body position did not change between selected time intervals. The time points for the start and end of the inspiration were detected using a breath detection algorithm ²⁵, and a functional tidal image was

derived. This was achieved by computing the difference between the
 impedances at end-inspiration and start-inspiration for each breath within
 the chosen interval in each image pixel (shown in Figure 1A). The tidal
 impedance variation (ΔZ) correlates with the tidal volume ¹⁵. Regional ΔZ
 were computed for different regions of interest (shown in Figure 1B),
 representing regional tidal volume. Tidal impedance variation was
 calculated from the entire thoracic image area. Inspiratory time (ms) and
 the respiratory cycle time (ms) were calculated from the EIT signal as a
 time difference between the start of and the end of the inspiration and as
 a difference between the start of two consecutive breaths, respectively
 (shown Figure 1A). To investigate differences in the distributions of
 inspiratory and respiratory cycle times and ΔZ between the groups, the
 standard deviation was used as a measure of distribution spread. [An
 example of an individual EIT signal representing respiratory patterns both
 on PCV and NAVA, including the change of ventilation mode, is shown in
 Figure 1C.](#)

The ventilation distribution was characterised by calculating the fraction
 of ventilation (%) across all regions of interest and determining the center
 of ventilation (CoV). The CoV was analysed both in the ventral-to-dorsal
 (CoV V-D) and right-to-left (CoV R-L) axis, a value greater than 50%
 indicates a distribution that is more towards the dorsal or left side of the
 thorax, respectively. The fractions of regional ventilation were computed
 for each breath and subsequently averaged across the designated period.
 Differences in global and regional ΔZ across ventilation modes were

assessed case by case and then normalised against the individual mean global ΔZ in the PVC. Silent spaces were defined as areas with less than 10% impedance variation.

The primary endpoint of this study was to evaluate changes in global and regional ventilation parameters (ΔZ) across the two modes of invasive ventilation. The secondary endpoints were the amount of silent spaces, CoVs, and changes in respiratory patterns. Because the study population was formed from patients included in the CRADL study, no sample size calculations were done. Statistical analysis was performed using IBM SPSS version 25.0. A Wilcoxon signed-rank test and a one-sample t-test were used to compare group means. P values below 0.05 were considered statistically significant.

Results

16 premature infants with a mean gestational age of 32.9 weeks (range 28.0 – 37.3) and a mean postnatal age of 26 hours (range 3 – 120) at the study inclusion were enrolled in this study. One patient was excluded due to a data collection error. During the change in ventilation mode, 8 infants were in right lateral, 5 in supine, and 3 in left lateral postures. Table 1 presents detailed physiological characteristics of the study participants.

The mean duration of the EIT recording intervals on PCV and NAVA was 59.4 s (SD 2.42) and 61.0 s (SD 14.8), respectively. The selected stable EIT recordings on PCV occurred 9.2 min (SD 4.1) before the change of the ventilation mode and on NAVA 18 min (SD 7.8) after the change.

Global and regional ventilation distribution and silent spaces

There were no significant changes in the mean global ΔZ , regional tidal impedance variations or CoVs between PCV and NAVA. A tendency towards more dorsal CoV during NAVA was observed with a mean difference of 1.3% (SD 2.8, $P = 0.084$). The distribution and volume of silent spaces were similar between the ventilation modes. The regional mean differences in ΔZ , CoVs and silent spaces are presented in Figure 2 with descriptive statistics in the online supplement E-table 1.

Changes in respiratory patterns

No significant changes in the mean respiratory rate, the duration of the inspiratory time or respiratory cycle time were observed between PCV and NAVA (shown in Table 2). However, variability (standard deviation) of the

respiratory cycle time was significantly higher on NAVA ($P < 0.05$), while the standard deviation of the inspiratory time was consistent with PCV (shown in Table 2 and E-figure 2). Figure 3 illustrates the overall distribution of the duration of the normalized respiratory cycle for all breaths on both ventilation support modes. There was a significantly higher variability (SD) in global tidal ΔZ ($P < 0.05$) in NAVA, showing greater diversity in breath sizes (shown in Figure 4). During PCV, the distribution of the respiratory cycle duration and the global tidal ΔZ were more concentrated around the mean length, suggesting more uniform breathing pattern shown in Figures 3 and 4. Heart rate, systolic and diastolic blood pressures, and peripheral oxygen saturation remained unchanged between the two ventilation modes. Detailed statistical descriptives are shown in Table 2.

Correlations between the variability in tidal volume and respiratory cycle and inspiratory time

Altogether, 734 and 729 breaths were analysed for PCV and NAVA, with the mean number of breaths per patient being 46 (SD 11) and 46 (SD 13), respectively. A Spearman's rank-order correlation showed only a mild positive correlation on NAVA between the respiratory cycle duration and global tidal ΔZ , $r_s(727) = .35$. The effect size for the respiratory cycle indicates that only 12% ($r^2 = 0.119$) of the variability of the global tidal ΔZ is explained by a longer or shorter respiratory cycle. Additionally, only a mild correlation was found between the inspiratory time and global tidal ΔZ , $r_s(727) = .27$, suggesting that 7% ($r^2 = 0.073$) of the variability of the

tidal volume change on NAVA is explained by changes in the inspiration time. During NAVA, 38 breaths (ΔZ range 101 – 251%), accounting for 5% of all breaths, were more than twice the size of an average breath on PCV. In comparison, during PCV only 6 breaths (ΔZ range 102 – 273%) reached that size (shown in E-table3).

Discussion

This is the first study using EIT to investigate differences in ventilation distribution during PCV and NAVA. The respiratory rate remained unchanged, while NAVA showed greater variation in tidal volumes and the duration of the respiratory cycle compared to PCV. These findings indicate that when preterm infants controlled their breathing pattern, they preferred to take shorter and longer as well as smaller and bigger breaths, still resulting in the same mean tidal volumes compared to a patient-triggered PCV. Despite these changes during NAVA, EIT did not show systematic differences in global or regional ventilation distribution compared to PCV. If NAVA was conclusively more lung-protective than conventional ventilation, one might also expect observable differences in ventilation distribution. However, carefully optimised PCV may also fulfil the criteria for lung protective ventilation, leading to differences that were too subtle to observe.

The fundamental principle of NAVA differs from other forms of MV: during NAVA, the ventilatory assistance is proportional to the electrical activity of the diaphragm, allowing the infant to control the timing, size, and inspiration time independently for every breath ^{2,9}. Changes in breathing

patterns started shortly after infants were allowed to self-regulate. Interestingly, the inspiratory time derived from the EIT signal remained unchanged between the ventilation modes. The key differences laid mostly in the expiration and the interval between the breaths, and only 7% of the variability of the tidal volume change on NAVA was explained by changes in the inspiration time. EIT enables the monitoring of tidal volumes for each breath separately ^{14,15}. This study showed that large sighs were rare during NAVA. Tidal volumes varied more than in PCV, and smaller volumes were also shown on NAVA than during PCV. Five per cent of breaths on NAVA were more than twice the size of an average breath on PCV, and clinically, these were interpreted as sighs. Previously, it has also been suggested that NAVA permits infants to recruit the lungs by sighing ¹³. This study did not observe significant changes in silent spaces, an indicator of non-ventilated areas, which can be either atelectatic or overdistended, after the change from PCV to NAVA, which might reflect relatively good lung condition of the patients and open lung already during PCV. Further studies are needed to show if spontaneous lung recruitment during NAVA occurs in more severely ill neonates.

It is commonly known that preterm infants have a unique breathing pattern known as periodic breathing, which is characterised by frequent sighs and following pauses ²⁶. This study showed that this physiological phenomenon was easily achieved during NAVA, demonstrated by the increased number of sighs. Preterm infants represent a unique group of mechanically ventilated patients, requiring respiratory support due to the

immaturity of their developing lungs, as well as respiratory centres. Due to immaturity, they may require prolonged duration of invasive ventilation, which may increase the risk for VILI^{12,22}. A more physiological approach with NAVA may be preferable for this population and those at risk of bronchopulmonary dysplasia (BPD), particularly during the weaning phase from MV^{27,28}. However, the long-term benefits of such approaches still require confirmation.

There are some limitations in this study. Our relatively small study population was from a single tertiary centre where PCV was commonly used, and ventilator settings followed routine protocol during PCV without volume guarantee. This may have emphasised the uniform nature of PCV more than in a multicentre setting, but not to such an extent that it would explain the observed differences between the ventilation modes. In addition, extremely preterm infants were excluded from the CRADL study, so our study population consisted of very preterm and moderate to late preterm infants suffering RDS and being mainly in the weaning phase of MV, which may partly explain similar ventilation distribution findings. If the transition to NAVA had occurred earlier, greater differences might have been observed due to poorer lung compliance and stronger breathing drive. Future studies are needed to evaluate the impact of NAVA in different stages of RDS and BPD. Finally, due to the observational nature of this study, infants were positioned in three different body positions at the time of the change in ventilation mode. Comparisons between ventilation modes were made while infants remained in the same

positions. Still, this may have masked subtle changes in ventilation distribution.

Conclusion

In conclusion, NAVA allowed more variable breathing patterns during invasive ventilation than patient-triggered PCV. However, variability in the respiratory cycle and tidal volume did not lead to systematic changes in ventilation distribution or silent spaces.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Acknowledgements

We extend our heartfelt gratitude to the families and infants who participated in this study, as well as to the nursing staff in the NICU at the Oulu University Hospital, whose dedication and supervision made possible the reliable recording of EIT data for 72 hours per infant in both this study and the CRADL project. Our thanks also go to Mervi Väisänen for her assistance in acquiring the data from Clinisoft, and Professor Esa Rahtu and Professor Okko Räsänen for their expertise in the technical field and data analysis.

References

387 1. Beck J, Sinderby C. Neurally Adjusted Ventilatory Assist in Newborns. Clin
388 Perinatol 2021 [accessed 2024 Oct 18];48(4):783–811.

389 2. Fang SJ, Chen CC, Liao DL, Chung MY. Neurally adjusted ventilatory assist in
390 infants: A review article. Pediatr Neonatol 2023;64(1):5–11.

391 3. Firestone KS, Fisher S, Reddy S, White DB, Stein HM. Effect of changing NAVA
392 levels on peak inspiratory pressures and electrical activity of the diaphragm in
393 premature neonates. Journal of Perinatology 2015;35(8):612–616.

394 4. Baudin F, Wu HT, Bordessoule A, Beck J, Jouvét P, Frasch MG, Emeriaud G.
395 Impact of ventilatory modes on the breathing variability in mechanically
396 ventilated infants. Front Pediatr 2014;2(NOV).

397 5. Protain AP, Firestone KS, McNinch NL, Stein HM. Evaluating peak inspiratory
398 pressures and tidal volume in premature neonates on NAVA ventilation. Eur J
399 Pediatr 2021 [accessed 2024 Nov 13];180(1):167–175.
400 <https://pubmed.ncbi.nlm.nih.gov/32627057/>

401 6. Longhini F, Ferrero F, De Luca D, Cosi G, Alemani M, Colombo D, Cammarota
402 G, Berni P, Conti G, Bona G, et al. Neurally adjusted ventilatory assist in preterm
403 neonates with acute respiratory failure. Neonatology 2015;107(1):60–67.

404 7. Bordessoule A, Emeriaud G, Morneau S, Jouvét P, Beck J. Neurally adjusted
405 ventilatory assist improves patient-ventilator interaction in infants as compared
406 with conventional ventilation. Pediatr Res 2012;72(2):194–202.

407 8. Hunt KA, Dassios T, Greenough A. Proportional assist ventilation (PAV) versus
408 neurally adjusted ventilator assist (NAVA): effect on oxygenation in infants with
409 evolving or established bronchopulmonary dysplasia. Eur J Pediatr
410 2020;179(6):901–908.

411 9. Lefevère J, van Delft B, Decaluwe W, Derriks F, Cools F. Neurally adjusted
412 ventilatory assist in preterm infants: A systematic review and meta-analysis.
413 Pediatr Pulmonol 2024.

414 10. Kallio M, Peltoniemi O, Anttila E, Pokka T, Kontiokari T. Neurally adjusted
415 ventilatory assist (NAVA) in pediatric intensive care - A randomized controlled
416 trial. Pediatr Pulmonol 2015;50(1):55–62.

417 11. Kallio M, Koskela U, Peltoniemi O, Kontiokari T, Pokka T, Suo-Palosaari M,
418 Saarela T. Neurally adjusted ventilatory assist (NAVA) in preterm newborn infants
419 with respiratory distress syndrome—a randomized controlled trial. Eur J Pediatr
420 2016;175(9):1175–1183.

421 12. Harris C, Greenough A. The prevention and management strategies for
422 neonatal chronic lung disease. Expert Rev Respir Med 2023;17(2):143–154.

- 423 13. Kallio M, Rahtu M, van Kaam AH, Bayford R, Rimensberger PC, Frerichs I.
424 Electrical impedance tomography reveals pathophysiology of neonatal
425 pneumothorax during NAVA. Clin Case Rep 2020;8(8):1574–1578.
- 426 14. Shono A, Kotani T. Clinical implication of monitoring regional ventilation using
427 electrical impedance tomography. J Intensive Care 2019 [accessed 2024 Nov
428 13];7(1):1–10. [https://jintensivecare.biomedcentral.com/articles/10.1186/s40560-](https://jintensivecare.biomedcentral.com/articles/10.1186/s40560-019-0358-4)
429 019-0358-4
- 430 15. Frerichs I, Amato MBP, Van Kaam AH, Tingay DG, Zhao Z, Grychtol B,
431 Bodenstein M, Gagnon H, Böhm SH, Teschner E, et al. Chest electrical impedance
432 tomography examination, data analysis, terminology, clinical use and
433 recommendations: Consensus statement of the TRanslational EIT developmeNt
434 stuDY group. Thorax 2017 [accessed 2022 Mar 23];72(1):83–93.
- 435 16. Mansouri S, Alharbi Y, Haddad F, Chabcoub S, Alshrouf A, Abd-Elghany AA.
436 Electrical Impedance tomography – Recent applications and developments. J
437 Electr Bioimpedance 2021;12(1):50–62.
- 438 17. Becher TH, Miedema M, Kallio M, Papadouri T, Karaoli C, Sophocleous L,
439 Rahtu M, van Leuteren RW, Waldmann AD, Strodthoff C, et al. Prolonged
440 Continuous Monitoring of Regional Lung Function in Infants with Respiratory
441 Failure. Ann Am Thorac Soc 2022 [accessed 2023 Apr 30];19(6):991–999.
442 <https://pubmed.ncbi.nlm.nih.gov/34898392/>
- 443 18. Rahtu M, Frerichs I, Waldmann AD, Strodthoff C, Becher T, Bayford R, Kallio
444 M. Early Recognition of Pneumothorax in Neonatal Respiratory Distress
445 Syndrome with Electrical Impedance Tomography. Am J Respir Crit Care Med
446 2019 [accessed 2022 May 20];200(8):1060–1061. [https://pubmed-ncbi-nlm-nih-](https://pubmed-ncbi-nlm-nih-gov.pc124152.oulu.fi:9443/31091957/)
447 gov.pc124152.oulu.fi:9443/31091957/
- 448 19. Miedema M, Frerichs I, De Jongh FHC, Van Veenendaal MB, Van Kaam AH.
449 Pneumothorax in a preterm infant monitored by electrical impedance
450 tomography: a case report. Neonatology 2011 [accessed 2022 May 21];99(1):10–
451 13. <https://pubmed-ncbi-nlm-nih-gov.pc124152.oulu.fi:9443/20588065/>
- 452 20. Miedema M, McCall KE, Perkins EJ, Sourial M, Böhm SH, Waldmann A, Van
453 Kaam AH, Tingay DG. First real-Time visualization of a spontaneous
454 pneumothorax developing in a preterm lamb using electrical impedance
455 tomography. Am J Respir Crit Care Med 2016 [accessed 2022 May
456 21];194(1):116–118. www.atsjournals.org.
- 457 21. Steinmann D, Engehausen M, Stiller B, Guttman J. Electrical impedance
458 tomography for verification of correct endotracheal tube placement in paediatric
459 patients: a feasibility study. Acta Anaesthesiol Scand 2013 [accessed 2022 May
460 21];57(7):881–887. [https://pubmed-ncbi-nlm-nih-](https://pubmed-ncbi-nlm-nih-gov.pc124152.oulu.fi:9443/23750708/)
461 gov.pc124152.oulu.fi:9443/23750708/

462 22. Sweet DG, Carnielli VP, Greisen G, Hallman M, Klebermass-Schrehof K, Ozek
463 E, Te Pas A, Plavka R, Roehr CC, Saugstad OD, et al. European Consensus
464 Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update.
465 Neonatology 2023 [accessed 2024 Feb 22];120(1):3.
466 /pmc/articles/PMC10064400/

467 23. Kalikkot Thekkeveedu R, El-Saie A, Prakash V, Katakam L, Shivanna B.
468 Ventilation-Induced Lung Injury (VILI) in Neonates: Evidence-Based Concepts and
469 Lung-Protective Strategies. J Clin Med 2022 [accessed 2022 May 20];11(3).
470 <https://pubmed-ncbi-nlm-nih-gov.pc124152.oulu.fi:9443/35160009/>

471 24. Sophocleous L, Frerichs I, Miedema M, Kallio M, Papadouri T, Karaoli C,
472 Becher T, Tingay DG, van Kaam AH, Bayford R, et al. Clinical performance of a
473 novel textile interface for neonatal chest electrical impedance tomography.
474 Physiol Meas 2018 [accessed 2020 Apr 1];39(4):044004.
475 <http://www.ncbi.nlm.nih.gov/pubmed/29516865>

476 25. Khodadad D, Nordebo S, Müller B, Waldmann A, Yerworth R, Becher T,
477 Frerichs I, Sophocleous L, Van Kaam A, Miedema M, et al. Optimized breath
478 detection algorithm in electrical impedance tomography. Physiol Meas 2018
479 [accessed 2022 Mar 23];39(9). [https://pubmed-ncbi-nlm-nih-](https://pubmed-ncbi-nlm-nih-gov.pc124152.oulu.fi:9443/30074906/)
480 [gov.pc124152.oulu.fi:9443/30074906/](https://pubmed-ncbi-nlm-nih-gov.pc124152.oulu.fi:9443/30074906/)

481 26. Erickson G, Dobson NR, Hunt CE. Immature control of breathing and apnea of
482 prematurity: the known and unknown. Journal of Perinatology 2021;41(9):2111-
483 2123.

484 27. Fang SJ, Su CH, Liao DL, Chen CC, Chung MY, Chen FS, Huang HC, Ou-Yang
485 MC. Neurally adjusted ventilatory assist for rapid weaning in preterm infants.
486 Pediatrics International 2023 [accessed 2025 Feb 20];65(1):e15360.
487 <https://onlinelibrary.wiley.com/doi/full/10.1111/ped.15360>

488 28. Lee Y, Lee J. Neurally adjusted ventilatory assist improves survival, and its
489 early application accelerates weaning in preterm infants. Pediatrics International
490 2024 [accessed 2025 Feb 20];66(1):e15831.
491 <https://onlinelibrary.wiley.com/doi/full/10.1111/ped.15831>

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Figure Legends

1 Fig.1.A. Global tidal impedance variation (ΔZ) is calculated by measuring
2 the difference between end-inspiration and start-inspiration in the EIT
3 signal. The duration of inspiratory time (ms) and respiratory cycle time
4 (ms) are determined by the interval between the start and end of the
5 inspiration, and the interval between the beginnings of two consequent
6 breaths, respectively. An example of a functional tidal image illustrating
7 the distribution of tidal volume is presented in section B. High-intensity
8 areas correspond to ventilated regions of the right and left hemithorax in
9 a cross-sectional view of the chest, as obtained in a supine subject.
10 Regional impedance variations were computed for ten regions: four larger
11 and six smaller regions. An example of the EIT signal from a single study
12 participant is illustrated in section C, demonstrating differences in tidal
13 volumes and respiratory patterns on a breath-by-breath basis. The dashed
14 line indicates the ventilation mode change. EIT = Electrical Impedance
15 Tomography. PCV = Pressure Controlled Ventilation. NAVA = Neurally
16 Adjusted Ventilatory Assist. ΔZ = Tidal impedance variation.

17 Fig. 2. The effect of ventilation support change from PCV to NAVA on
18 regional ventilation distribution (ΔZ) and CoVs. Differences in global and
19 regional ΔZ across ventilation modes were assessed case by case and
20 then normalised against the individual mean global ΔZ in the PCV. There
21 were no systematic changes in the mean global ΔZ , regional tidal
22 impedance variations or CoVs between NAVA and PCV. A tendency
23 towards more dorsal CoV during NAVA was observed with a mean
24 difference of 1.3% (SD 2.8, $P = 0.084$). Data is presented as the mean

difference between NAVA and PCV (95% CI). ΔZ = Tidal impedance variation. PCV = Pressure Controlled Ventilation. NAVA = Neurally Adjusted Ventilatory Assist. CoV R-L = Center of Ventilation right-to-left. CoV V-D = Center of Ventilation ventral-to-dorsal.

Fig.3. Distribution of the respiratory cycle time (ms) for both PCV (blue bars) and NAVA (black bars); the bluish-grey areas represent overlap with the two ventilation modes. Each respiratory cycle was normalized by subtracting the individual mean cycle time in PCV. Negative values represent a shorter duration of the respiratory cycle, and positive values present longer respiratory cycles compared to the mean cycle time in PCV. A significantly greater variability in the respiratory cycle time was observed when NAVA was used ($P < 0.05$). ΔZ = Tidal impedance variation. PCV = Pressure Controlled Ventilation. NAVA = Neurally Adjusted Ventilatory Assist.

Fig. 4. Distribution of tidal volume (%) for both PCV (blue bars) and NAVA (black bars), bluish-grey areas represent overlap with the two ventilation modes. Values were normalized by the individual mean tidal volume observed during PCV, meaning that negative or positive values are proportionally smaller or larger in size than an average size breath in PCV (0%), respectively. This visualization highlights a significantly greater variability in tidal volumes ($P < 0.05$). A dashed line indicates the threshold for breaths exceeding twice the average size, clinically identified as sighs. Sighs occurred more frequently during NAVA than PCV, at 5.2% vs 0.8%, respectively). ΔZ = Tidal impedance variation. PCV =

49 Pressure Controlled Ventilation. NAVA = Neurally Adjusted Ventilatory
50 Assist.

51

Figure 1

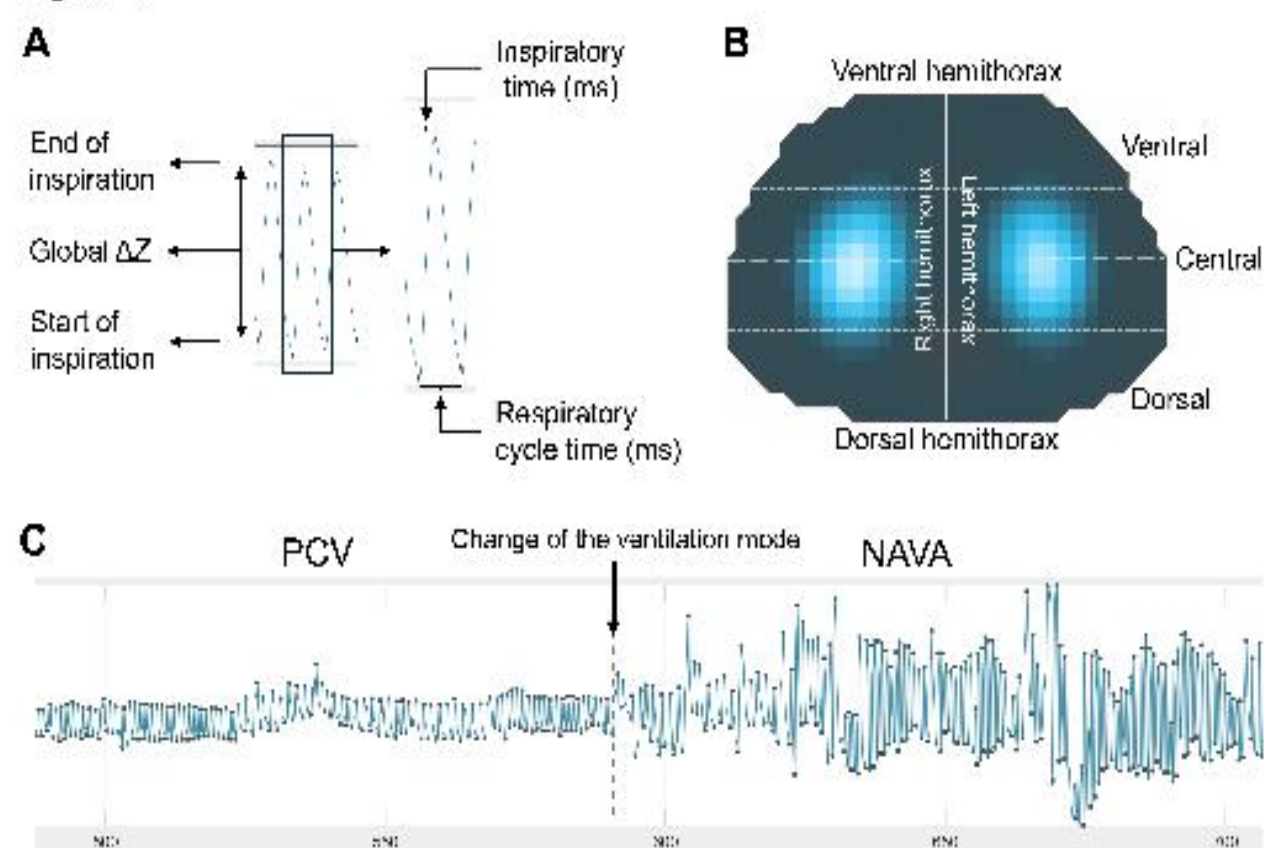
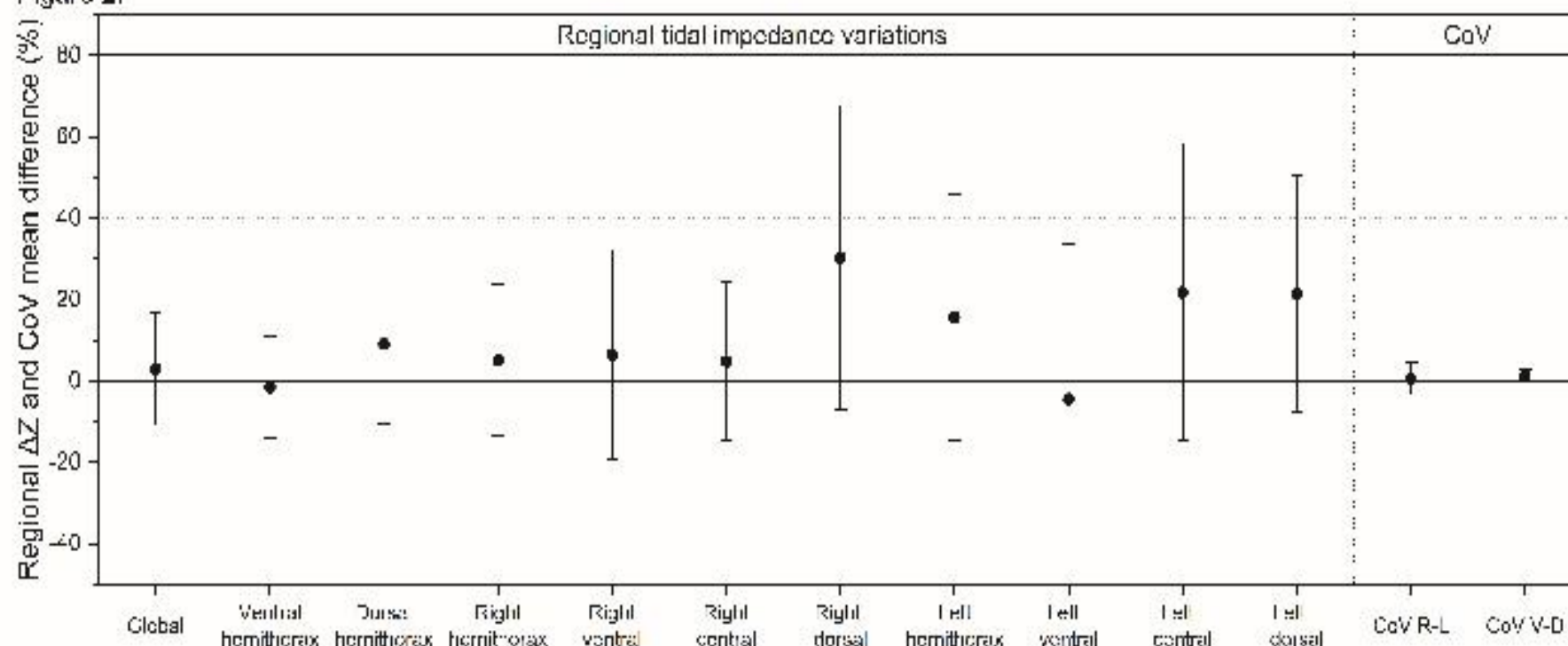


Figure 2.



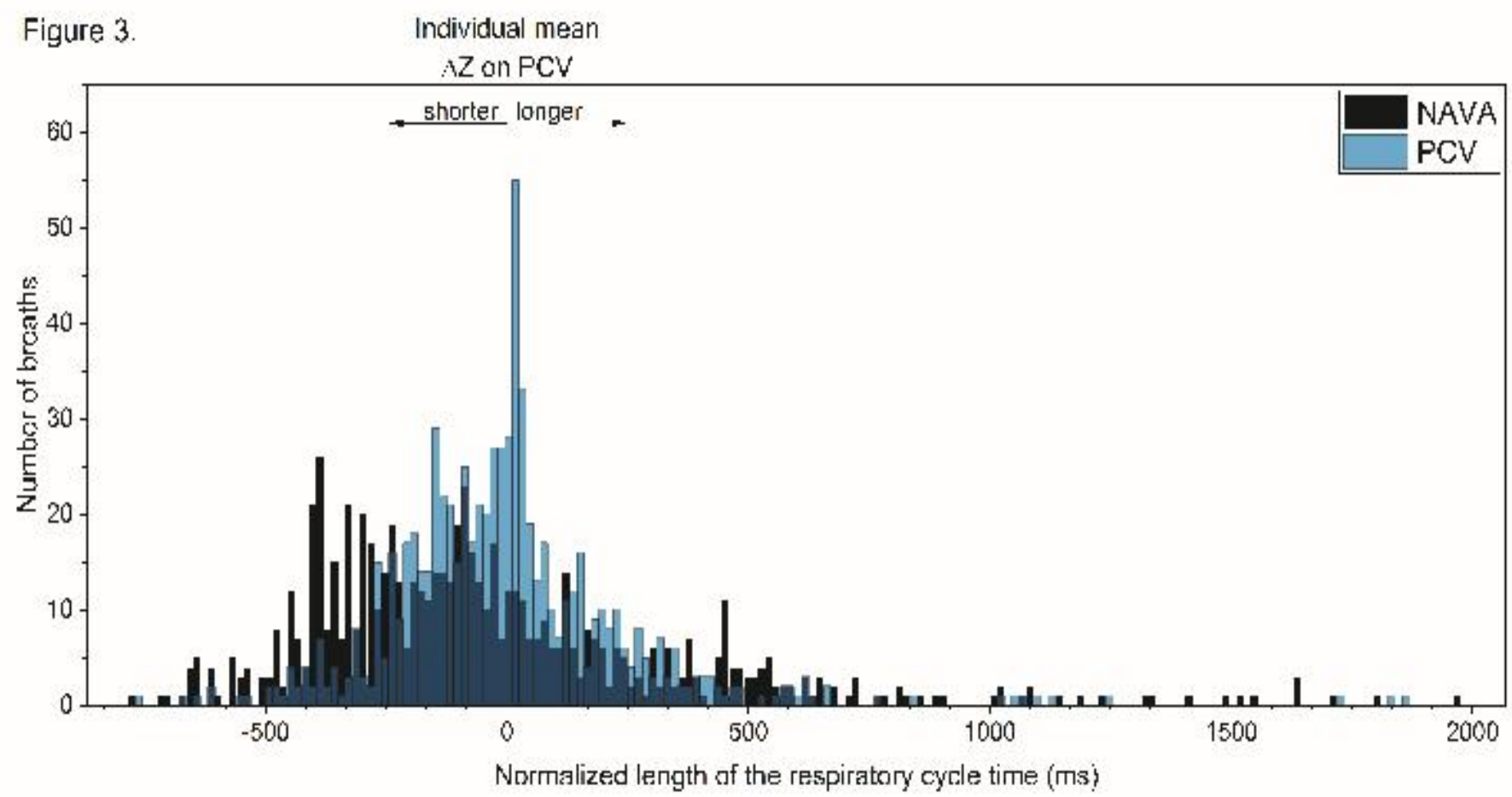


Figure 4.

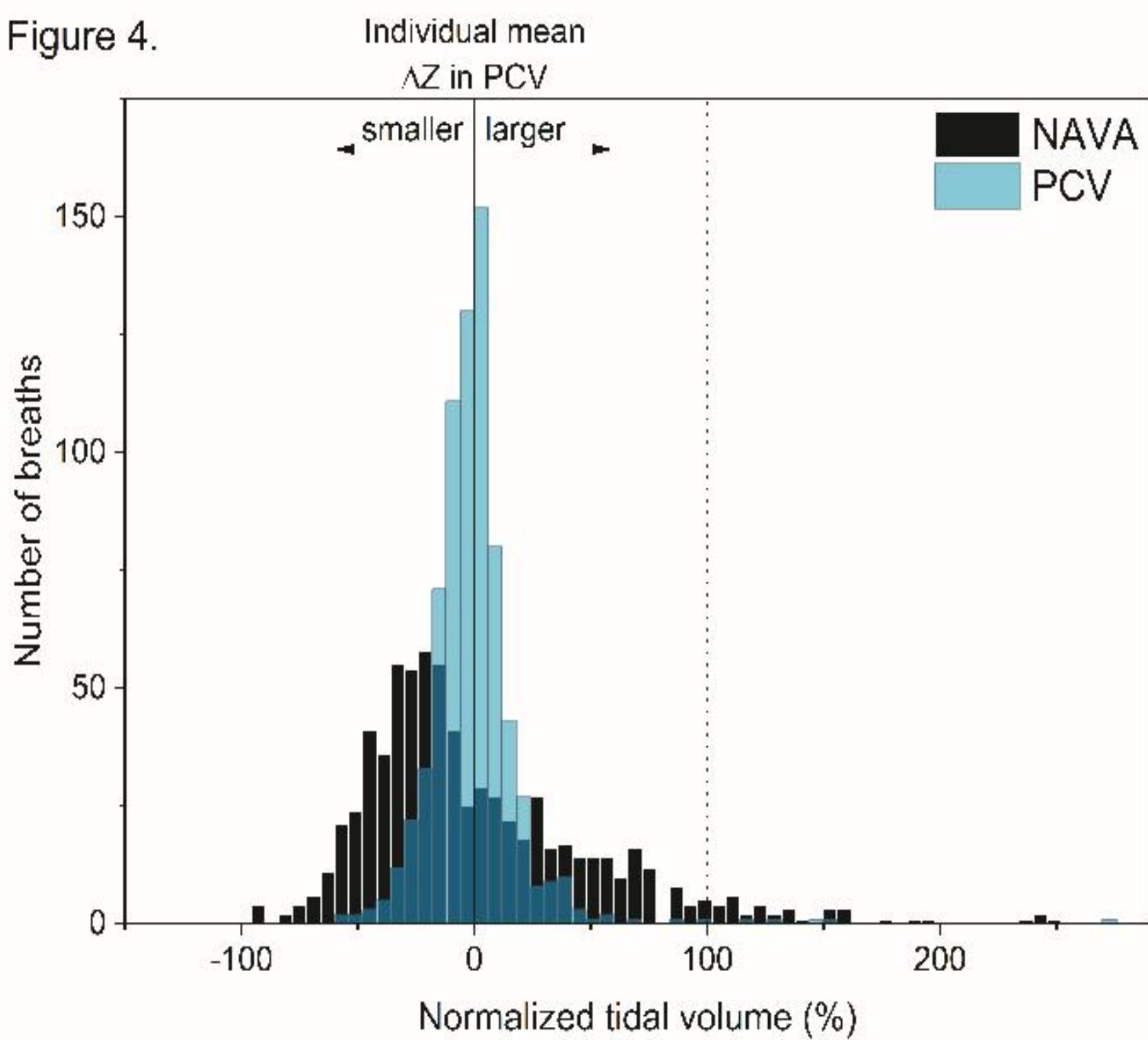


Table 1. Physiological characteristics.

	n (%)		
Males	8 (50)		
RDS	16 (100)		
Surfactant treatment	16 (100)		
	Mean	SD	Range
Postnatal age (<i>hours</i>)	26	35	[2.5, 120]
Gestational age (<i>weeks</i>)	32.9	2.8	[28.0, 37.3]
Height (<i>cm</i>)	41.2	3.4	[32.0, 45.3]
Weight (<i>kg</i>)	1.92	0.6	[1.14, 3.26]

% = per cent. SD = Standard Deviation. RDS = Respiratory Distress Syndrome.
n = number of patients.

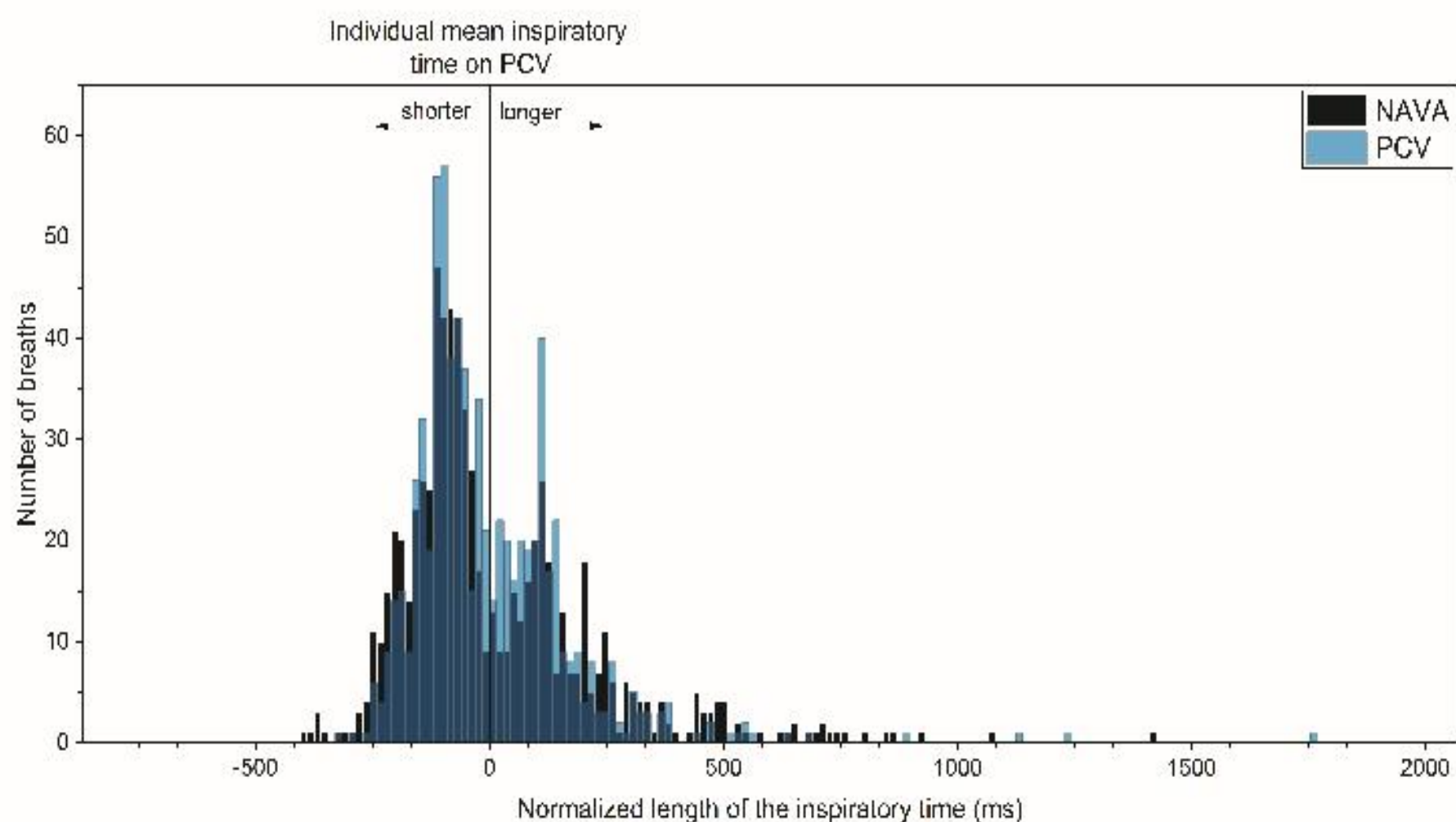
Table 2. Observed EIT and physiological parameters during PCV and NAVA.

Variable	PCV	NAVA	Mean	P value
EIT	Mean (SD)	Mean (SD)	Difference	
Respiratory rate EIT (<i>breaths/min</i>)	50.7 (12.4)	50.3 (14.2)	-0.4	0.605
Inspiratory time (<i>ms</i>)	480 (98)	505 (163)	25	0.605
Inspiratory time SD (<i>ms</i>)	174.9 (74.7)	198.2 (55.1)	23.4	0.215
Respiratory cycle time (<i>ms</i>)	1259 (355)	1324 (556)	66	0.717
Respiratory cycle time SD (<i>ms</i>)	257.8 (145.6)	528.3 (210.0)	270.6	< 0.05
Global ΔZ SD (%)	19.1 (13.3)	44.9 (19.7)	25.9	< 0.05

Physiologic				
Heartrate (<i>beats</i> <i>/min</i>)	135.7 (22.3)	137.2 (24.8)	1.5	0.698
Systolic blood pressure (<i>mmHg</i>) ^a	57.6 (8.2)	55.2 (7.1)	-2.4	0.056
Diastolic blood pressure (<i>mmHg</i>) ^a	37.9 (5.8)	37.4 (6.7)	-0.4	0.733
SpO ₂ (%)	94.7 (3.6)	94.9 (4.0)	0.2	0.379
FiO ₂ (%)	24.7 (6.3)	22.6 (3.3)	-2.1	0.161

PCV = Pressure Controlled Ventilation. NAVA = Neurally Adjusted Ventilatory Assist. SD = Standard Deviation. EIT = Electrical Impedance Tomography. ΔZ = Tidal impedance variation. mmHg = Millimetre of mercury. SpO₂ = Peripheral oxygen saturation. FiO₂ = Fraction of inspired oxygen. ^aInformation on 15 subjects. Arterial blood pressure values were measured except for

one study subject with a noninvasive measurement. The Wilcoxon signed-ranked test was used to compare groups. Asymp. Sig. (2-tailed) P value < 0.05 was considered statistically significant.



E-figure 2. Distribution of the normalized length of the inspiratory time (ms) for both PCV (blue bars) and NAVA (black bars), bluish-grey area represent overlap with the two ventilation modes. Each inspiratory time was normalized by subtracting the individual mean inspiratory time in PCV. Negative values indicate a shorter inspiratory time while positive values indicate a longer inspiratory time compared to the mean inspiratory time in PCV.

PCV = Pressure Controlled Ventilation. NAVA = Neurally Adjusted Ventilatory Assist. ms = Millisecond.

E-table 1. Regional ΔZ (AU), CoV and silent spaces (AU) mean differences compared between NAVA and PCV.

	Mean difference (%)	SD	95% CI	p value
Global	3.0	25.7	[-10.7, 16.6]	0.651
CoV R-L	0.55	7.5	[-3.4, 4.5]	0.770
CoV V-D	1.3	2.8	[-1.9, 2.7]	0.084
Ventral hemithorax	-1.5	23.6	[-14.1, 11.0]	0.799
Dorsal hemithorax	9.1	36.7	[-10.5, 28.6]	0.338
Right hemithorax	5.1	34.9	[-13.5, 23.7]	0.568
Ventral area	6.4	48.1	[-19.2, 32.1]	0.600
Central area	4.9	36.7	[-14.7, 24.4]	0.604
Dorsal area	30.2	70.2	[-7.2, 67.6]	0.106
Left hemithorax	15.6	56.8	[-14.6, 45.9]	0.288
Ventral area	-4.5	71.8	[-42.7, 33.8]	0.806
Central area	21.7	68.6	[-14.8, 58.3]	0.224
Dorsal area	21.3	54.6	[-7.8, 50.4]	0.139
Silent spaces	0.3	13.8	[-7.1, 7.6]	0.943
Non-dependent area	0.3	6.0	[-2.9, 3.4]	0.865
Dependent area	0.0	8.2	[-4.4, 4.4]	0.997

ΔZ = Impedance variation. AU = Arbitrary unit. CoV = Center of Ventilation. NAVA = Neurally Adjusted Ventilation Assist. PCV = Pressure Controlled Ventilation. SD = Standard Deviation. CI = Confidence Interval of the Difference. CoV R-L = Center of Ventilation Right-to-Left. CoV V-D Center of Ventilation Ventral-to-Dorsal. Silent spaces area = an area where impedance variation was less than 10%. Calculations on EIT data between the two ventilation modes were first made within the study subjects. One-Sample T-Test was used to compare if the group mean difference is other than 0. P value < 0.05 was considered statistically significant.

E-table 3. Distribution of tidal volumes (%).

Breath size	PCV	NAVA
< -100%	0.0	0.5
-100% - 0	53.3	59.9
0 - 100%	45.9	34.3
> 100%	0.8	5.2
Total (n) X ² = 42.7; freedom = 3; P < 0.001	100 (734)	100 (729)

Tidal volume is proportional to tidal impedance variation (ΔZ), which was calculated for every breath. An individual mean ΔZ during PCV was calculated and used as a reference for an averaged breath (0%) for every infant separately. > 100% breath size indicates twice the average breath in PCV, which was interpreted as a sigh. PCV = Pressure Controlled Ventilation. NAVA = Neurally Adjusted Ventilatory Assist. X² = Chi-Square.