Physiological Measurement

ACCEPTED MANUSCRIPT

Bronchodilator effect on regional lung function in pediatric viral lower respiratory tract infections

To cite this article before publication: Claas Strodthoff *et al* 2022 *Physiol. Meas.* in press https://doi.org/10.1088/1361-6579/ac9450

Bronchodilator effect on regional lung function in pediatric viral lower respiratory tract infections

Claas Strodthoff[a], Toni Kähkönen[b], Richard H. Bayford[c], Tobias Becher[a], Inéz Frerichs[a], Merja Kallio[b,d]

[a] *Department of Anaesthesiology and Intensive Care Medicine, University Medical Centre Schlewig-Holstein, Kiel, Germany*
[b] *PEDEGO Research Unit, Medical Research Center Oulu, University of Oulu, Oulu, Finland*
[c] *Department of Natural Sciences, Middlesex University, London, United Kingdom*
[d] *Department of Children and Adolescents, Oulu University Hospital, Oulu, Finland*

Abstract

Objective Viral lower respiratory tract infections (LRTI) are the leading cause for acute admission to the intensive care unit in infants and young children. Nebulized bronchodilators are often used when treating the most severe cases. Aim of this study was to investigate the bronchodilator effect on respiratory mechanics during intensive care with electrical impedance tomography (EIT) and to assess the feasibility of EIT in this context.

Approach We continuously monitored the children with chest EIT for up to 72h in an observational study design. The treatment decisions were done by clinical assessment, as the clinicians were blinded to the EIT information during data collection. In a retrospective analysis, clinical parameters and regional expiratory time constants determined by EIT were used to assess the effects of bronchodilator administration, especially regarding airway resistance.

Main results We included six children from 11 to 27 months of age requiring intensive care due to viral LRTI and receiving bronchodilator agents. Altogether 131 bronchodilator administrations were identified during EIT monitoring. After validation of the exact timing of events and EIT data quality, 77 administrations were included in the final analysis. Fifty-five bronchodilator

Email address: claas.strodthoff@uksh.de (Claas Strodthoff)

events occurred during invasive ventilation and 22 during high-flow nasal cannulae treatment. Only 17% of the bronchodilator administrations resulted in a relevant decrease in calculated expiratory time constants.

Significance Continuous monitoring with EIT might help to optimize the treatment of LRTI in pediatric intensive care units. Especially EIT-based regional expiratory time constants would allow objective assessment of the effects of bronchodilators and other respiratory therapies.

Keywords: Pediatric Intensive Care Units, Respiratory Tract Infections, Bronchodilator Agents, Airway Resistance, Electrical Impedance, Tomography

1. Introduction

Viral lower respiratory tract infections (LRTI) are the leading cause of hospitalization and acute intensive care admission in infants and young children [1, 2]. Respiratory syncytial virus (RSV) and human rhinovirus (HRV) are the most common pathogens causing respiratory failure in this population [3, 4, 5, 6]. Respiratory distress and airway obstruction during viral LRTI in children are caused by a combination of mucosal edema, secretions and bronchoconstriction [7].

Treatment for severe LRTI consists of supplemental oxygen, respiratory support, and other supportive measures, such as suctioning of secretions from the airway. Noninvasive types of respiratory support, especially high-flow nasal cannulae (HFNC), are increasingly being used in pediatric intensive care units (PICU) [2, 3]. However, invasive ventilation is still often required for the most severely ill children. Symptom-relieving medication includes nebulized bronchodilators and adrenaline, corticosteroids, pain killers and sedation for agitated patients [8, 9, 10]. Antibiotics are also frequently given due to the risk of bacterial co-infections in critically ill patients [8, 11].

Although routine administration of salbutamol is not recommended for pediatric patients under two years of age suffering from LRTIs, a subgroup of infants (age above 6 months, wheezing on arrival and HRV as the cause) may benefit from bronchodilator treatment and thus, it is often used when treating severe cases in PICUs [12, 13, 8, 14]. Nebulization via the HFNC system instead of using traditional face masks improves patient comfort, but lung deposition of the drug has been shown to be very sensitive to the flow rate used. Moreover, during invasive ventilation the correct placement of the nebulizer within the circuit is essential [15, 16, 17, 18]. Clinical assessment is insufficient to recognize salbutamol responders reliably [19], so additional tools are needed to better guide the treatment.

Electrical impedance tomography (EIT) is a noninvasive continuous monitoring method for lung aeration and regional ventilation [20]. The method was validated using established radiological methods like computed tomography [21, 22, 23, 24, 25], positron emission tomography [26] or single-photon emission CT [27]. Recently it has been applied to pediatric patients with COVID-19 [28]. EIT has been successfully used to observe bronchodilator effects in both children and adults [29, 30, 31]. Nebulization of bronchodilators is expected to reduce airway resistance, which is one of the factors that determine the expiratory time constant. Since the time constant is the product of expiratory airway resistance and respiratory system compliance, a reduction in airway resistance through nebulization is expected to result in a reduction of regional expiratory time constants. The feasibility and reliability of EIT-derived assessment of time constants have been demonstrated in adult patients [32, 33]. The aim of this study was to use EIT in assessing the effect of bronchodilators in pediatric LRTI during PICU treatment.

2. Methods

2.1. Data source: CRADL clinical trial

This work is a retrospective analysis of a subset of the data from the prospective observational multicenter EIT trial Continuous Regional Analysis Device for Neonate Lung (CRADL). Two hundred neonates and children less than 36 months of age were included in the CRADL trial from November 2016 to March

2019 at four European study sites with tertiary NICUs and one PICU (CiniclTrials.gov identifier: NCT02962505) [34]. The Ethical Committee of the Northern Ostrobothnia Health Care District approved the protocol (EETTMK: 35/2017), and written informed consent was obtained from a parent or legal guardian before performing any procedures related to the study. Continuous chest EIT monitoring (48 scans/s) was carried out for up to 72 hours with a 32-electrode belt connected to an EIT system (SenTec BB^2, Landquart, Switzerland) [35]. A graphical user interface was used to report all interventions, and a video recording was used to confirm the events. All study participants had or were "at risk" of respiratory failure.

LRTI was the cause of respiratory failure in eleven PICU patients. Six of them were above 6 months of age and received nebulized bronchodilators due to wheezing during their treatment in the PICU, and were included in this study. Detailed patient characteristics are presented in table 1.

2.2. Bronchodilator administration

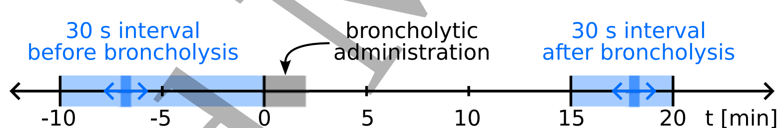

Figure 1: Timeline for the selection of analysis intervals. Start of broncholytic administration at time t=0.

Patient files were used to collect information on all bronchodilator administrations during the study period. The exact timing of drug administration was confirmed from the video recordings. The quality of EIT data was checked, and 30-second sequences of EIT signal without patient movement and failing electrodes were selected for analysis 0-10 minutes before the start of nebulization and 15-20 minutes after confirmed nebulization. Video information was also used to confirm that the patient position did not change significantly between the selected time sequences. Various clinical parameters were aggregated within the confirmed analysis intervals. The doses were 0.075 to 0.15 mg/kg

Salbutamol with repeated doses every 2 to 4 hours. 125 µg of Ipratropium was administered about every 6 hours. The decision on whether to give only salbutamol or both, and how frequently, was made on clinical basis by the doctor responsible for the treatment. A circuit integrated nebulizer was used both during invasive ventilation and HFNC. The duration of inhalation was 2 to 3 minutes. Figure 1 visualizes the measurement protocol.

2.3. Exponential modelling of expiration

A common way to approach airway resistance is via time constants, as with passive expiration the change of air volume in the lung may be described as follows [36]:

$$V(t) = V_0 \cdot \mathrm{e}^{-\frac{t}{\tau}} + V_{\mathrm{FRC}} \tag{1}$$

with the expiratory time constant τ being the product of respiratory system compliance and airway resistance. $V(t)$ is the lung volume at time t, starting with $t = 0$ at the end of expiration. V_{FRC} is the functional residual lung capacity. We performed exponential regression to assess the regional distribution of expiratory time constants by applying the following workflow:

All individual pixel values were summed to yield the global EIT sum signal, which closely correlates with the thoracic gas volume [23]. Global maxima and minima were detected in the sum signal, corresponding to the time points of maximal inspiration and expiration. Because not all image pixels reach their respective minima/maxima at the same time in a breathing cycle, we allowed for a shift of each pixel maximum of up to half the time to the next global minimum in every pixel (analog for minima). Using these individually adjusted pixel minima and maxima we selected the time points where the impedance values were between the 10^{th} and 90^{th} percentile of this range. This means for every individual pixel, the first and last part of the expiration was discarded. This is a compromise between keeping as much data as possible and discarding parts that are either misleading or particularly noisy [37]. For the pixelwise detection of maxima/minima and for the selection of the respective data interval, we applied a low-pass filter to the data (3^{rd} order Butterworth filter with fixed cutoff frequency 2 Hz) to reduce high-frequency noise like cardiac oscillations. With the data preselected in this fashion, we performed least-squares fits for every expiration and every pixel based on the following formula on the unfiltered data (analog to equation (1)):

$$Z(t) = Z_0 \cdot \mathrm{e}^{-\frac{t}{\tau}} + Z_{\mathrm{res}} \quad (2)$$

with Z(t) being the raw pixel impedance signal at time t with $t = 0$ at the end of expiration with respect to a reference image, and τ being the expiratory time constant. Z_0 is a positive scale factor, which is proportional to the static compliance. The residual constant Z_{res} is necessary because of the varying regional baseline impedances as well as the arbitrary impedance baseline. The latter is a product of the EIT image reconstruction where impedance changes with respect to an arbitrary reference are calculated rather than absolute values [20]. Within each selected interval the median of all successful fits for a pixel was calculated if there was a successful fit for this pixel in at least half of the globally detected breaths. A fit was considered successful if the R^2 value exceeded 0.8. The result of this procedure is a map of time constants within the thoracic cross-section.

2.4. Statistical analysis

For statistical calculations on these maps, we used functional lung contours, which we defined as all pixels with at least 10% of the maximum (positive) tidal impedance variation [38]. For each of these maps we calculated the weighted mean expiratory time constant $\bar{\tau}_w$, weighted mean standard deviation $\mathrm{SD}_{\bar{\tau}_w}$ and weighted coefficient of variation $\mathrm{CV}_{\bar{\tau}_w}$ with the weights being proportional to the corresponding pixel values in the tidal image. We also report the global expiratory time constant $\tau_{\mathrm{glob.}}$, which was calculated on a per-breath basis from the global impedance sum signal. Independent of the time constant calculation, we also calculated the center of ventilation in the right/left and ventral/dorsal directions as established EIT parameters of ventilation distribution [20].

To discern effective bronchodilator administrations we investigated the change in weighted mean expiratory time constants. Events with a decrease in the weighted mean expiratory time constant of at least 20% were considered successful [19].

Depending on the assumed variable distribution, we used a paired Student's t-test for normally distributed variables and a (paired) Wilcoxon-Mann-Whitney test for non-normally distributed variables. The significance level was 5%.

3. Results

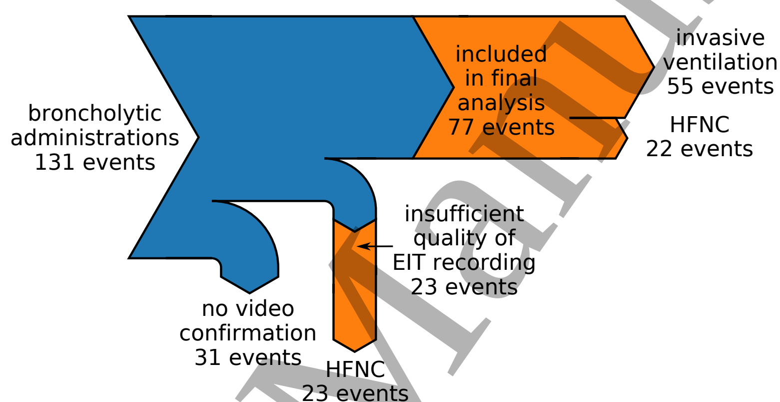

Figure 2: Flow chart of the data acquisition. EIT: electrical impedance tomography, HFNC: high-flow nasal cannulae.

From the larger CRADL study, we included all patients above 6 months of age who received bronchodilators. Altogether, 131 doses of nebulized bronchodilators were administered during EIT monitoring to this group of viral LRTI patients. 31 of these events could not be validated using the video log which was captured alongside the EIT signal. Further 23 events were excluded because of insufficient EIT signal quality (e.g. because of electrodes losing contact). The remaining 77 events were included in the final analysis (figure 2). Nebulized bronchodilators led to a mild increase in heart rate and a slight reduction in the peripheral O_2 saturation to fraction of inspired O_2 (SF) ratio, while the other clinical parameters remained stable (table 2).

Figure 3 shows the time constant maps for two broncholysis events of the same patient along with the chest X-ray taken in between. The patient is an infant suffering from a viral LRTI caused by bocavirus (last row in table 1). Hazy clustered nodules together with mild overinflation of the right lower lobe, both typical findings in LRTI, are seen in the X-ray. The correct positions of the intubation tube, the nasogastric tube, and the EIT belt around the chest were confirmed. In **a**, before the intervention, we see high expiratory time constants (over 1 s) in the left lung and ventral areas of the right lung. After the intervention, the time constants in the left lung became lower and more homogenous. Also, parts of the right lung have decreased time constants compared to before the intervention, which becomes evident when inspecting the difference plot. Subplot **c** depicts a later broncholysis event of the same patient. Neither the ventilation distribution nor the time constants changed relevantly during this event.

In table 3, we present the numeric results derived from the time constant calculations and tidal images. There were no significant changes in the considered parameters when comparing before and after the broncholytic administration.

Table 4 shows the success rates of administration of broncholytics split up for the different subgroups. Each of the six patients had both events considered successful and unsuccessful.

4. Discussion

Based on this observational study, continuous monitoring with EIT is suitable for the assessment of bronchodilator effects in severe cases of pediatric LRTI in PICU. Administration of bronchodilators only rarely led to significant improvement in the expiratory time constant, and the majority of nebulizations either had no effect or worsened the airflow.

To the best of our knowledge, this is the first time EIT is used in assessing the effect of a bronchodilator in pediatric viral LRTI. We used a somewhat arbitrary limit of 20% improvement in the expiratory time constant, as it has been used previously in a similar setting [39]. With this limit, the vast minority of bronchodilator administrations resulted in a better expiratory time constant, but the drug administration was often followed by quite an opposite response, possibly due to the stirring of secretions. In addition, the response within the same patient changed from time to time. Hence, in our opinion, the patients should not be classified simply as responders or non-responders [39], but instead monitored carefully throughout the PICU period and treated following the respiratory physiology at each point in time.

Many of the patients in this work exhibited relevant spontaneous breathing efforts; some were even breathing completely spontaneously (HFNC group). The applicability of the analysis of expiratory time constants in this population is uncertain. Nonetheless, there are strong indications that the expiratory time constants calculated in this work are useful even under these circumstances. First, the time constants that were calculated here are in a plausible range [32], and the expiration was well-modeled by an exponential function. Second, even if the calculated time constants did not reflect the true time constant of the respiratory system as measured without spontaneous breathing effort, they would still be a useful tool for comparing relative flow in different lung regions or at different times. Thus, a decrease in time constants could confidently be interpreted as either an decrease of the airway resistance or the respiratory system compliance.

The role of bronchodilators in treating pediatric viral LRTI in PICU is constantly debated for several reasons, such as concern for potential drug-related adverse events and the fact that critically ill children are often excluded from randomized controlled trials, so there are no valid data on this group of patients [40, 41]. Children below two years of age are often considered as one group despite the fact that they present a very heterogenous population [2, 42]. Recent data suggests that a subgroup of patients over 6 months of age potentially benefit from bronchodilators, and it is common that clinicians prescribe them when treating severe cases in PICU [13]. More detailed assessment of pulmonary function in RCTs designed to assess treatment for pediatric viral LRTI is needed [41, 42]. Our patients were between one and two years of age and represented typical group of patients wheezing during viral LRTI. We were able to confirm the viral etiology of illness in all patients. The ability of EIT to assess regional lung function in this patient population makes it a potential tool for research as well as for individually optimizing treatment.

However, further product development is needed to ensure adequate data quality during noninvasive respiratory support and in spontaneously moving infants: all of the events that were excluded due to insufficient EIT signal quality occurred during noninvasive respiratory support with HFNC. Improved belts, electrodes, contact agents or image reconstruction techniques are options that might mitigate measurement problems in these difficult measurement conditions where patients are hardly sedated.

The main limitation of this study was the fact that it involved a subgroup of patients in a purely observational multicenter trial, so the drug administration and patient monitoring did not follow any strict protocol. However, we believe that the data are valuable for assessing the usability of EIT in real-world situations. The decision to use a bronchodilator was based solely on clinical assessment, and clinical records confirmed that wheezing was observed prior to the prescription of bronchodilators. We were also able to confirm the exact timing of the drug administrations with the video recording, and the patient position was confirmed to have not changed between the selected time intervals. The fact that we observed a slight increase in heart rate and a mild reduction in oxygenation confirms that the selected time intervals represented the times that the drug had been administered [43]. Many of the patients were given bronchodilators regularly without routine assessment after every dose, which may have led to a situation in which the wheezing had already been resolved at time of administration, resulting in a no-response situation. Unfortunately, due to the design of the CRADL clinical trial and its focus on feasibility and safety of long-term EIT monitoring, no validation measurements like ventilator flow curves were taken. Also one has to keep in mind that spirometric measurements are not easily achievable in spontaneously breathing patients (like under HFNC).

5. Conclusion

In conclusion, continuous monitoring with EIT might help to optimize the treatment of pediatric viral LRTI in PICU. Continuous information on ventilation distribution and time constants could provide a meaningful guidance for individualized dosing and timing of bronchodilator therapy and would allow objective assessment of the effects of bronchodilators and other respiratory therapies.

Acknowledgements

Funding

This project received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 668259.

Conflicts of interest/Competing interests

There were no conflicts of interest.

Ethics approval

The research was conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements. The Ethical Committee of the Northern Ostrobothnia Health Care District approved the protocol (EETTMK: 35/2017).

Personal acknowledgements

The authors wish to thank all the PICU nurses for their diligent work during data collection.

References

[1] H. C. Meissner, Viral bronchiolitis in children, N Engl J Med 374 (18) (2016) 1791–1794. doi:10.1056/nejmc1601509.
URL https://doi.org/10.1056/nejmc1601509

[2] L. J. Schlapbach, L. Straney, B. Gelbart, J. Alexander, D. Franklin, J. Beca, J. A. Whitty, S. Ganu, B. Wilkins, A. Slater, E. Croston, S. Erickson, A. Schibler, Burden of disease and change in practice in critically ill infants with bronchiolitis, Eur Respir J 49 (6) (2017) 1601648. doi:10.1183/13993003.01648-2016.
URL https://doi.org/10.1183/13993003.01648-2016

[3] K. D. Coletti, D. N. Bagdure, L. K. Walker, K. E. Remy, J. W. Custer, High-flow nasal cannula utilization in pediatric critical care, Respiratory Care 62 (8) (2017) 1023–1029. doi:10.4187/respcare.05153.
URL https://doi.org/10.4187/respcare.05153

[4] M. Duyu, Z. Karakaya, Viral etiology and outcome of severe lower respiratory tract infections among critically ill children admitted to the PICU, Medicina Intensiva (May 2020). doi:10.1016/j.medin.2020.04.023.
URL https://doi.org/10.1016/j.medin.2020.04.023

[5] M. E. Smith, P. T. Wilson, Human rhinovirus/enterovirus in pediatric acute respiratory distress syndrome, Journal of Pediatric Intensive Care 09 (02) (2019) 081–086. doi:10.1055/s-0039-3400466.
URL https://doi.org/10.1055/s-0039-3400466

[6] M. C. Spaeder, J. W. Custer, A. H. Miles, L. Ngo, N. P. Morin, S. Scafidi, M. M. Bembea, X. Song, A multicenter outcomes analysis of children with severe rhino/enteroviral respiratory infection, Pediatric Critical Care Medicine 16 (2) (2015) 119–123. doi:10.1097/pcc.0000000000000308.
URL https://doi.org/10.1097/pcc.0000000000000308

[7] K. Douros, M. L. Everard, Time to say goodbye to bronchiolitis, viral wheeze, reactive airways disease, wheeze bronchitis and all that, Frontiers in Pediatrics 8 (2020) 218. doi:10.3389/fped.2020.00218.
URL https://doi.org/10.3389/fped.2020.00218

[8] M. L. Bradshaw, A. Déragon, P. Puligandla, G. Emeriaud, A.-M. Canakis,

P. S. Fontela, Treatment of severe bronchiolitis: A survey of canadian pediatric intensivists, Pediatr Pulmonol 53 (5) (2018) 613–618. doi:10.1002/ppul.23974.
URL https://doi.org/10.1002/ppul.23974

[9] T. Kanjanapradap, J. Deerojanawong, S. Sritippayawan, N. Prapphal, Does nebulized hypertonic saline shorten hospitalization in young children with acute viral wheezing?, Pediatr Pulmonol 53 (2) (2017) 138–144. doi:10.1002/ppul.23924.
URL https://doi.org/10.1002/ppul.23924

[10] S. J. Foster, M. N. Cooper, S. Oosterhof, M. L. Borland, Oral prednisolone in preschool children with virus-associated wheeze: a prospective, randomised, double-blind, placebo-controlled trial, The Lancet Respiratory Medicine 6 (2) (2018) 97–106. doi:10.1016/s2213-2600(18)30008-0.
URL https://doi.org/10.1016/s2213-2600(18)30008-0

[11] A. C. van de Pol, T. F. Wolfs, C. E. Tacke, C. S. Uiterwaal, J. Forster, A. M. van Loon, J. L. Kimpen, J. W. Rossen, N. J. Jansen, Impact of PCR for respiratory viruses on antibiotic use: Theory and practice, Pediatr Pulmonol 46 (5) (2010) 428–434. doi:10.1002/ppul.21385.
URL https://doi.org/10.1002/ppul.21385

[12] K. H. Shanahan, M. C. Monuteaux, J. Nagler, R. G. Bachur, Early use of bronchodilators and outcomes in bronchiolitis, Pediatrics 148 (2) (2021) e2020040394. doi:10.1542/peds.2020-040394.
URL https://doi.org/10.1542/peds.2020-040394

[13] C. E. Rodriguez-Martinez, G. Nino, J. A. Castro-Rodriguez, R. Acuña-Cordero, M. P. Sossa-Briceño, F. Midulla, For which infants with viral bronchiolitis could it be deemed appropriate to use albuterol, at least on a therapeutic trial basis?, Allergologia et Immunopathologia 49 (1) (2021) 153–158. doi:10.15586/aei.v49i1.12.
URL https://doi.org/10.15586/aei.v49i1.12

[14] S. L. Ralston, A. S. Lieberthal, H. C. Meissner, B. K. Alverson, J. E. Baley, A. M. Gadomski, D. W. Johnson, M. J. Light, N. F. Maraqa, E. A. Mendonca, K. J. Phelan, J. J. Zorc, D. Stanko-Lopp, M. A. Brown, I. Nathanson, E. Rosenblum, S. Sayles, S. Hernandez-Cancio, Clinical practice guideline: The diagnosis, management, and prevention of bronchiolitis, Pediatrics 134 (5) (2014) e1474–e1502. doi:10.1542/peds.2014-2742.
URL `https://doi.org/10.1542/peds.2014-2742`

[15] A. Berlinski, Pediatric aerosol therapy, Respiratory Care 62 (6) (2017) 662–677. doi:10.4187/respcare.05298.
URL `https://doi.org/10.4187/respcare.05298`

[16] S. Kesavan, I. Amirav, Is aerosol delivery by high-flow nasal cannula in children an effective alternative to face mask aerosol nebulization?, Pediatr Pulmonol 54 (12) (2019) 1873–1874. doi:10.1002/ppul.24480.
URL `https://doi.org/10.1002/ppul.24480`

[17] J. Li, L. Gong, A. Ari, J. B. Fink, Decrease the flow setting to improve trans-nasal pulmonary aerosol delivery via "high-flow nasal cannula" to infants and toddlers, Pediatr Pulmonol 54 (6) (2019) 914–921. doi:10.1002/ppul.24274.
URL `https://doi.org/10.1002/ppul.24274`

[18] J. Valencia-Ramos, A. Mirás, A. Cilla, C. Ochoa, J. Arnaez, Incorporating a nebulizer system into high-flow nasal cannula improves comfort in infants with bronchiolitis, Respiratory Care 63 (7) (2018) 886–893. doi:10.4187/respcare.05880.
URL `https://doi.org/10.4187/respcare.05880`

[19] C. M. Schramm, K. A. Sala, C. L. Carroll, Clinical examination does not predict response to albuterol in ventilated infants with bronchiolitis, Pediatric Critical Care Medicine 18 (1) (2017) e18–e23. doi:10.1097/pcc.0000000000000999.
URL `https://doi.org/10.1097/pcc.0000000000000999`

[20] I. Frerichs, M. B. P. Amato, A. H. van Kaam, D. G. Tingay, Z. Zhao, B. Grychtol, M. Bodenstein, H. Gagnon, S. H. Böhm, E. Teschner, O. Stenqvist, T. Mauri, V. Torsani, L. Camporota, A. Schibler, G. K. Wolf, D. Gommers, S. Leonhardt, A. Adler, Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the translational eit development study group, Thorax 72 (1) (2017) 83–93. arXiv:https://thorax.bmj.com/content/72/1/83.full.pdf, doi:10.1136/thoraxjnl-2016-208357.
URL https://thorax.bmj.com/content/72/1/83

[21] H. Wrigge, J. Zinserling, T. Muders, D. Varelmann, U. Günther, C. von der Groeben, A. Magnusson, G. Hedenstierna, C. Putensen, Electrical impedance tomography compared with thoracic computed tomography during a slow inflation maneuver in experimental models of lung injury, Critical Care Medicine 36 (3) (2008) 903–909. doi:10.1097/ccm.0b013e3181652edd.
URL https://doi.org/10.1097/ccm.0b013e3181652edd

[22] T. Meier, H. Luepschen, J. Karsten, T. Leibecke, M. Grossherr, H. Gehring, S. Leonhardt, Assessment of regional lung recruitment and derecruitment during a PEEP trial based on electrical impedance tomography, Intensive Care Med. 34 (3) (2008) 543–550.

[23] I. Frerichs, J. Hinz, P. Herrmann, G. Weisser, G. Hahn, T. Dudykevych, M. Quintel, G. Hellige, Detection of local lung air content by electrical impedance tomography compared with electron beam CT, Journal of Applied Physiology 93 (2) (2002) 660–666. doi:10.1152/japplphysiol.00081.2002.
URL https://doi.org/10.1152/japplphysiol.00081.2002

[24] G. Elke, M. K. Fuld, A. F. Halaweish, B. Grychtol, N. Weiler, E. A. Hoffman, I. Frerichs, Quantification of ventilation distribution in regional lung injury by electrical impedance tomography and xenon com-

puted tomography, Physiological Measurement 34 (10) (2013) 1303–1318. doi:10.1088/0967-3334/34/10/1303.
URL https://doi.org/10.1088/0967-3334/34/10/1303

[25] J. A. Victorino, J. B. Borges, V. N. Okamoto, G. F. J. Matos, M. R. Tucci, M. P. R. Caramez, H. Tanaka, F. S. Sipmann, D. C. B. Santos, C. S. V. Barbas, C. R. R. Carvalho, M. B. P. Amato, Imbalances in regional lung ventilation, American Journal of Respiratory and Critical Care Medicine 169 (7) (2004) 791–800. doi:10.1164/rccm.200301-133oc.
URL https://doi.org/10.1164/rccm.200301-133oc

[26] J. Richard, C. Pouzot, A. Gros, C. Tourevieille, D. Lebars, F. Lavenne, I. Frerichs, C. Guérin, Electrical impedance tomography compared to positron emission tomography for the measurement of regional lung ventilation: an experimental study, Critical Care 13 (3) (2009) R82. doi:10.1186/cc7900.
URL https://doi.org/10.1186/cc7900

[27] J. Hinz, P. Neumann, T. Dudykevych, L. G. Andersson, H. Wrigge, H. Burchardi, G. Hedenstierna, Regional ventilation by electrical impedance tomography, Chest 124 (1) (2003) 314–322. doi:10.1378/chest.124.1.314.
URL https://doi.org/10.1378/chest.124.1.314

[28] M. S. Nascimento, G. C. Alcala, A. I. A. Guzman, L. C. Corrêa, D. M. Baggio, F. S. Rossi, L. P. Fascina, M. B. P. Amato, C. do Prado, Electrical impedance tomography in pediatric patients with COVID-19, the first reports, BMC Pulmonary Medicine 21 (1) (Nov. 2021). doi:10.1186/s12890-021-01716-y.
URL https://doi.org/10.1186/s12890-021-01716-y

[29] I. Frerichs, Z. Zhao, T. Becher, P. Zabel, N. Weiler, B. Vogt, Regional lung function determined by electrical impedance tomography during bronchodilator reversibility testing in patients with asthma, Physiol Meas 37 (6)

(2016) 698–712. doi:10.1088/0967-3334/37/6/698.
URL https://doi.org/10.1088/0967-3334/37/6/698

[30] C. Ngo, F. Dippel, K. Tenbrock, S. Leonhardt, S. Lehmann, Flow-volume loops measured with electrical impedance tomography in pediatric patients with asthma, Pediatr Pulmonol 53 (5) (2018) 636–644. doi:10.1002/ppul.23962.
URL https://doi.org/10.1002/ppul.23962

[31] B. Vogt, Z. Zhao, P. Zabel, N. Weiler, I. Frerichs, Regional lung response to bronchodilator reversibility testing determined by electrical impedance tomography in chronic obstructive pulmonary disease, American Journal of Physiology-Lung Cellular and Molecular Physiology 311 (1) (2016) L8–L19. doi:10.1152/ajplung.00463.2015.
URL https://doi.org/10.1152/ajplung.00463.2015

[32] C. Karagiannidis, A. D. Waldmann, P. L. Róka, T. Schreiber, S. Strassmann, W. Windisch, S. H. Böhm, Regional expiratory time constants in severe respiratory failure estimated by electrical impedance tomography: a feasibility study, Critical Care 22 (1) (2018) 221. doi:10.1186/s13054-018-2137-3.
URL https://doi.org/10.1186/s13054-018-2137-3

[33] R. Pikkemaat, K. Tenbrock, S. Lehmann, S. Leonhardt, Electrical impedance tomography: New diagnostic possibilities using regional time constant maps, Applied Cardiopulmonary Pathophysiology 16 (2012) 212–225.

[34] T. H. Becher, M. Miedema, M. Kallio, T. Papadouri, C. Karaoli, L. Sophocleous, M. Rahtu, R. W. van Leuteren, A. D. Waldmann, C. Strodthoff, R. Yerworth, A. Dupré, M.-R. Benissa, S. Nordebo, D. Khodadad, R. Bayford, R. Vliegenthart, P. C. Rimensberger, A. H. van Kaam, I. Frerichs, Prolonged continuous monitoring of regional lung function in infants with respiratory failure, Annals of the American Thoracic Society (Dec. 2021).

doi:10.1513/annalsats.202005-562oc.
URL https://doi.org/10.1513/annalsats.202005-562oc

[35] L. Sophocleous, I. Frerichs, M. Miedema, M. Kallio, T. Papadouri, C. Karaoli, T. Becher, D. G. Tingay, A. H. van Kaam, R. Bayford, A. D. Waldmann, Clinical performance of a novel textile interface for neonatal chest electrical impedance tomography, Physiol Meas 39 (4) (2018) 044004. doi:10.1088/1361-6579/aab513.
URL https://doi.org/10.1088/1361-6579/aab513

[36] J. Guttmann, L. Eberhard, B. Fabry, W. Bertschmann, J. Zeravik, M. Adolph, J. Eckart, G. Wolff, Time constant/volume relationship of passive expiration in mechanically ventilated ARDS patients, Eur. Respir. J. 8 (1) (1995) 114–120.

[37] M. Lourens, B. van den Berg, J. Aerts, A. Verbraak, H. Hoogsteden, J. Bogaard, Expiratory time constants in mechanically ventilated patients with and without COPD, Intensive Care Med 26 (11) (2000) 1612–1618. doi:10.1007/s001340000632.
URL https://doi.org/10.1007/s001340000632

[38] S. Pulletz, H. R. van Genderingen, G. Schmitz, G. Zick, D. Schädler, J. Scholz, N. Weiler, I. Frerichs, Comparison of different methods to define regions of interest for evaluation of regional lung ventilation by EIT, Physiol Meas 27 (5) (2006) S115–S127. doi:10.1088/0967-3334/27/5/s10.
URL https://doi.org/10.1088/0967-3334/27/5/s10

[39] C. L. Carroll, K. Sala, A. R. Zucker, C. M. Schramm, Pulmonary mechanics following albuterol therapy in mechanically ventilated infants with bronchiolitis, J Asthma 49 (7) (2012) 688–696. doi:10.3109/02770903.2012.685541.
URL https://doi.org/10.3109/02770903.2012.685541

[40] L. Aagaard, E. H. Hansen, Paediatric adverse drug reactions following use of asthma medications in europe from 2007 to 2011, International Journal

of Clinical Pharmacy 36 (6) (2014) 1222–1229. doi:10.1007/s11096-014-0020-0.
URL https://doi.org/10.1007/s11096-014-0020-0

[41] A. C. Koumbourlis, Evidence based medicine and common sense: The case of bronchiolitis, Paediatric Respiratory Reviews 32 (2019) 16–17. doi:10.1016/j.prrv.2019.09.003.
URL https://doi.org/10.1016/j.prrv.2019.09.003

[42] S. Chandelia, D. Kumar, N. Chadha, N. Jaiswal, Magnesium sulphate for treating acute bronchiolitis in children up to two years of age, Cochrane Database of Systematic Reviews 12 (12) (2020) CD012965. doi:10.1002/14651858.cd012965.pub2.
URL https://doi.org/10.1002/14651858.cd012965.pub2

[43] M. Ozer, B. Buyuktiryaki, U. M. Sahiner, O. Teksam, B. Karaatmaca, O. Soyer, B. E. Sekerel, Repeated doses of salbutamol and aeroallergen sensitisation both increased salbutamol-induced hypoxia in children and adolescents with acute asthma, Acta Paediatr 107 (4) (2018) 647–652. doi:10.1111/apa.14202.
URL https://doi.org/10.1111/apa.14202

Age (months)	Weight (g)	Sex	GA (weeks)	LRTI diagnosis (pathogen)	Broncho-lytic agents	Respiratory support	Antibiotics	Sedation	Cortico-steroids	SpO_2/FiO_2 at study inclusion
11	9700	F	39	obstructive bronchitis (rhinovirus)	salbutamol, ipratropium	HFNC	i.v.> 48 h	no	yes	243
27	12800	F	37	pneumonia (RSV)	salbutamol	HFNC	i.v.> 48 h	no	no	278
26	9700	M	24	pneumonia (RSV)	salbutamol	invasive ventilation, HFNC	i.v.> 48 h	yes	yes	90
14	9400	M	40	obstructive bronchitis (rhinovirus)	salbutamol, ipratropium	HFNC	i.v.> 48 h	yes	yes	384
11	7600	F	40	pneumonia (rhinovirus)	salbutamol	invasive ventilation	no	yes	no	200
13	7550	F	26	obstructive bronchitis (bocavirus)	salbutamol, ipratropium	HFNC, invasive ventilation, HFNC	no	yes	yes	240

Table 1: Patient characteristics. GA: gestational age, LRTI: lower respiratory tract infection, SpO_2: peripheral oxygen saturation, FiO_2: fraction of inspired oxygen, F: female, M: male, RSV: respiratory syncytial virus, HFNC: high-flow nasal cannulae, i.v.: intravenous, ipratropium: ipratropium bromide.

Parameter	# events	pre-broncholysis median (IRQ)	post-broncholysis median (IQR)	p-value
Heart rate (bpm)	77	149 (48)	157 (50)	**0.001**
Systolic BP (mmHg)	73	105 (14)	105 (15)	0.216
Diastolic BP (mmHg)	73	69 (16)	69 (15)	0.295
Oxygen saturation (%)	77	94.1 (3.8)	93.6 (4.2)	**0.001**
Breathing rate (min^{-1})	57	29.3 (12.9)	29.4 (12.2)	0.740
FiO_2	77	0.42 (0.25)	0.44 (0.24)	**0.035**
SF ratio	77	221 (119)	206 (113)	**0.001**
HFNC (l/min)	22	8 (4)	8 (4)	1.000
PEEP (cmH_2O)	55	5.9 (1.6)	5.9 (1.7)	0.814
MAP (cmH_2O)	55	8.9 (2.7)	9.0 (3.0)	**0.046**
PIP (cmH_2O)	55	18.9 (5.9)	18.9 (5.3)	0.207
TV_e (ml/kg)	55	10.4 (4.7)	10.4 (4.0)	0.232
MV_e (l/min)	55	2.52 (0.53)	2.42 (0.48)	0.986

Table 2: Vital and ventilatory parameters before and after bronchodilator administration. IQR: interquartile range, BP: blood pressure, FiO_2: fraction of inspired oxygen, SF ratio: ratio between peripheral oxygen saturation and fraction of inspired oxygen, HFNC: high-flow nasal cannulae, PEEP: positive end expiratory pressure, MAP: mean airway pressure, PIP: peak inspiratory airway pressure, TV_e: expiratory tidal volume, MV_e: expiratory minute ventilation.

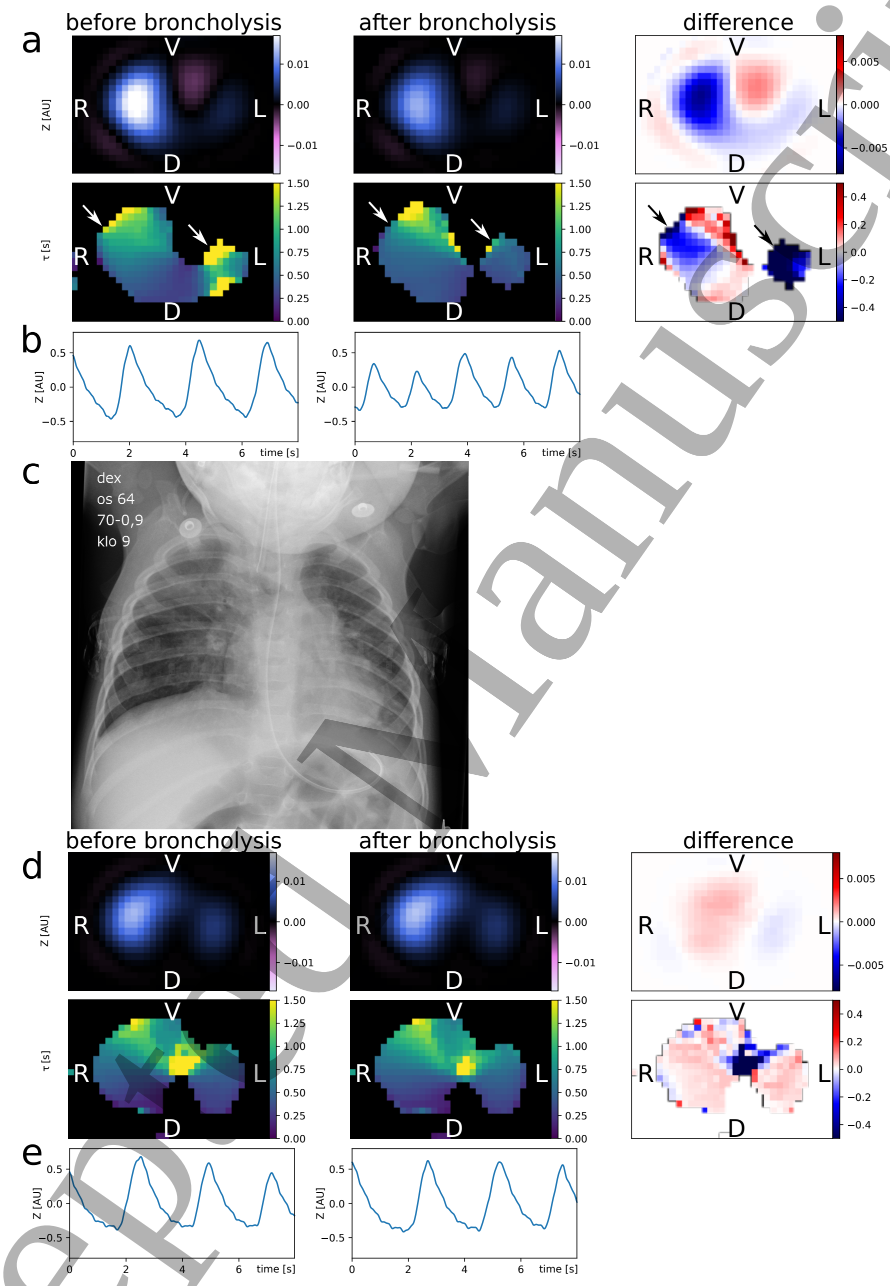

Figure 3: Maps of calculated values of regional respiratory mechanics for two broncholysis events from the last patient in table 1 under invasive ventilation. **a** & **d**: in rows: tidal impedance variation image Z, expiratory time constant τ; in columns: pre-broncholysis, post-broncholysis, difference. All maps are axial slices seen from below with the patient's back at the bottom of the map (R: right, L: left, V: ventral, D: dorsal). In **a**, we see a decrease in time constants in the left lung and ventrolateral parts of the right lung (broncholysis considered successful); in **d**, the time constants are mostly unchanged (broncholysis considered unsuccessful). **b** & **e** show the impedance sum of the whole thoracic cross-section over time in the same intervals. Between them is the X-ray (**c**) taken on the same day between the events, showing the patient's anatomy, belt position and endotracheal tube.

Parameter	pre-broncholysis median (IQR)	post-broncholysis median (IQR)	p-value
$\bar{\tau}_w$ (s)	0.7811 (0.3786)	0.7852 (0.4864)	0.233
$SD_{\bar{\tau}_w}$	0.4724 (0.9511)	0.5053 (1.201)	0.281
$CV_{\bar{\tau}_w}$	0.5934 (0.663)	0.6019 (0.6505)	0.309
$\tau_{glob.}$ (s)	0.7332 (0.2584)	0.7546 (0.3753)	0.070
CoV r/l	0.4187 (0.1019)	0.4208 (0.1200)	0.211
CoV v/d	0.4916 (0.02790)	0.4897 (0.03443)	0.073

Table 3: EIT-derived parameters for all patients/events before and after bronchodilator administration. $\bar{\tau}_w$: weighted mean expiratory time constant, CV: coefficient of variation, CoV r/l: center of ventilation in the right-to-left direction, CoV v/d: center of ventilation in the ventrodorsal direction, $\tau_{glob.}$: global expiratory time constant.

Group	# events	successful events	success rate
all events	77	13	16.88%
Salbutamol	63	10	15.87%
Ipratropium	14	3	21.43%
invasive ventilation	55	6	10.91%
HFNC	22	7	31.82%

Table 4: Success rates of administration of broncholytics. Events with a decrease of weighted mean expiratory time constant of at least 20% were considered successful.