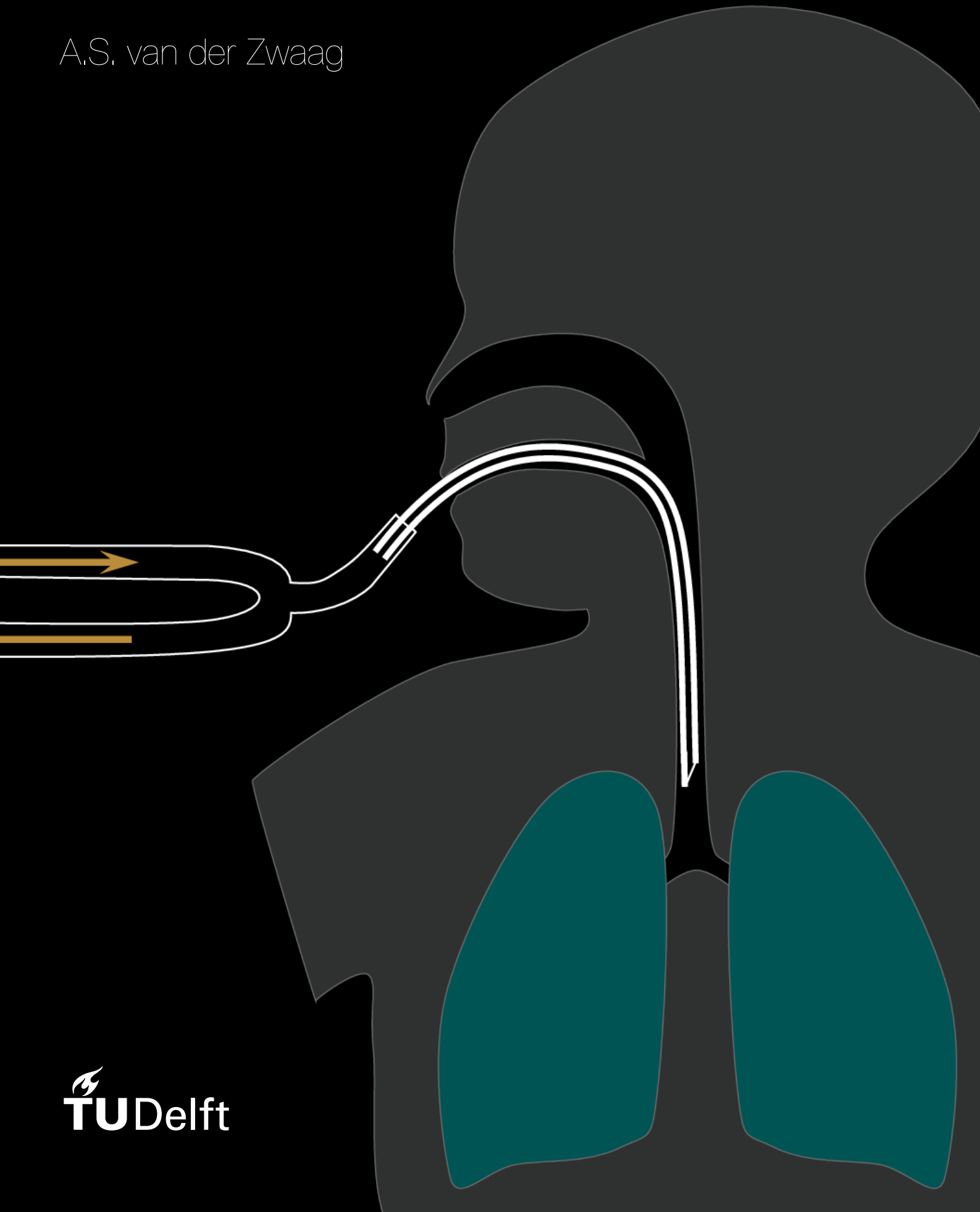
Electrical Impedance Tomography applications for the preterm neonate

A.S. van der Zwaag



TU Delft

Electrical Impedance Tomography applications for the preterm neonate

By

A.S. van der Zwaag

in partial fulfilment of the requirements for the degree of

Master of Science
in Biomedical Engineering

at the Delft University of Technology,
to be defended publicly on Friday October 25, 2019 at 14:00 PM.

Thesis committee:	Prof. dr. J. Dankelman	TU Delft
	Dr. T.M.L. da Costa	TU Delft
	T. G. Goos, MSc	TU Delft / Erasmus MC
	P. Somhorst, MSc	Erasmus MC

TU Delft

Preface

Before I present my master thesis I would like to thank all of the people that made it possible. First of all I would like to thank my daily supervisor Tom Goos, who not only supported me a lot during my thesis research, but also helped me find my internship at SenTec in Switzerland. This internship turned out to be my first encounter with electrical impedance tomography, the technology that would become the main topic of my thesis research. During our meetings Tom has always really taken the time to help me with all of my questions. Secondly, I would like to thank Jenny Dankelman. Although we did not meet very often, Jenny's feedback was of significant value, and helped me increase the scientific value of my research.

Thirdly, I would like to thank "The Squad", my friends and companions in the life of a master thesis student. Without our "present at 9:15"-rule and the (most of the time) well-deserved coffee and lunch breaks, this project would probably have lasted a lot longer and, more importantly, it would have been a lot less fun. A special thanks is for Gailey an Hugo, owners of "The Two Passes" that provided free coffee during the whole year.

Furthermore, I would like to thank my proof-readers Florianne and Noor, who took the time to read my thesis and provide me with very helpful feedback. Without them, there would still be an '*and'* written as *'ant'* somewhere in my thesis, and that would have been embarrassing.

An important word of thanks is for my #1 supporter Thomas, who helped me in many different ways. He provided insights and advice about my research, proof-read my thesis, and helped me clear my head from all thesis-related thoughts when I needed to.

Finally, I would like to thank my family for supporting me throughout my entire studies.

Anne-Sea van der Zwaag
Delft, October 2019

Content

1 Introduction **1**
2 Research Article **3**
Appendix A: Algorithm parameters **10**
Appendix B: Summary of instructions for graders **15**
Appendix C: Patient Information Letter (Dutch) **16**
Appendix D: METC Protocol **18**
(Appendix E: Published Article ..... 42)

1 Introduction

The World Health Organization estimates that in 2018, 15 million babies were born preterm, and this number is rising.[1] Due to medical advances 9 out of 10 babies worldwide survive their premature birth.[2] In order for them to survive, special care immediately after delivery is vital. Many of those that survive premature birth, however, still have high chances of developing mental and/or physical disability. The neonates' bodies are often simply not fully prepared to live in the world outside their mother's womb and require delicate care. One of the main areas of concern is the newborn's lungs, since these typically mature at a late stage of pregnancy. Often, preterm neonates require breathing support to survive their first hours.

This support is not without its own risk however. Mechanical ventilation is well known to produce complications, especially in neonates.[3] Limiting the time spent on the ventilator environment is essential for the wellbeing and outcome of these patients, but determining the right moment for reducing or halting the support proves to be a great challenge.[4] A promising solution would be to adapt ventilation strategies to the specific needs of the individual patient.

The application of Electrical Impedance Tomography (EIT) presents an possible solution for this challenge. EIT is a non-invasive medical imaging technology that allows for real-time monitoring respiratory parameters. The main focus of my thesis work has been to investigate the use of EIT for different applications that aim to improve the care for preterm neonates.

As a former preterm neonate, I am proud to have spent the last year of my education advancing this state of the art field of research, investigating different applications of EIT for preterm neonates. Please note that this thesis report covers multiple studies and applications, each exploring a different aspect of Electrical Impedance Tomography for the preterm neonate. Not all aspects are directly related to each other and therefore the rest of this chapter is dedicated to presenting the structure of this report in the order with which it is presented.

Study standardisation of data selection in EIT research

Chapter 2 of my thesis presents the main part of my thesis: the article about the research I have performed during my graduation in 2019. It presents a novel procedure to standardise the selection of reliable EIT data using a classification algorithm. This is needed because data selection is time consuming, as approaches and criteria have not yet been standardised, which hinders comparability of research. The research proves the potential for quick and reliable data selection with the help of my developed classification algorithm.

Algorithm parameters

Aside from the classification algorithm which forms the main part of my thesis research, I developed an additional algorithm for the breath detection which is needed to calculate EIT parameters. For the development of both algorithms many choices had to be made regarding the specific parameters. Since the article was too short to go into every detail of the algorithm development, the choices made are elaborated in appendix A of this report. A key component in the creation of valid algorithms is their validation. Appendix B contains the instructions for the graders that performed manual classification used to define the reference standard for validation of the classification algorithm.

Setup of clinical pilot study

Combining my knowledge of EIT gained from the previously mentioned internship with the neonatal expertise of my supervisor Tom Goos, we initially chose to pursue a clinical pilot study with the Swisstom EIT system for my thesis research. A lot of effort has been put in setting up this research, but unfortunately, due to many delays we ultimately choose not to continue with subject for my thesis research. To present to you the work that has been done for setting

[1] "Preterm Birth." *World Health Organization*, World Health Organization, 19 Feb. 2018, https://www.who.int/news-room/fact-sheets/detail/preterm-birth. Accessed 14 Oct. 2019.
[2].Liu, Li, et al. "Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals." *The Lancet* 388.10063 (2016): 3027-3035.
[3] Attar, Mohammad Ali, and Steven M. Donn. "Mechanisms of ventilator-induced lung injury in premature infants." *Seminars in Neonatology*. Vol. 7. No. 5. WB Saunders, 2002.
[4] Shalish, Wissam, et al. "Prediction of Extubation readiness in extremely preterm infants by the automated analysis of cardiorespiratory behavior: study protocol." *BMC pediatrics* 17.1 (2017): 167.

up this study, the two main preparational documents are included in the appendix of this thesis. Appendix C contains the information letter for parents, which was written in Dutch, and Appendix D contains the study protocol that was written and submitted to the medical ethics committee of the Erasmus MC. In the meantime, the protocol has been approved by the ethics committee, and the study will be performed by my supervisor Tom Goos.

Study on the effect of surfactant treatment on EIT parameters

Appendix E presents a published article to which I contributed during my master thesis. I first learned about EIT when I did an internship at Swisstom in the summer of 2018. During the internship I performed data analysis for the CRADL project, a multicentre observational study in which EIT measurements were collected in 200 neonates (http://cradlproject.org/). For this study I analysed the data of all included patients that received surfactant treatment during EIT measurement. My assignment was to report EIT parameters around the time of the surfactant administration.

After my internship I stayed involved in the surfactant study, and performed the data analysis for each newly included patient with received surfactant administration. After all patients were included and analysed, I was involved in combining the data and writing the article, which was recently published in Neonatology (https://doi.org/10.1159/000502612). For my thesis committee, the article is included in in this thesis, but do to copyright infringement this appendix will not be included in the electronic version of my thesis.

A new standard in electrical impedance tomography research: Automatic selection of reliable data with a classification algorithm

Anne-Sea van der Zwaag

***Abstract*—Data analysis for electrical impedance tomography (EIT) research requires manual selection of sequences with a normal breathing pattern. This procedure is lengthy and the lack of a standardised approach results in different practices among EIT studies, limiting the potential and comparability of the research.**

This article presents a new approach to solving this problem, using automatic detection of EIT sequences with normal breathing pattern. An algorithm was developed to differentiate between normal and disturbed breathing patterns. To facilitate data analysis, it was implemented in an application that allows for EIT parameter calculation of selected sequences.

EIT recordings of three patients recruited in an observational study were used to develop the algorithm. A reference standard was defined as the majority vote of five biomechanical engineering students performing manual classification. Frequency and time domain properties were compared between the signals that these graders classified as reliable and unreliable, and were used to define classification rules for the algorithm. Matlab was used to create the classification algorithm and implement it in an application. The developed algorithm was validated with a new data set containing EIT recordings of an additional three patients, classified by the same volunteers. Qualitative analysis was performed to investigate the causes of conflict between manual and automated data selection.

The resulting algorithm achieved a sensitivity of 92.8% (95% CI, 92.6%-92.9%) and a specificity of 85.5% (95% CI, 85.1%-85.8%) on the EIT files used for development. On the validation set the algorithm accomplished a sensitivity of 86.5% (95% CI, 86.3%-86.7%), and specificity of 79.7% (95% CI, 79.4%-80.0%). Most differences between manual and automatic data selection were found to be around the edges of the selected sequences. Other discrepancies can be explained by difference in data selection behaviour for varying recording qualities during manual selection.

The presented algorithm proves its potential for quick and reliable data classification of EIT recordings. It not only provides a new standard for data selection in EIT research, but also reduces the time investment of researchers. The freely available data analysis application enables easy implementation of the algorithm. The presented study therefore provides a first step towards a uniform approach in EIT research, improving comparability of studies and increasing the scientific value of their findings.

I. Introduction

The vast majority of extremely preterm infants (born before 28 weeks of gestation) are admitted to the neonatal intensive care unit [1]. Many of these patients have trouble breathing due to their underdeveloped lungs and respiratory drive, and to survive, these patients are in need of invasive respiratory support with the help of a mechanical ventilator [2]. Although lifesaving, this treatment is accompanied by high risk of adverse effects such as the development of chronic lung diseases and neurological impairment [3–5]. Mechanisms that play an important role in the development of ventilator induced lung damage are overdistension of the lungs or (partial) collapse of lung tissue [6]. At the point of writing this article, no ventilation protocol has succeeded in the prevention of these serious adverse effects [7]. A possible solution would be to adapt ventilation strategies to the specific needs of the individual patients.

Electrical impedance tomography (EIT) could be the right technology to solve this problem. EIT is a non-invasive imaging technique that allows physicians to continuously monitor lung mechanics of individual patients [8]. In previous studies, EIT has been used to estimate overdistension and collapse of the lungs [9, 10]. The working principle of EIT is based on impedance differences between air in the lungs and the surrounding tissues, and the changes in air volume during a respiratory cycle. The technology makes use of a belt with a series of equally spaced electrodes, placed around the chest of the patient. Small currents are injected between electrode pairs in a cyclical pattern. The resulting voltages are measured in the other electrodes, and the impedance images are reconstructed with back-projection algorithms (Figure 1) [11].

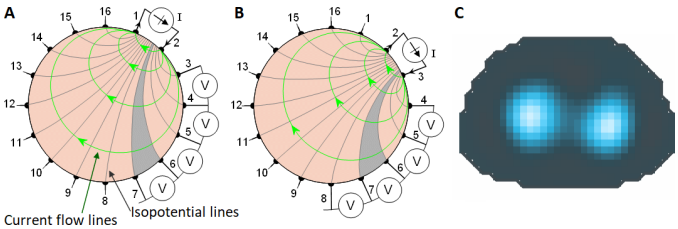


Fig. 1: A, B: Current injections and voltage measurements of an EIT measurement. The first 2 current injections, out of a cycle of 16, are pictured (adapted from [12]). C: One cycle corresponds to one EIT image (Image created with Ibex software [13]).

A drawback of EIT technology, however, is that the measurements are sensitive to disturbances caused by movement of the patient, variable electrode contact or other artefacts [14, 15]. The result is that EIT researchers must manually select artefact free data sequences for reporting EIT parameters. The approach in data selection has not been standardised, and different selection criteria are used in different studies [16, 17].

This study was conducted in order to develop a standardised approach for data selection for a specific EIT application - an ongoing observational study where EIT measurements will be performed on preterm neonates. For this purpose, an algorithm was developed to recognise data sequences that are both stable and artefact free. The developed algorithm was implemented in a data analysis application that can also be used to calculate EIT parameters of selected sequences. Although the context in which they were developed is quite specific, the algorithm and application can be used in all other neonatal EIT studies where data selection needs to be performed, with potential to

be extended to adult studies as well. The uniform approach that is proposed will improve comparability of studies and therefore the quality of research.

II. Methods

The aim of this study is to provide a tool that standardises data selection for analysis in EIT research. To achieve this, first an algorithm was developed to distinguish between reliable data sequences and disturbed ones. Secondly, the algorithm was implemented in an application in which the user can load files for analysis and generate EIT output parameters. Finally the algorithm was validated with a data set of EIT recordings not used during development. Additional information about the selection of algorithm parameters is provided in Appendix A.

A. Classification algorithm

The classification algorithm was developed in Matlab (R2018a, Mathworks, Natick, MA, USA), and is based on three EIT recordings of variable qualities, from different preterm infants that were included in the multicenter observational CRADL study (gestational age < 37 weeks) [18]. Each recording has a length of approximately 1200 s. Permission to use EIT data from the study was obtained from the corresponding researcher. All three recordings were collected in Oulu University Hospital, Finland, with the BB^2 EIT monitor and belts (Swisstom, Landquart, Switzerland) [19].

To establish a reference standard, five graders performed manual classification of the three EIT recordings, as well as a validation set of three other EIT recordings. All of these graders were biomechanical engineering students in the last phase of their studies. They were first given a presentation about EIT to get familiar with the subject, and then they received more detailed instructions for manual classification. A summary of the instructions is included as an appendix.

A majority vote was implemented to define the standard, i.e. when at least three graders marked a sequence as reliable, it was accepted as reliable. The manually classified reference standard was inspected to find out differences between reliable and unreliable sequences, that can be used for automatic classification. Four categories of unreliability could be distinguished:

- Absence of a signal due to poor electrode contact
- Baseline shift due to failing electrodes: Image reconstruction in the Swisstom EIT system is designed in such a way that it can compensate for up to 6 electrodes with failing contact. However, compensation is accompanied by a possible baseline shift of the signal.
- Irregular breathing patterns such as crying, apneas or coughing
- Other disturbances such as measurement noise

The first two categories can be detected in time domain using information about electrode quality that is stored in the EIT files that contain the recording. It should be noted that not all baseline shifts are caused by the compensation algorithm, since a change in ventilator settings (specifically adjustment of end expiratory pressure) can also change the baseline impedance. Because information on the number of failing electrodes is stored in the recordings, it is possible to distinguish between these two situations. The latter two categories showed different frequency behaviour compared to reliable data. The created algorithm consist of multiple steps, which are depicted in Figure 2. Each step is explained separately in the following subsections.

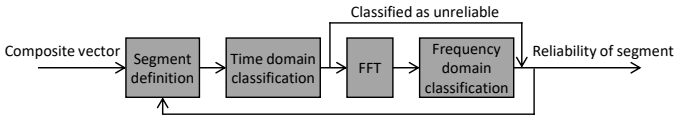


Fig. 2: Flowchart representation of the classification algorithm. Each iteration, a specific segment of the composite signal is evaluated for reliability. If a segment is not classified as unreliable in time domain, additional evaluation will be done in frequency domain. Output of the iteration is a value of 0 *(reliable) or* 1 *(unreliable). FFT: Fast Fourier transform.*

Input - Composite vector: The input of the algorithm is the composite EIT vector, with summed impedance values of the 32 by 32 pixels in each image. This vector represents the total impedance over time. The simplification of the $32 \times 32 \times n$ '*two-dimensional impedance over time*'-matrix to a $1 \times n$ '*summed impedance over time*'-vector results in a significantly reduced calculation time, since the amount of data points is 1024 times smaller. Because of this simplification, the distribution of impedance cannot be regarded during reliability analysis. However, the composite vector contains enough information to check for reliability of the signal.

1) Segment definition: The first step of the algorithm itself is to divide the recording into smaller parts, for which reliability can be determined. Two segments are defined in each iteration of the algorithm: an analysis segment in the composite vector (input) and a classification segment in the reliability vector (output) (Figure 3).

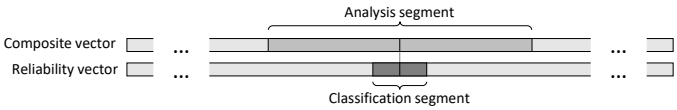


Fig. 3: Segments used in one iteration of the classification algorithm. The analysis segment is evaluated to determine the reliability of the classification segment.

The minimum length of the analysis segment is limited by the required resolution in frequency domain. The expected breath rate of infants is up to 1.2 Hz [20], and to sufficiently capture the frequency behaviour in this region the optimal resolution was determined to be 0.1 Hz. The final length of the analysis segment is 10 s. Because every analysis segment contains around 10 breaths, the choice was made to implement a running window, which allows for evaluation on a higher resolution. This was done by returning the output of the analysis segment to the smaller segment of the reliability vector. The length of the classification segment was set to be 1.5 s in order to achieve evaluation for individual breaths, while keeping the computational time acceptable. After one iteration, both segments are shifted along the vectors, with a

step size equal to the length of the classification segment. More information about the choice of segment lengths is provided in Appendix A.

Segment definition is adjusted during the first and last iteration, where the analysis segment would exceed the vector bounds. In these cases the boundaries of the first or last classification segment are expanded to the first or last entry of the reliability vector.

2) Time domain classification: In the first part of the actual classification, the time domain signal is analysed. This part of the algorithm consists of three steps, which are explained below.

i Set window: Because the time signal has a high resolution, there is no need to use the complete analysis segment for classification. Therefore, a smaller segment is defined with the same length and location as the classification segment for which the output is determined.
ii Check for baseline shift: A vector with the number of failing electrodes for each frame, which is stored in the recordings made with the Swisstom EIT system, is used to detect these shifts.
iii Check for absence of signal: When more than 6 electrodes fail, the system can no longer compensate. This results in a flat line signal, which is detected by a variance of zero in the algorithm.

When the signal passes the time domain checks, it is assumed to be reliable. The signal is then analysed in frequency domain.

3) Frequency domain classification: In the second part of classification the complete analysis segment is first transformed to frequency domain with the Fast Fourier transform (FFT). After observing that the specific frequency behaviour of disturbed signals is present at frequencies lower than the respiratory rate, a region of interest was defined between 0.1 and $2\,\mathrm{Hz}$. All frequencies outside the region of interest are set to zero. Unreliable data shows high amplitudes in lower frequencies and reliable data typically shows an isolated peak at the respiratory rate. A series of two checks are therefore defined to determine reliability in frequency domain:

i Check for high magnitudes in low frequencies: The magnitudes of frequencies from $0.1-0.8\,\mathrm{Hz}$, and those between $0.9-2.0\,\mathrm{Hz}$ are summed. If the summed magnitude is higher in the low region than in the high region, the signal is marked as unreliable.
ii Check for highest peak: If the highest peak is located at a frequency lower than $0.4\,\mathrm{Hz}$, the signal is not dominated by the respiratory rate, and the signal is marked as unreliable.

The exact values of the parameters mentioned are elaborated in Appendix A. The output of one iteration in the algorithm is the reliability of the classification segment.

Output - Reliability of classification segment: The reliability of the analysed segment is stored in the reliability vector, in the classification segment. The output of the completed algorithm is a logical vector, with in which for each frame a classification as either reliable or unreliable.

B. Data analysis application

Matlab's App Designer environment (R2018a, Mathworks, Natick, MA, USA) was used to create the user interface for the data analysis application. The interface was designed to implement the classification algorithm in a user-friendly way, enabling researchers with different levels of EIT knowledge to use the same approach in data selection and analysis. The created application consists of two tabs: The default *analyse file* tab where the classification algorithm is implemented, and the *output parameters* tab that can be used when a file is analysed for reliability. Both tabs of the application are shown in Figure 4.

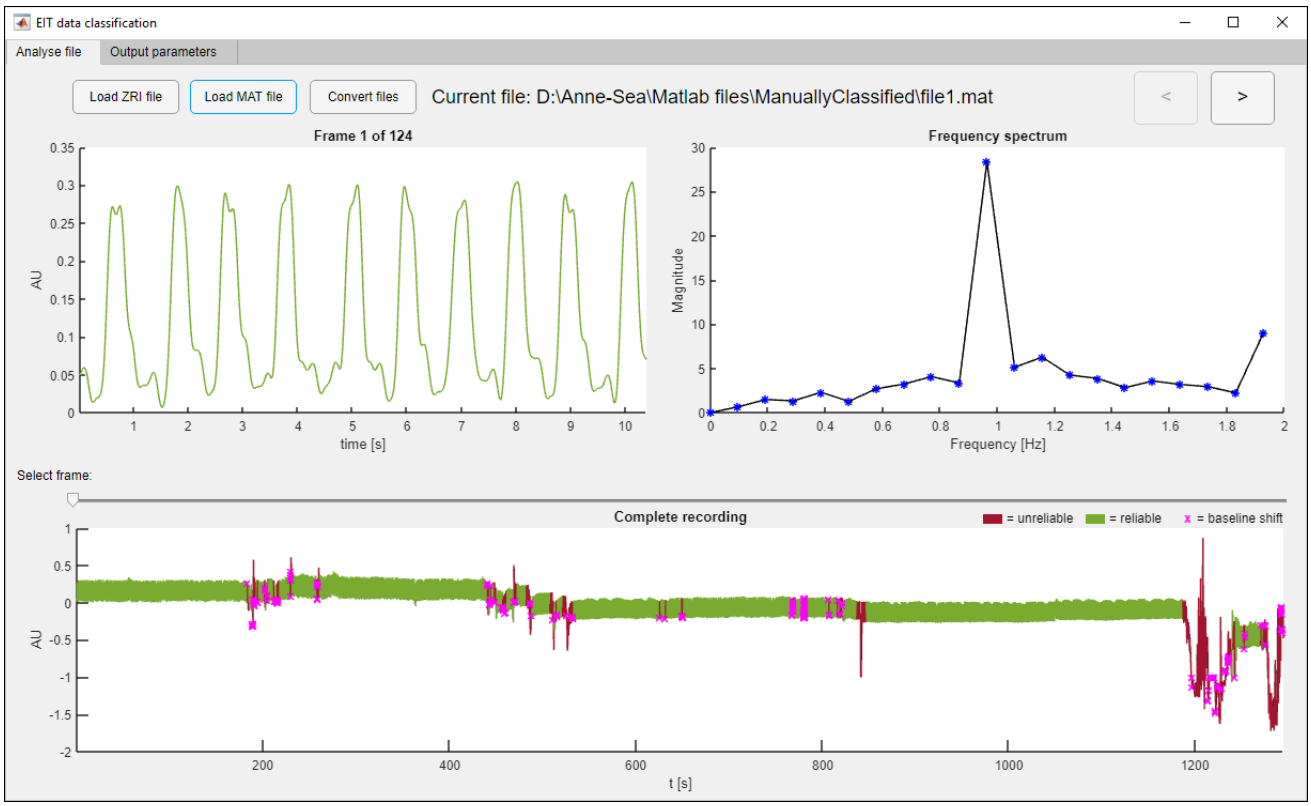
1) Analyse file tab: The first tab is the main part of the application, where the classification algorithm is executed to analyse EIT files. The user can choose between three options: Load a ZRI file, load a MAT file, or convert ZRI files to MAT files.

ZRI is the file format that the Swisstom EIT system generates. This file format can be loaded directly in the application, but due to the large file size, it takes a while to load (20 -$80\,\mathrm{s}$, depending on computing power). Therefore another option is to load a MAT file with reduced size and loading time. The reason for the large ZRI file size is the fact that for each EIT image, the impedance value for each pixel inside the 32 by 32 image is stored. This information is not needed for the algorithm, and is deleted when reduced MAT files are created from ZRI files. To create the reduced files, the user presses a *Convert files* button, and selects a folder in the appeared dialog box. All ZRI files in the selected folder are listed, and converted to MAT format.

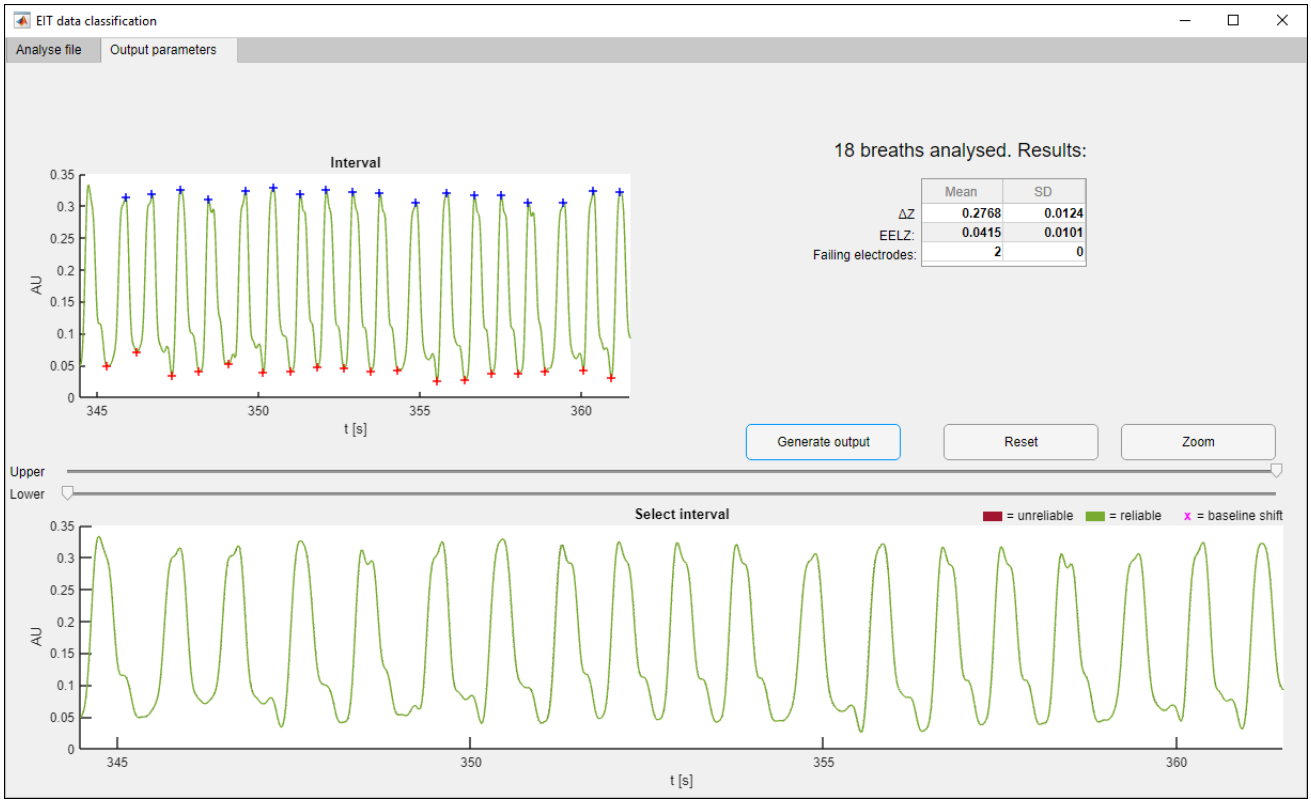
The classification algorithm is executed when the user loads an EIT file with the *Load ZRI file* or *Load MAT file* button. The result of the classification algorithm is a logical reliability vector, which is then also stored in the file of the corresponding EIT recording if the user has loaded a MAT file, enabling the program to skip the algorithm if a file has already been classified. The reliability vector is used to plot the results, with different colours for reliable and unreliable data. The user can look into the classified recording with more detail by selecting a part of the signal with a slider along the recording. The selected part of the signal is plotted next to its frequency spectrum.

2) Output parameters tab: When a file is loaded and analysed in the first tab, the user can generate output parameters in the second tab. The complete recording, together with its calculated reliability is plotted, and with sliders the user can zoom in on specific parts. Finally, the user selects the sequence they wish to use for data analysis, and after pressing the *Generate output* button, the EIT output parameters are provided in a table. Generation of output parameters is performed in two steps: breath detection and parameter calculation.

A breath detection algorithm was developed in order to detect the valleys and peaks that correspond with the start- and endpoints of inspiration. The composite signal is smoothed before peak and valley detection, because measurement noise



(a)



(b)

Fig. 4: (a) First tab of the data analysis application. The user can load a MAT or ZRI file for which the classification algorithm will be performed. After analysis, the classified recording is shown in the bottom plot. With the slider a specific frame can be selected for which the composite signal and frequency spectrum are shown in the top left and top right plots respectively. (b) Second tab of the application. When a MAT or ZRI file is classified, the user can select a sequence of analysed signal in the bottom plot with the sliders and Zoom *button. When the* Generate output *button is pressed, the top left plot will show the selected sequence, with start of inspiration marked with a red plus sign, and end of inspiration marked with a blue plus sign. The output parameters are displayed in the top right table. ΔZ: Tidal impedance change, calculated for each breath by subtracting end inspiratory impedance from start inspiratory impedance. EELZ: End expiratory lung impedance.*

disturbs correct peak detection. The developed breath detection algorithm is summarised in Figure 5, and further elaborated in Appendix A.

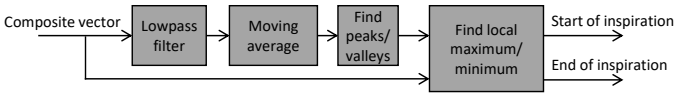


Fig. 5: Flowchart representation of the breath detection algorithm. The composite signal is filtered twice, first with a 1.5 Hz *low-pass filter, and then through a moving average filter with a window of* 20 *frames. Peaks and valleys are detected on the processed signal, and then compared with the original signal. A correction is performed to find the local optimum of the original signal within a range of* 21 *frames around the detected locations for peak and valleys.*

To calculate the EIT output parameters the unfiltered signal is combined with the detected locations of the start and endpoints of inspiration. Two parameters are calculated:

- Tidal impedance change (ΔZ)
- End expiratory lung impedance (EELZ).

ΔZ is a measure of tidal volume, and is calculated for each breath by subtracting the impedance value at the start of inspiration from the impedance value at the end of inspiration. EELZ represents the amount of air remaining in the lungs after expiration, and is equal to the impedance value at the end of expiration. Besides the mentioned EIT parameters, the application shows the number of analysed breaths and the amount of failing electrodes during the selected sequence.

C. Validation

Quantitative validation of the developed algorithm was performed with three randomly chosen EIT files of preterm infants that were also included in the CRADL study. These files were also manually classified by the five students, using their majority vote to define the reference standard. Performance measures of the algorithm on both the development data set and validation data set were calculated with 2×2 tables for which sensitivity and specificity could be calculated. 95% confidence intervals were calculated as "exact" Clopper-Pearson intervals [21]. A qualitative analysis was performed to investigate the causes of conflict between manual and automatic selection.

III. Results

A quantitative analysis was performed to calculate the performance measures of the algorithm, and a qualitative analysis was used to investigate the differences between manual classification (the reference standard) and the algorithm. The results of the quantitative and qualitative analysis will be explained separately below.

A. Quantitative analysis

The development data set included 3883 seconds of recording, of which 74.3% were classified as reliable in the reference standard. Quality of the recordings were widely spread. In the recording with the lowest quality 60.3% was reliable, and for the recording with the highest quality the percentage was 84.7%. The validation set consisted of 3880 seconds of EIT data with a total reliability of 66.7%, as defined in the reference standard, with even larger range of quality. In these files the reliable percentage of the recording ranged from 47.0% to 90.8%.

The classification algorithm achieved a sensitivity of 92.8% (95% CI, 92.6%-92.9%) and a specificity of 85.5% (95% CI, 85.1%-85.8%)in the development data set. On the validation set the algorithm accomplished a sensitivity of 86.5% (95% CI, 86.3%-86.7%), and specificity 79.7% (95% CI, 79.4%-80.0%).

B. Qualitative analysis

In many cases where the results of the algorithm conflicted with manual classification the difference could be appointed to one of three situations.

1) Edge behaviour: A recurring location of conflict between the algorithm and manual classification is around the edges of longer segments of reliable data. In these cases the algorithm tends to select a larger margin around a disturbance than the human grader. One example can be seen in Figure 6. A likely explanation for this edge behaviour is the running window design of the algorithm which used a larger signal than the segment that is classified.

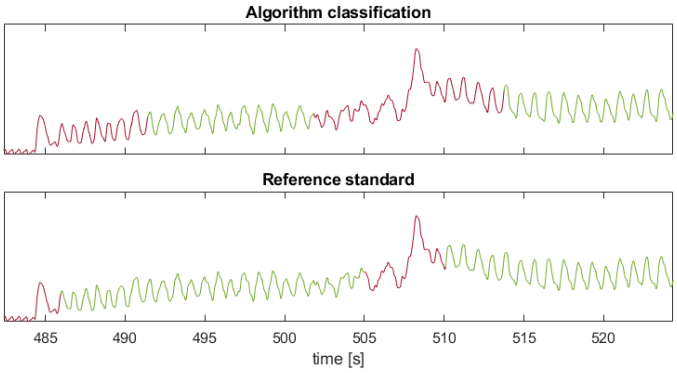


Fig. 6: Different edge behaviour between automatic and manual classification of the same EIT sequence. Both classifications correctly exclude the clear disturbance in the signal, but the algorithm also excludes a certain margin around the high peak.

2) Minimum sequence duration: Another cause of conflict between the algorithm and the human graders is the fact that the algorithm allows for classification of very short segments as reliable. During manual classification these very short sequences are excluded because only sequences larger than a couple of breaths are useful for reporting EIT parameters. An example of this behaviour is shown in Figure 7.

3) Small disturbances: The third type of situations where the results of the algorithm contradict manual classification is at the location of small disturbances when the amplitude of disturbances does not exceed the regular amplitude of the breathing pattern. These are usually short interruptions of the breathing pattern. An example of this situation can be seen in Figure 8. At this point, the algorithm is not yet able to correctly detect this type of behaviour.

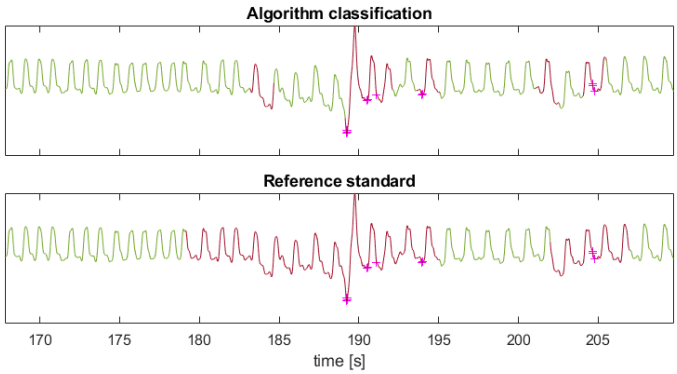


Fig. 7: Example of an EIT sequence where automatic data classification classifies very short segments of the signal as reliable. During manual classification these small segments are excluded.

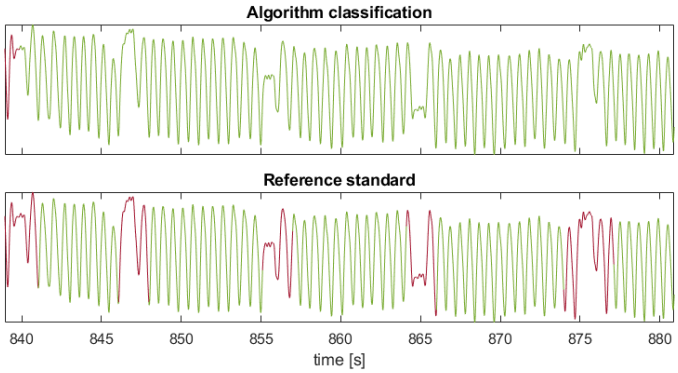


Fig. 8: Example of a sequence where smaller disturbances without amplitude peaks are not detected by the algorithm.

IV. Discussion

This article presents the first algorithm created for automatic detection of reliable electrical impedance tomography (EIT) data. The most important benefit of this research is that it provides a uniform classification method for all EIT recordings. This is a significant improvement from the current method, where the recorded signals have to be inspected manually, which could lead to different results for every researcher.

Automatic selection of EIT data enables large quantities of data to be processed, expanding the possibilities for EIT research. The data analysis application makes the classification algorithm accessible to other researchers, speeding up the analysis process without the need for advanced knowledge of the algorithm.

The created algorithm produces consistent results that have been verified with a validation data set. From the qualitative analysis it has become clear that most differences between the algorithm and manual classification can be explained by human behaviour versus machine behaviour. Further research is recommended to explore if the algorithm should be adapted to reach the same results as manual selection, or maybe the results of the algorithm are more desirable, because of the consistent approach. More research should also be performed in order to investigate the robustness of the algorithm using EIT data measured in different patient groups and conditions.

Some limitations of this study should be considered. First of all, the binary output of the classification algorithm might not be the best option. Another approach would be to calculate a 'reliability likelihood' score between 0 and 1. This would allow for variation of the threshold value for unreliability, providing more insight in the algorithm and allowing researchers to adapt the threshold to the quality of a recording. It would also allow for assigning weights to different criteria, which could be used to make specific adjustments to further improve the algorithm.

Furthermore, the reference data set was classified by volunteers with relatively little knowledge about EIT. Their lack of experience with EIT decreases the trustworthiness of the results, leaving room for improvement. An important step towards scientific implementation of the algorithm could be to collect manual classification from experienced researchers in the EIT field to add more value to the performance measures of the algorithm.

Finally, the specific use for which the application and algorithm were created limits the use in other EIT research. One example is the manufacturer-specific ZRI file format which is used as input. EIT measurements from other manufacturers might result in different behaviour of the algorithm. However, it is reasonable to assume every EIT manufacturer can provide a vector of the composite signal over time, which is enough for the algorithm to classify the data. Another example is that the reliability criteria are defined for preterm neonates only. Yet, to expand its use to wider applications small adjustments are expected to be sufficient. For example, application of the algorithm to older patients would probably only require the adjustment of the filters to the lower expected breath rate.

V. Conclusion and Outlook

This research set out to achieve a quick and reliable method for recognising the normal breathing patterns in EIT recordings. To this end a data classification algorithm was developed, and implemented in an application that can be used for data analysis in EIT studies of preterm infants.

Testing and validation of the created algorithm demonstrated that the results are trustworthy and consistent. The data classification algorithm can aid researchers during the data analysis phase of their electrical impedance tomography studies. Using the algorithm will save time investigating the recordings, and provides a uniform approach, contrary to current practice requiring each file to be inspected manually.

Further research is needed to investigate the use of the algorithm in other EIT studies, using systems from other manufacturers, or study applications in the field of paediatric and adult research.

Availability

The source code of the classification algorithm and the data analysis application is made available at http://doi.org/10.4121/uuid:43c5128c-48d2-405f-b7c3-546a426314a0, and can be freely downloaded.

REFERENCES

[1] W. Harrison and D. Goodman, "Epidemiologic trends in neonatal intensive care, 2007-2012," *JAMA pediatrics*, vol. 169, no. 9, pp. 855–862, 2015.

[2] B. J. Stoll, N. I. Hansen, E. F. Bell, M. C. Walsh, W. A. Carlo, S. Shankaran, A. R. Laptook, P. J. Sanchez, K. P. Van Meurs, M. Wyckoff, A. Das, E. C. Hale, M. B. Ball, N. S. Newman, K. Schibler, B. B. Poindexter, K. A. Kennedy, C. M. Cotten, K. L. Watterberg, C. T. D'Angio, S. B. DeMauro, W. E. Truog, U. Devaskar, and R. D. Higgins, "Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012.," *Journal of the American Medical Association*, vol. 314, no. 10, pp. 1039–1051, 2015.

[3] J. P. Kinsella, A. Greenough, and S. H. Abman, "Bronchopulmonary dysplasia," *The Lancet*, vol. 367, no. 9520, pp. 1421–1431, 2006.

[4] M. C. Walsh, B. H. Morris, L. A. Wrage, B. R. Vohr, W. K. Poole, J. E. Tyson, L. L. Wright, R. A. Ehrenkranz, B. J. Stoll, and A. A. Fanaroff, "Extremely Low Birthweight Neonates with Protracted Ventilation: Mortality and 18-Month Neurodevelopmental Outcomes," *The Journal of Pediatrics*, vol. 146, no. 6, pp. 798–804, 2005.

[5] V. Venkatesh, V. Ponnusamy, J. Anandaraj, R. Chaudhary, M. Malviya, P. Clarke, A. Arasu, and A. Curley, "Endotracheal intubation in a neonatal population remains associated with a high risk of adverse events," *European journal of pediatrics*, vol. 170, no. 2, pp. 223–227, 2011.

[6] M. A. Attar and S. M. Donn, "Mechanisms of ventilator-induced lung injury in premature infants," *Seminars in Neonatology*, vol. 7, pp. 353–360, oct 2002.

[7] G. M. Sant'Anna and M. Keszler, "Developing a neonatal unit ventilation protocol for the preterm baby," *Early Human Development*, vol. 88, no. 12, pp. 925–929, 2012.

[8] A. Adler, J. H. Arnold, R. Bayford, A. Borsic, B. Brown, P. Dixon, T. J. C. Faes, I. Frerichs, H. Gagnon, Y. Gärber, B. Grychtol, G. Hahn, W. R. B. Lionheart, A. Malik, R. P. Patterson, J. Stocks, A. Tizzard, N. Weiler, and G. K. Wolf, "GREIT: a unified approach to 2D linear EIT reconstruction of lung images," *Physiological Measurement*, vol. 30, no. 6, pp. S35–S55, 2009.

[9] C. Gomez-Laberge, J. H. Arnold, and G. K. Wolf, "A unified approach for EIT imaging of regional overdistension and atelectasis in acute lung injury," *IEEE transactions on medical imaging*, vol. 31, no. 3, pp. 834–842, 2012.

[10] J. B. Borges, F. Suarez-Sipmann, S. H. Bohm, G. Tusman, A. Melo, E. Maripuu, M. Sandström, M. Park, E. L. V. Costa, and G. Hedenstierna, "Regional lung perfusion estimated by electrical impedance tomography in a piglet model of lung collapse," *American Journal of Physiology-Heart and Circulatory Physiology*, 2011.

[11] D. C. Barber and B. H. Brown, "Applied potential tomography," *Journal of Physics E: Scientific Instruments*, vol. 17, no. 9, pp. 723–733, 1984.

[12] J. Malmivuo and R. Plonsey, "Bioelectromagnetism. 26. Impedance Tomography," pp. 420–427, jan 1995.

[13] Swisstom, "ibeX - free EIT management," *http://www.swisstom.com/en/products/ibex, accessed on 19-03-2019*.

[14] S. Dunlop, J. Hough, T. Riedel, J. F. Fraser, K. Dunster, and A. Schibler, "Electrical impedance tomography in extremely prematurely born infants and during high frequency oscillatory ventilation analyzed in the frequency domain," *Physiological measurement*, vol. 27, no. 11, p. 1151, 2006.

[15] M. Soleimani, C. Gómez-Laberge, and A. Adler, "Imaging of conductivity changes and electrode movement in EIT," *Physiological measurement*, vol. 27, no. 5, p. S103, 2006.

[16] S. Heinrich, H. Schiffmann, A. Frerichs, A. Klockgether-Radke, and I. Frerichs, "Body and head position effects on regional lung ventilation in infants: an electrical impedance tomography study," *Intensive Care Medicine*, vol. 32, no. 9, p. 1392, 2006.

[17] J. Schramel, C. Nagel, U. Auer, F. Palm, C. Aurich, and Y. Moens, "Distribution of ventilation in pregnant Shetland ponies measured by Electrical Impedance Tomography," *Respiratory Physiology & Neurobiology*, vol. 180, no. 2, pp. 258–262, 2012.

[18] I. Frerichs, "Continuous Regional Analysis Device for Neonate Lung - Full Text View," *https://clinicaltrials.gov/ct2/show/NCT02962505, accessed on 19-03-2019*, 2016.

[19] L. Sophocleous, I. Frerichs, M. Miedema, M. Kallio, T. Papadouri, C. Karaoli, T. Becher, D. G. Tingay, A. H. van Kaam, R. Bayford, and A. D. Waldmann, "Clinical performance of a novel textile interface for neonatal chest electrical impedance tomography," *Physiological Measurement*, vol. 39, no. 4, p. 44004, 2018.

[20] K. W. Cross and T. E. Oppe, "The respiratory rate and volume in the premature infant," *The Journal of physiology*, vol. 116, no. 2, p. 168, 1952.

[21] C. J. Clopper and E. S. Pearson, "The use of confidence or fiducial limits illustrated in the case of the binomial," *Biometrika*, vol. 26, no. 4, pp. 404–413, 1934.

Appendix A Algorithm parameters

In this appendix more information is given about the development of the two algorithms mentioned Chapter 2. The classification algorithm will be discussed first, followed by the breath detection algorithm. For both algorithms the selection process of the relevant parameters is elaborated.

Classification algorithm

For the classification algorithm the following parameters were set:

1. Length of analysis segment
2. Length of classification segment
3. Region of interest in frequency domain
4. Lower frequency magnitude boundary
5. Highest peak boundary

In order to find the parameters that resulted in the best performance of the classification algorithm, different combinations of parameters were tested to reach the optimal values for sensitivity and specificity. The settings and argumentation for the final value of ach parameter are discussed separately below. A sensitivity analysis was also performed. This analysis will be discussed after discussion of the parameter values.

1. *Length of analysis segment*

The optimal length of the analysis segment is a trade-off between frequency resolution and classification accuracy. When the analysis segment is too short, the frequency resolution will be too low to detect the behaviour around the respiratory frequencies. When the segment is too long, very large parts of the signal will be dismissed around one disturbance. The expected breath rate is up to 1.2 Hz (K. W. Cross, 1952), and the first segment length was first set at 495 frames, resulting in a frequency resolution of 0.1 Hz. This segment length was tested and turned out to be performing quite well (Figure 1). To evaluate the segment length, the size of the analysis segment was doubled, and the classification algorithm was performed again. This resulted in lower performance (sensitivity -15.0%, specificity +4.4%), and visibly larger sequences that are classified as unreliable (Figure 2). Therefore the initial segment length was preferred.

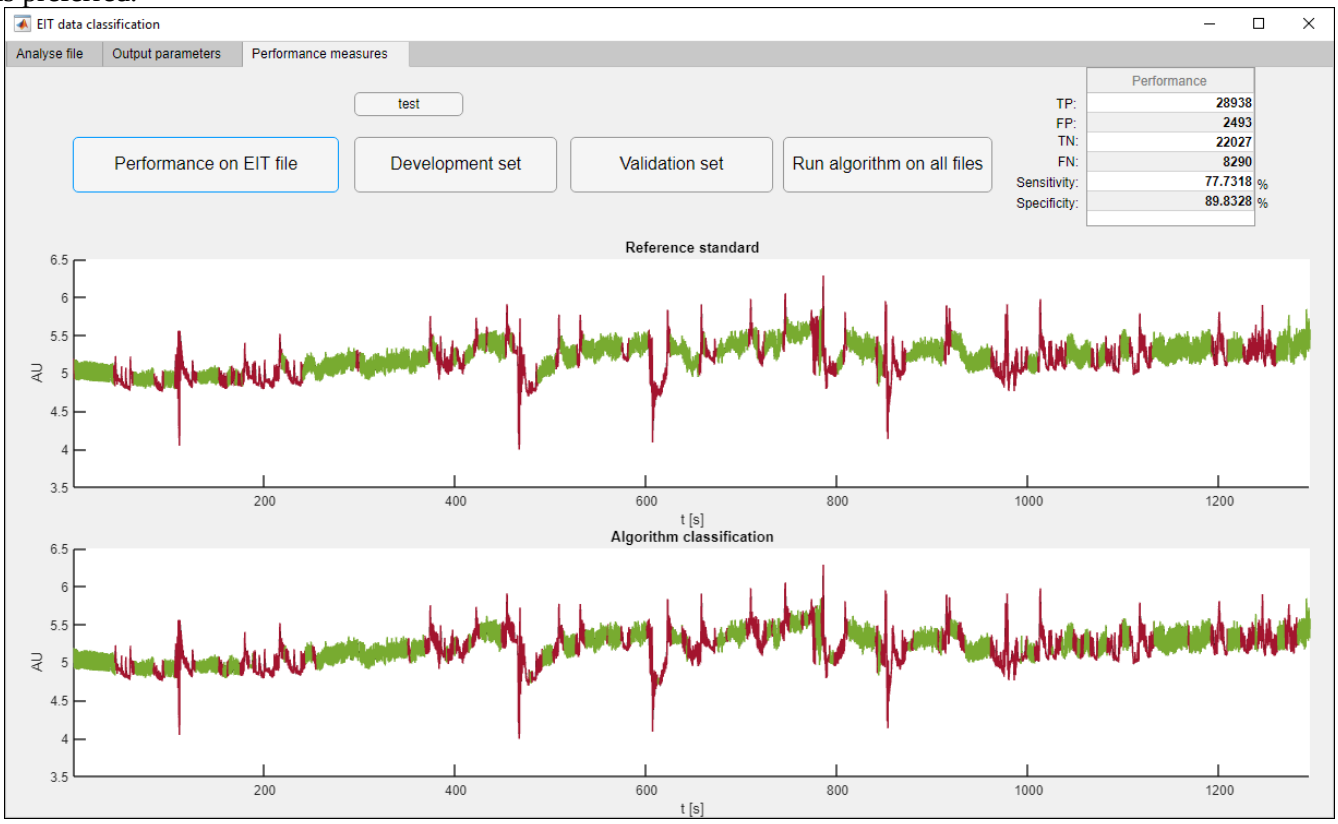


Figure 1: Result of the classification algorithm with the chosen analysis segment length of 495 frames

Figure 2: Result of the classification algorithm with an analysis segment length twice the size of the chosen segment length.

2. *Length of classification segment*

The length of the classification segment is limited by the calculation time. A typical EIT file contains over 60,000 frames. If the reliability is calculated for each frame, the algorithm has to be evaluated the same amount of times. Furthermore, shifting the boundaries of the 495 frame long analysis segment by one frame will very rarely result in a different outcome. The maximum segment length was set at 71 frames (about 1.5 seconds), such that roughly each breath is evaluated separately. Using this maximum segment length resulted in an acceptable calculation time and good performance measures (as reported in Chapter 2).

To examine the effect of the length of the segment, an alternative segment length of 35 frames was used to run the algorithm again. This resulted in lower performance measures of the algorithm (sensitivity + 0.07%, specificity – 1.7%), proving that reducing the size of the classification segment does not improve the algorithm.

3. *Region of interest in frequency domain*

Not all of the information in the calculated Fourier transform of the analysis segment is used in the classification algorithm. When inspecting the different Fourier spectra, it was observed that disturbed signals showed high magnitudes in regions lower than the respiratory frequencies. All signals showed very low magnitudes at frequencies higher than 2 Hz, and therefore only frequencies between 0.1 and 2 Hz were used for classification.

4. *Lower frequency magnitude boundary*

The first reliability criterium of the algorithm is the summed magnitude of the lower frequency regions. The low frequency magnitudes that dominated sequences without a normal breathing pattern were observed in a range between 0.1 and 0.7 Hz, and therefore the boundary was first set at 0.7 Hz. This value was later increased to 0.8 Hz after a sensitivity analysis together with the highest peak boundary.

5. *Highest peak boundary*

The last reliability criterium is the location of the highest peak in the frequency spectrum. All observed breath rates from the preterm infants data set were higher than 0.7 Hz, and sequences that showed a normal breathing pattern were dominated by a high peak at the respiratory rate. Therefore a classification step was implemented to check the location of the highest frequency peak. The algorithm finds the highest peaks and checks if it is above or below the determined

boundary. The boundary location was first set at a value of 0.7 Hz, and later decreased to 0.5 Hz when the combination of the two boundaries was fine-tuned with a sensitivity analysis.

Sensitivity analysis

To investigate the parameter values of the lower frequency magnitude boundary and the highest peak boundary, a sensitivity analysis was performed. For the lower frequency boundary the tested range was between 0.3 and 1.0 Hz, with a step size of 0.1 Hz. For the highest peak boundary the frequency range between 0.1 and 0.7 Hz was tested, with a step size of 0.1 Hz. This resulted in 7 x 8 = 56 tested parameter combinations. For all combinations the sensitivity and specificity of the algorithm on the development data set were calculated. The results of the sensitivity analysis are shown in Figure 3.

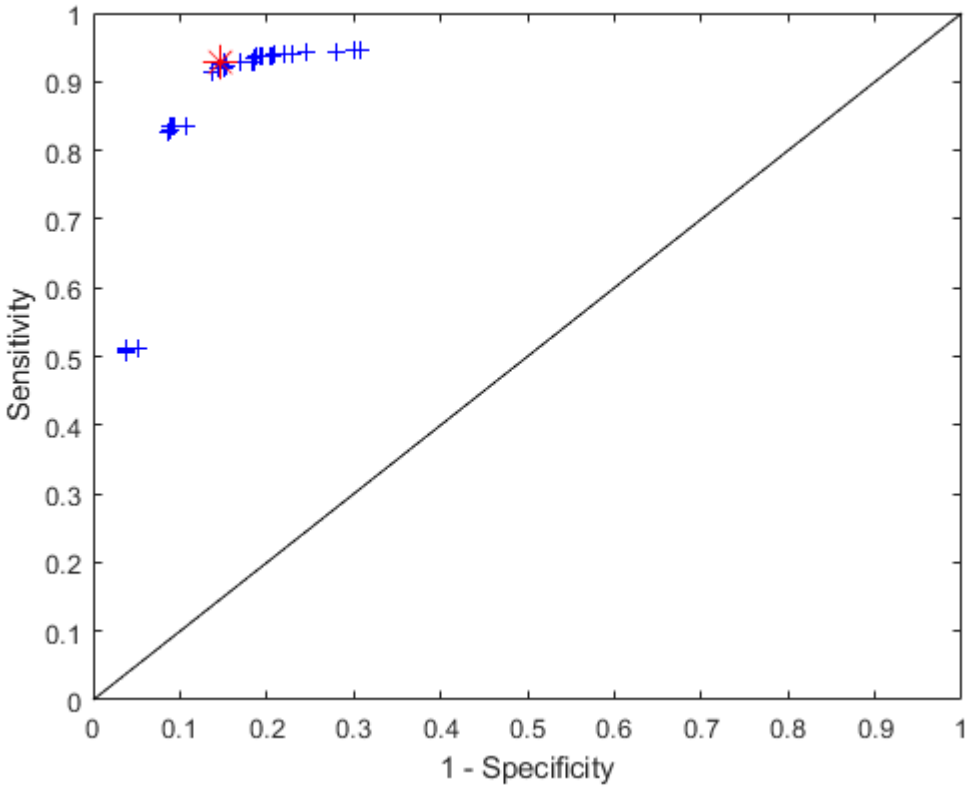


Figure 3: ROC curve of the different combinations of the boundaries for the lower frequency and highest peak classification rules. The red star represents the operating point that was chosen for the final parameters in the classification algorithm

Breath detection algorithm

There was limited time to develop the breath detection algorithm. The reason for this is the fact that the Swisstom EIT system contains its own breath detection, which is saved in the recorded files, and it was long assumed that this breath detection would suffice for the developed application. However, it was later discovered that was not the case for some recordings (see Figure 4 for an example). Therefore, the decision was made to develop a new breath detection algorithm.

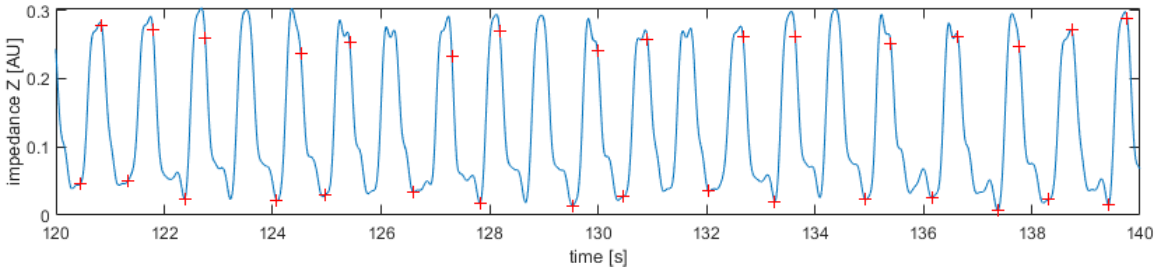


Figure 4: Example of a recording where the built-in breath detection of the Swisstom EIT system is not able to capture the true breaths.

Due to the limited time a simple but efficient method for the detection of start and end of inspiration was searched for. The easiest way to accomplish this is by rigorously simplifying the impedance signal such that it approaches a sinusoid, and then applying peak detection. A low-pass and a moving average filter were implemented to smoothen and simplify the signal sufficiently for correct peak detection. To correct the detected peak locations to the true locations in the unfiltered signal, the algorithm was then programmed to find the local minimum/maximum around each detected location. All three steps are discussed in detail below.

1. *Low-pass filter*

The low-pass filter was implemented in order to remove smaller peaks that are caused by measurement noise or cardiac-related impedance changes and do not represent the breathing pattern. The low-pass filter defeats its purpose if it filters out the breathing signal. Therefore the minimum cutoff value is equal to the highest expected breath rate, which is 1.2 Hz, as referenced in the previous chapter (K. W. Cross, 1952). In order to keep a margin around this minimum value, the cutoff value was set to 1.5 Hz. The result is shown in Figure 5.

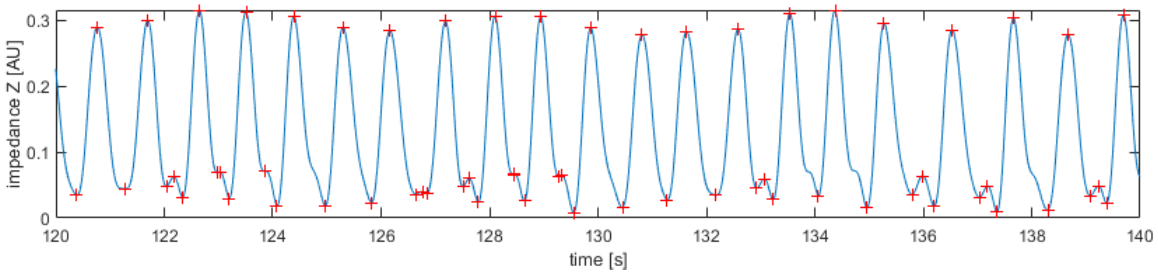


Figure 5: Impedance signal of the EIT recording after applying a 1.5 Hz low-pass filter, with detected peaks and valleys marked in red. The signal is still not simplified enough to use peak detection to find the start and end of inspiration.

2. *Moving average*

The low-pass filter is not able to remove all of the smaller peaks seen in the signal. Therefore a moving average filter was implemented to smoothen out the signal even further. The window length of the moving average filter should be long enough to smoothen the smaller peaks and not the breath related peaks. The lowest expected breath rate of 1.2 Hz would result in breaths than span around 40 frames, since the sample frequency of the Swisstom EIT system is ±48 Hz. The window should not reach the breath minimum breath length, and was therefore set at 20 frames, which is half the maximum length. The moving average filter showed good results, as can be seen in Figure 6.

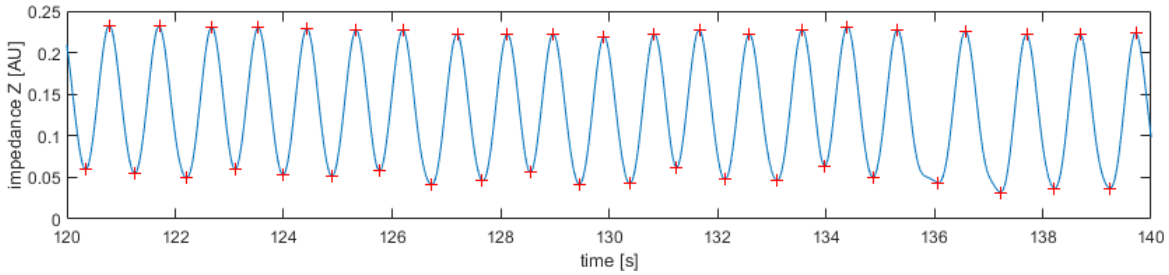


Figure 6: Impedance signal of the EIT recording after applying a moving average filter with a window of 20 frames, with detected peaks and valleys marked in red. Peak detection now correctly captures the start and end of inspiration.

3. *Find local minima*

The signal that is used for breath detection has been heavily processed and can therefore not be used to report EIT parameters like tidal impedance amplitude and end expiratory lung impedance. For example, the moving average filter decreases the values of tidal impedance amplitude. When we plug the detected locations back into the unfiltered signal we can see that they roughly represent the start and end of inspiration, but are spread around the true maxima/minima (Figure 7).

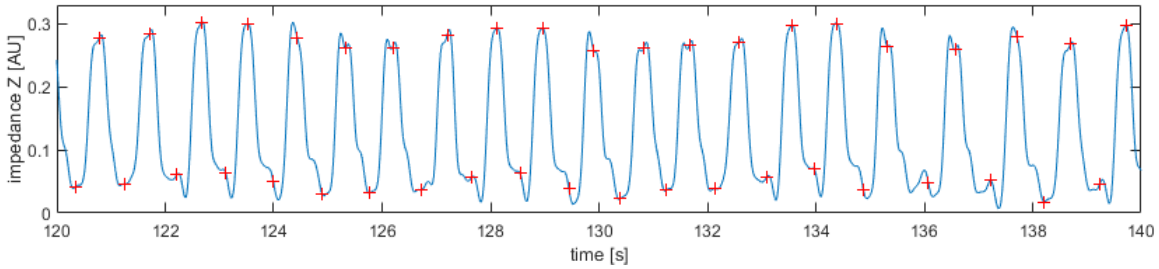


Figure 7: Unfiltered signal of the EIT recording with the locations of start and end of inspiration (marked in red), as detected in the filtered signal. The detected locations are spread around the true minimum/maximum of the unfiltered signal.

To solve this problem, a last step was implemented in the breath detection algorithm. This step was designed to find the true start and end of inspiration in the unfiltered signal. For all of the detected start- and endpoints of inspiration in the smoothed signal, the nearest maximum of minimum is searched within a window of ten frames before and ten frames after the detected location. This length of the window was chosen by increasing the window until it proved to achieve the desired results. The results of the final breath detection algorithm is shown in Figure 8.

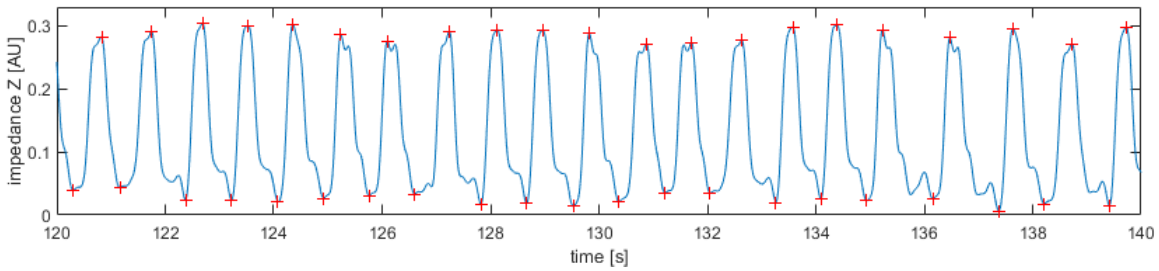


Figure 8: Final breath detection algorithm, after the detected breath locations are updated with the unfiltered signal. The values now correctly represent the local minima and maxima of the signal.

The advantage of this new breath detection algorithm is that it is no longer dependent on the Swisstom breath detection. This makes it easier to adapt the developed application to EIT files recorded with systems from other manufacturers.

Appendix B Instructions for manual graders

Thank you for helping me with manual classification of data sequences for EIT research.
I will start with a presentation. In this presentation I will explain EIT and its applications, followed by why I need your help with my research. I will then give instructions for your specific task in this research. A summary of the instructions is provided in this document.

Files:

ManualClassification.m	Matlab script for manual classification
ManualClassification.xlsx	Excel file to report the start- and end indices of reliable sequences
file1.m to file6.m	Matlab files containing the EIT recordings you will classify

Goal

Report **data sequences** you would select for **reporting representative EIT parameters**, e.g.:

- Tidal volume (DeltaZ)
- End expiratory lung volume (EELZ)

Instructions

1. Open Matlab Script (ManualClassification.m)
2. Get familiar with the data
    a. Run script and click through some of the recordings
    b. The purple "+" sign indicates a change in number of failing electrodes. This is sometimes accompanied by a switch of the baseline impedance value, and therefore **unreliable**
3. Report sequences that you deem suitable for parameter reporting:
    a. Log the start and end indices of the **suitable** indices in the ManualClassification.xlsx file, for each recording

Appendix C Patient information letter (Dutch)

Geachte heer/mevrouw,

Uw kindje is opgenomen op de afdeling neonatologie van het Sophia Kinderziekenhuis. Momenteel krijgt hij/zij ondersteuning met het ademen, door middel van een buisje. Wanneer de longen van uw kindje genoeg zijn aangesterkt, is het buisje niet meer nodig. Het buisje zal worden weggehaald, waarna uw kindje ondersteuning krijgt zonder buisje, door middel van een masker of sprietjes in de neus.
U wordt nu gevraagd mee te doen aan een wetenschappelijk onderzoek. U beslist zelf of u hieraan wilt meedoen. Voordat u de beslissing neemt, is het belangrijk om meer te weten over het onderzoek. Lees daarom deze informatiebrief rustig door. Meer algemene informatie over medisch-wetenschappelijk onderzoek vindt u in de Algemene brochure. Heeft u na het lezen van de informatie nog vragen? Dan kunt u hiervoor terecht bij de onderzoeker, op bladzijde ?? van deze brief vindt u zijn contactgegevens.

Wat is het doel van het onderzoek?

In dit onderzoek willen we onderzoeken of de ondersteuning van de ademhaling die regulier gegeven wordt na het weghalen van het buisje voldoende is. Dit willen we doen door de hoeveelheid lucht in de longen van uw kindje te meten voor en nadat het ademhalingsbuisje wordt weggehaald. Wanneer uw zoon/dochter met een buisje ondersteund wordt kan het beademingsapparaat precies meten hoe veel lucht er in de longen terechtkomt, maar bij het masker of de sprietjes kan dit niet meer. Op dit moment is er in het Sophia Kinderziekenhuis nog geen manier om te meten hoe veel lucht er in de longen terechtkomt bij de ondersteuning zonder buisje, maar een nieuw apparaat zou dit wel kunnen meten.
Met dit nieuwe apparaat zal het onderzoek gedaan worden. Het apparaat bestaat uit bandje van textiel, met daarin sensoren, en een monitor waarop de gegevens worden verzameld. In deze studie gaan we kijken naar de veranderingen in de hoeveelheid lucht in de longen in de periode voor het weghalen van het buisje en de periode erna. Het onderzoek heeft geen invloed op de behandeling die uw zoon/dochter krijgt.

Hoe wordt het onderzoek uitgevoerd?

Het onderzoek duurt maximaal 72 uur, waarbij we het bandje van textiel om de longen van uw kindje heen zullen leggen. Het omdoen van het bandje en aansluiten van de monitor duurt een paar minuten. Uw zoon/dochter heeft geen last van het bandje.
Ongeveer 24 uur voordat het beademingsbuisje wordt weggehaald bij uw kindje gaan we beginnen met meten. Het bandje waarmee we gaan meten zal rond de longen om het lichaam van uw kindje worden gelegd en vastgemaakt met klittenband. Om ervoor te zorgen dat we goede meetresultaten krijgen zal er eerst een spray worden aangebracht op het bandje. Vervolgens kan het bandje blijven zitten tot het einde van het onderzoek, maar het kan ook voorkomen dat het bandje tijdelijk eventjes wordt afgedaan vanwege een behandeling die hoort bij de zorg voor uw kindje.
Na 72 uur, ongeveer twee dagen nadat het beademingsbuisje is weggehaald, is het onderzoek afgelopen en zal ook het bandje worden weggehaald.

Wat is er meer of anders dan de reguliere behandeling(en) die hij/zij krijgt?

Deelname aan het onderzoek heeft geen gevolgen voor de behandeling die uw zoon/dochter krijgt. Het bandje wordt bevestigd om uw kind en vervolgens wordt de reguliere behandeling hervat. Drie keer per dag wordt gecontroleerd of het bandje nog goed zit. Na 72 uur wordt het bandje weer weggehaald.

Wat zijn mogelijke voor- en nadelen van deelname aan dit onderzoek?

Uw zoon/dochter zal zelf geen voordeel hebben van deelname aan het onderzoek, omdat we niets veranderen aan de behandeling van uw kindje. Voor kinderen die in de toekomst te vroeg geboren worden kunnen de resultaten van dit onderzoek wel nuttig zijn. Als we met het bandje goed in de gaten kunnen houden hoe veel lucht er in de longen terechtkomt tijdens de ondersteuning zonder buisje, kunnen we in de toekomst de hoogte van de ondersteuning hierop aanpassen. Als het werkt zoals we verwachten dan kan met deze techniek de hoogte van de ondersteuning worden aangepast op de specifieke behoeften van elk kindje. Dit zal gunstig zijn voor de gezondheid en ontwikkeling van deze patiënten.

Wat gebeurt er als u niet wenst deel te nemen aan dit onderzoek?

U beslist of uw kind meedoet aan het onderzoek. Deelname is vrijwillig. Als u besluit niet mee te doen, hoeft u verder niets te doen. U hoeft niets te tekenen en u hoeft ook niet uit te leggen waarom u niet wilt meedoen. Uw kind krijgt gewoon de behandeling die hij/zij anders ook zou krijgen. Als u besluit mee te doen, dan kunt u zich altijd bedenken en deelname stoppen, ook tijdens het onderzoek.

Bent u verzekerd wanneer u aan het onderzoek meedoet?

Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering dekt eventuele schade als gevolg van het onderzoek. Dit geldt voor schade die naar boven komt tijdens het onderzoek, of binnen vier jaar na het einde van het onderzoek. In de bijlage vindt u de verzekerde bedragen, de uitzonderingen en de adresgegevens van de verzekeraar.

Wat gebeurt er met uw gegevens?

In de algemene brochure is uitgelegd dat de onderzoekers gegevens over uw kind verzamelt en deze vertrouwelijk behandelt. De onderzoekers mogen zijn/haar medische status en de gegevens van het onderzoek inzien. De onderzoekers mogen de gegevens gebruiken voor dit onderzoek, maar zij mogen deze gegevens alleen bekend maken zonder daarbij uw kinds, uw naam, of andere persoonlijke gegevens te vermelden. Jullie identiteit blijft dus altijd geheim. De onderzoeker bewaart de persoonsgegevens met een code. Dit betekent dat op de studiedocumenten in plaats van uw kinds naam enkel een letter-cijfercode staat. Alleen de onderzoeker houdt een lijst bij waarop staat welke letter- cijfercode bij welke naam hoort. De personen die inzage kunnen krijgen in uw gegevens zijn:

- de medewerkers van het onderzoeksteam,
- de leden van de toetsingscommissie die de studie heeft goedgekeurd,
- de bevoegde medewerkers van de Inspectie voor de Gezondheidszorg

Wij zijn verplicht uw onderzoeksgegevens 15 jaar te bewaren. Daarvoor geeft u toestemming als u meedoet aan dit onderzoek. Als u dat niet wilt, dan kunt u niet meedoen aan dit onderzoek. Na deze 15 jaar worden de onderzoekgegevens vernietigd. De gegevens worden enkel voor dit onderzoek gebruikt.

Welke medisch-ethische toetsingscommissie heeft dit onderzoek goedgekeurd?

De Medisch Ethische Toetsings Commissie (METC) van het Erasmus MC heeft dit onderzoek goedgekeurd. Meer informatie over deze goedkeuring vindt u in de Algemene brochure.

Wilt u verder nog iets weten?

Indien u tijdens deze studie vragen of klachten heeft, vragen wij u contact op te nemen met de onderzoeker of uw behandelend arts.

Indien u twijfelt over deelname kunt u de onafhankelijke arts raadplegen die zelf niet bij het onderzoek betrokken is, maar die wel deskundig is op het gebied van dit onderzoek en beademde kinderen. Ook als u voor of tijdens de studie vragen heeft die u liever niet aan de onderzoekers stelt, kunt u contact opnemen met de onafhankelijke arts. Als u niet tevreden bent over het onderzoek of de behandeling, dan kunt u terecht bij de onafhankelijke klachtencommissie van het Erasmus MC.

De contactgegevens van de onderzoekers, de onafhankelijke arts en de klachtencommissie van het Erasmus MC vindt u onder de contactgegevens op de volgende pagina.

Appendix D METC protocol

EIT to determine lung volumes after extubation

(September 2018)

- May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans
- Sept 2015: adaptation section 9.1, 9.2 and 12.5: text in accordance to WMO amendment on reporting SAE and temporary halt (section 10 of WMO)
- Oct 2015: adaptation section 4.4 – comment [CCMO15], 8.2 and 10.1 with respect to methodology/statistics
- Sept 2018: adaptation section 12.1 and comment [CCMO46] due to applicability GDPR as of May, 2018

PROTOCOL TITLE: A pilot study on the use of electrical impedance tomography in preterm infants during extubation from mechanical ventilation to CPAP.

Protocol ID	*<include protocol ID given by sponsor or investigator>*
Short title	EIT to determine lung volumes after extubation
EudraCT number	Not applicable
Version	1
Date	12-06-2019
Coordinating investigator/project leader	Not applicable
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	Dr. A.A. Kroon, Kinderarts-neonatoloog. Wytemaweg 80. Sp 4455 Pieper *836004 A.A.kroon@erasmusmc.nl
Sponsor (in Dutch: verrichter/opdrachtgever)	Erasmus MC
Subsidising party	Not applicable
Independent expert (s)	Dr. E.D. Wildschut Department of Pediatrics
Laboratory sites	Not applicable
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
Sponsor or legal representative: Erasmus MC 's Gravendijkwal 230 3015 CE Rotterdam **Head of Department:** Prof Dr. E.H.H.M. Rings Head of the department of Pediatrics Prof. Dr. I.K.M. Reiss Head of the division of Neonatology		
[Coordinating Investigator/Project leader/Principal Investigator]: Dr. A. A. Kroon Neonatologist		

TABLE OF CONTENTS

1. INTRODUCTION AND RATIONALE 8
2. OBJECTIVES 9
3. STUDY DESIGN 10
4. STUDY POPULATION 11
4.1 Population (base) 11
4.2 Inclusion criteria 11
4.3 Exclusion criteria 11
4.4 Sample size calculation 11
5. TREATMENT OF SUBJECTS 12
5.1 Investigational product/treatment 12
5.2 Use of co-intervention (if applicable) 12
5.3 Escape medication (if applicable) 12
6. INVESTIGATIONAL PRODUCT 13
6.1 Name and description of investigational product(s) 13
6.2 Summary of findings from non-clinical studies 13
6.3 Summary of findings from clinical studies 13
6.4 Summary of known and potential risks and benefits 13
6.5 Description and justification of route of administration and dosage 13
6.6 Dosages, dosage modifications and method of administration 13
6.7 Preparation and labelling of Investigational Medicinal Product 13
6.8 Drug accountability 13
7. NON-INVESTIGATIONAL PRODUCT 14
7.1 Name and description of non-investigational product(s) 14
7.2 Summary of findings from non-clinical studies 14
7.3 Summary of findings from clinical studies 14
7.4 Summary of known and potential risks and benefits 14
7.5 Description and justification of route of administration and dosage 14
7.6 Dosages, dosage modifications and method of administration 14
7.7 Preparation and labelling of Non Investigational Medicinal Product 15
7.8 Drug accountability 15
8. METHODS 16
8.1 Study parameters/endpoints 16
8.1.1 Main study parameter/endpoint 16
8.1.2 Secondary study parameters/endpoints (if applicable) 16
8.1.3 Other study parameters (if applicable) 16
8.2 Randomisation, blinding and treatment allocation 16
8.3 Study procedures 16
8.4 Withdrawal of individual subjects 16
8.4.1 Specific criteria for withdrawal (if applicable) 17
8.5 Replacement of individual subjects after withdrawal 17
8.6 Follow-up of subjects withdrawn from treatment 17

8.7 Premature termination of the study 17
9. SAFETY REPORTING....18
9.1 Temporary halt for reasons of subject safety 18
9.2 AEs, SAEs and SUSARs 18
9.2.1 Adverse events (AEs)....18
9.2.2 Serious adverse events (SAEs)....18
9.2.3 Suspected unexpected serious adverse reactions (SUSARs) 18
9.3 Annual safety report....18
9.4 Follow-up of adverse events 18
9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee] 18
10.STATISTICAL ANALYSIS 19
10.1 Primary study parameter(s) 19
10.2 Secondary study parameter(s)....19
10.3 Other study parameters 19
10.4 Interim analysis (if applicable)....19
11.ETHICAL CONSIDERATIONS 20
11.1 Regulation statement....20
11.2 Recruitment and consent....20
11.3 Objection by minors or incapacitated subjects (if applicable) 20
11.4 Benefits and risks assessment, group relatedness 20
11.5 Compensation for injury....20
11.6 Incentives (if applicable) 20
12.ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION 21
12.1 Handling and storage of data and documents....21
12.2 Monitoring and Quality Assurance 21
12.3 Amendments 21
12.4 Annual progress report 21
12.5 Temporary halt and (prematurely) end of study report 21
12.6 Public disclosure and publication policy....21
13.STRUCTURED RISK ANALYSIS 22
13.1 Potential issues of concern....22
13.2 Synthesis....23
14.REFERENCES....24

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CPAP	**Continuous Positive Airway Pressure**
CT	**Computed tomography**
DeltaZ	**EIT measure of tidal volume. Defined as the difference between end inspiratory lung impedance and end-expiratory lung impedance.**
DSMB	**Data Safety Monitoring Board**
EELZ	**End-expiratory Lung Impedance**
EELV	**End-expiratory Lung Volume**
EIT	**Electrical Impedance Tomography**
EudraCT	**European drug regulatory affairs Clinical Trials**
FRC	**Functional Residual Capacity**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
NICU	**Neonatal Intensive Care Unit**
PEEP	**Positive End-expiratory Pressure**
(S)AE	**(Serious) Adverse Event**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
ROI	**Region Of Interest**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
V_T	**Tidal Volume**

SUMMARY

Rationale: After extubation of preterm neonates, ventilation support is continued with non-invasive ventilation modes. Non-invasive ventilation modes may be less efficient than invasive modes in delivering support, but it is difficult to determine the tidal volumes (Vt) inhaled by the patient, and impossible to determine the functional residual capacity (FRC) without using computed tomography (CT) scans. Electrical impedance tomography (EIT) is a non-invasive imaging technology able to measure impedance changes due to respiration. End-expiratory lung impedance (EELZ) is a measure related to end-expiratory lung volume (EELV), and tidal impedance change (DeltaZ) is a measure related to tidal volume (V_T). Measuring EIT parameters during invasive ventilation makes it possible to relate EELZ and DeltaZ to the known delivered volumes, and subsequently measuring these parameters during non-invasive ventilation enables monitoring of the volume changes after extubation. This way, it is possible to determine the efficiency loss between invasive and non-invasive ventilation modes.

Objective: To determine the changes in delivered lung volumes (EELV, FRC and V_T) during non-invasive ventilation modes, after extubation from invasive ventilation.

Study design: prospective, single center, observational pilot study.

Study population: Preterm born neonates admitted to the NICU in the Erasmus MC, born between 24 and 32 weeks of gestation and on invasive ventilation support.

Intervention (if applicable): Not applicable

Main study parameters/endpoints: The main study parameters are the changes in EIT measured end-expiratory lung impedance (EELZ) and tidal impedance change (DeltaZ) over time.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: This is an observational study in which preterm NICU patients are equipped with an electrode belt and measured for up to 72 hours. During measurement the patients are provided with routine care. The electrode belt is CE marked for neonatal use, and has been safely used in multiple studies involving preterm neonates, and there are no known risks. There are no potential benefits for subjects, due to the observational nature of the study.
The study can only be performed in preterm neonates because in this population it is common to extubate to non-invasive ventilation support, and CPAP is crucial to sustain FRC and reduce work of breathing.

1. INTRODUCTION AND RATIONALE

Many preterm infants need invasive mechanical ventilation after birth, due to their underdeveloped lungs [1]. Invasive ventilation support, however, is accompanied by adverse effects, such as increased risk of Bronchopulmonary Dysplasia (BPD), airway injuries and ventilator-associated pneumonia [2, 3]. Therefore it is recommended to extubate these patients as soon as possible. To facilitate early extubation, neonates are supported with non-invasive ventilation after extubation, initially with continuous positive airway pressure (CPAP) [4].

During invasive ventilation, the ventilator measures the volumes of air delivered via an endotracheal tube to the lungs. However, during CPAP, air is delivered to the infant in a non-invasive way, usually via nasal prongs. The nasal prongs are not free from air leakage, and exhaled air does not have to pass through them. Therefore it is difficult to determine the volumes of air delivered to the lungs [5]. Because of the leaky interface it is also possible that the CPAP pressure is not fully applied to the lungs. But because this pressure is not measured within the breathing circuit, its value is unknown. These factors combined make it challenging to choose a CPAP support level that is high enough to provide adequate support, but not higher then needed.

Electrical Impedance Tomography (EIT) is a non-invasive imaging technology that constructs images of the impedance differences between the various tissues within the measured intrathoracic area [6]. It makes use of a series of electrodes on the skin surface, injecting very small currents between two electrodes and measuring the voltages in the other electrodes. EIT provides continuous real-time information on the air distribution within the lungs, making it a useful bedside lung function monitoring tool [7].

Before extubation, EIT parameters of tidal impedance variation (DeltaZ) and end-expiratory lung impedance (EELZ) can be related to known values of tidal volume and positive end-expiratory pressure (PEEP). Continuing EIT measurements after extubation allows for monitoring of changes in these parameters, even when the ventilator cannot give this information. This study provides information on the possibility of using EIT as a lung function monitoring tool after extubation. Its results will produce knowledge about the support level that is routinely given to the patient after extubation. When a decrease in DeltaZ and EELI is observed, this might indicate that the infant is supported insufficiently. Eventually, EIT might enable us to provide optimal care to the ventilated infant, adjusting the ventilator settings to the specific needs of an individual.

2. OBJECTIVES

Primary Objective: To determine the relative changes in delivered support (Vt and FRC) during the transition from invasive to non-invasive ventilation, by comparing EIT measured EELZ and DeltaZ before and after extubation, and continuously measuring their change over time.
Hypothesis: Non-invasive ventilation used in the NICU after extubation is less effective in regard to maintaining the same lung volumes after extubation as invasive ventilation at the same CPAP level.

Secondary Objective(s): To compare the ventilation distribution before extubation with the ventilation distribution after extubation. The ventilation distribution is determined by the spatial distribution of respiratory related impedance changes. The main parameter that will be investigated is the ventral-dorsal ventilation ration.
Hypothesis: Invasive and non-invasive ventilation modes result in different ventilation distributions.

To explore the possibility to use the EIT measurement to determine heart and respiratory rate measurements, and compared them with the clinical measurements. If possible to measure these rates accurately it could mean that the ECG electrodes are not needed when a patient is monitored with EIT.

3. STUDY DESIGN

In this prospective, single centre, observational pilot study intubated neonates will be observed for up to 72 with electrical impedance tomography (EIT).

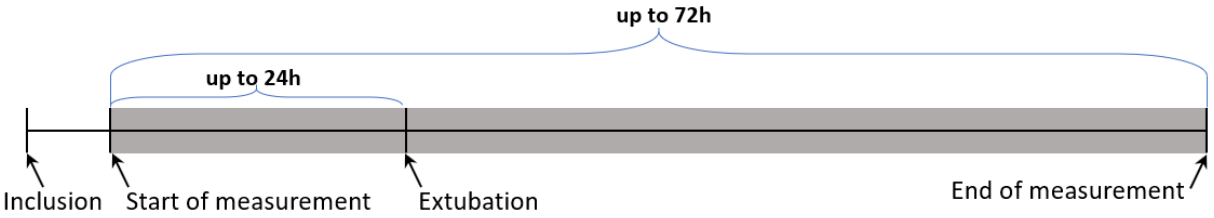


Figure 1: Timeline for subjects included in the study.

Written informed consent will be obtained from the parents when an neonate is intubated or admitted with an ET tube. After the written consent is obtained the patient can be included in the study. Measurement with the EIT device can be started when the extubation is planned for the next day, but no sooner than 24 hours before extubation (figure 1).

At the start of the measurement the chest circumference of the neonate is measured, and the right sized EIT belt chosen. Then a contact spray is applied to the EIT belt in order to achieve minimal contact impedance, guaranteeing good quality EIT measurements. The belt is then placed around the thorax of the patient, along the 6-7th intercostal space, and connected to the monitor. When this setup is completed, routine care for the patient is resumed. The measurement will not be shared with the clinicians, and will not influence clinical care. During the measurement the position of the patient is logged, because different positions can result in different EIT findings. Furthermore, other interventions that might affect EIT findings are also logged.

After 72 hours the measurement is stopped and the belt is detached from the patient. Earlier termination of measurement is possible if the parents request so, by decision of the attending physician, or when the patient is transferred to another hospital. The aim is to achieve a minimum of 24 hours measurement after extubation.

4. STUDY POPULATION

4.1 Population (base)

Twenty preterm neonates (gestational age above 24 weeks and under 32 weeks), admitted into the NICU of the Erasmus MC-Sophia and supported with invasive ventilation.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Gestational age above 24 weeks and under 32 weeks
- Clinically stable
- Intubated, planned to be extubated within 24 hours
- Written parental informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Thorax lesions
- Congenital anomalies

4.4 Sample size calculation

There are no published studies in which EIT data before and after extubation of preterm neonates are compared, or studies assessing the transfer from invasive to non-invasive respiratory support in any population. Thus, there is no way to calculate a sample size for a study of this nature.
Therefore this study is designed as a pilot study. With the results of this study, a sample size calculation of a subsequent, larger study will be made. The primary objectives of this study are comparison of EELZ between invasive and non-invasive ventilation, and comparison of DeltaZ between invasive and non-invasive ventilation.

5. TREATMENT OF SUBJECTS

Not applicable

5.1 Investigational product/treatment

Not applicable

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable

6.1 Name and description of investigational product(s)

Not applicable

6.2 Summary of findings from non-clinical studies

Not applicable

6.3 Summary of findings from clinical studies

Not applicable

6.4 Summary of known and potential risks and benefits

Not applicable

6.5 Description and justification of route of administration and dosage

Not applicable

6.6 Dosages, dosage modifications and method of administration

Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

EIT monitoring will be performed with a 32-electrode belt connected to an EIT image acquisition system (Sentec BB2, Landquart, Switzerland). The belt uses an offset of 4 electrodes, injects currents with an amplitude of 3 mA_{rms} and frequency of 200 kHz, and measures the resulting voltages in the remaining electrodes [8].

The textile band is CE approved, and consists of a flexible printed circuit board with 32 electrode contacts, enclosed in a textile cover. On the inside the cover is made up of a striped pattern of silver-coated conductive strips and non-conductive polyester strips. A Velcro strip is used to place the belt around the infant [8].

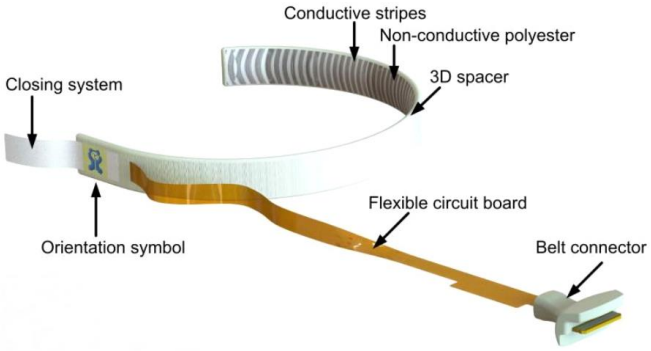


Figure 2: Neonatal electrode belt, as developed by SenTec. Figure from [8].

7.2 Summary of findings from non-clinical studies

Not applicable

7.3 Summary of findings from clinical studies

The belt in combination with the image acquisition system has been used successfully in many subjects. In 2008, a paper was published about the clinical ease of use and possible adverse effects of the EIT system [8]. The study included 30 preterm infants, which were measured for up to 72 hours. The authors conclude that the setup is suitable for long-term chest EIT imaging in neonates. There were no signs of discomfort or distress due to the electrode belt. In six patients, minor redness was observed on the skin close to the belt. All of these skin irritations disappeared within less than one hour after removal of the belt. None of the recordings were stopped early because of the EIT belt.

The system has also been used in a multicentre prospective observational EIT study “Continuous Regional Analysis Device for Neonate Lung” (NCT02962505). In this study 200 neonatal patients were included in four European NICUs from November 2016 to March 2019 [9]. The study protocol was approved by ethical committees in all four institutions.

7.4 Summary of known and potential risks and benefits

There is no potential benefit for subjects in this study, due to the observational setup. Routine care is provided to the patients during measurements. One minor effect can be identified. In a previous study the belt caused minor redness of the skin. In all of the identified cases the skin redness was harmless and disappeared quickly after removal of the belt.

7.5 Description and justification of route of administration and dosage

Not applicable

7.6 Dosages, dosage modifications and method of administration

Not applicable

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable

7.8 Drug accountability

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The main study parameters are EIT measures for lung volumes:
- EELZ (end-expiratory lung impedance)
- DeltaZ (tidal impedance variation)

The parameters are determined by the total impedance change, summer over the EIT image.

8.1.2 Secondary study parameters/endpoints (if applicable)

The secondary study parameters are EIT measures for ventilation distribution:
- Ventral-dorsal distribution
- Left lung-right lung distribution
- Ventilation distribution over predefined regions of interest (ROIs)

The parameters are determined by the spatial distribution of respiratory related impedance changes.

8.1.3 Other study parameters (if applicable)

For each included patient the following data will be collected from the patient data management system:
- Gestational age (weeks)
- Birth weight (grams)
- Sex (male/female)
- Postmenstrual age at inclusion (weeks)
- Postnatal age (days)
- Weight at inclusion (grams)
- Ventilator settings and measurements (including pressures, volumes, and flows)
- Physiological parameters measured as part of routine care (including heartrate, respiratory rate, oxygen saturation and pulse rate)
- Transcutaneous parameters measured as part of routine care (partial pressure of oxygen and carbon dioxide)
- Surfactant administration prior to or during inclusion (timing and doses)

The following parameters will collected during measurement:
- Position of the patient
- Medical interventions

8.2 Randomisation, blinding and treatment allocation

Not applicable

8.3 Study procedures

At the start of the measurement the chest circumference of the included neonate is measured, and the right sized EIT belt is chosen. Then a contact spray is applied to the EIT belt in order to achieve minimal contact impedance, maximizing the quality of EIT images. The belt is then placed around the thorax of the patient, along the 6-7th intercostal space, and connected to the monitor. With this setup is completed, routine care for the patient is resumed.

During measurement the position of the patient is logged, because different positions can result in different EIT findings. Furthermore, other interventions that might affect EIT findings are also logged. Every eight hours, the neonate is checked for skin irritation around the EIT belt.

After 72 hours the measurement is stopped and the belt is detached from the patient.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

If a subject is withdrawn before a sufficient amount of data is recorded for analysis, one extra subject will be included in the study, in order to reach the goal of 20 patients.

8.6 Follow-up of subjects withdrawn from treatment

Subjects that are withdrawn will not be followed.

8.7 Premature termination of the study

The study will be terminated if any serious problem occurs, compromising the safety of included patients.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Annual safety report

Not applicable

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

No previous published study has been performed on the use of EIT in preterm neonates during extubation. Therefore, no prediction can be made to what the data will show. This pilot study is designed to investigate the change of parameters over time during the extubation period. After completion of this study, the orders of magnitude of the investigated parameters are known, and a statistical power can be calculated for a larger study on the same topic.

10.2 Secondary study parameter(s)

Not applicable

10.3 Other study parameters

Not applicable

10.4 Interim analysis (if applicable)

Not applicable

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (2008), and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

Parents or legal guardians will be asked for their informed consent. Consent will be asked by the primary investigator and/or co-investigators. Parents or legal guardians will receive an informational document and are given a minimum of 24 hours to make a decision about participation. The investigator will answer all questions the caregiver's have regarding the study. Consent can be obtained if a neonate is intubated and meets the inclusion criteria.

11.3 Objection by minors or incapacitated subjects (if applicable)

The Code of conduct relating to expressions of objection by minors participating in medical research is applicable. Both parents, care givers or all legal representatives must give consent for the inclusion of the neonate into this study.

11.4 Benefits and risks assessment, group relatedness

There are no additional risks for the patients included in this study.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.
The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data will be stored in a patient data management system, used on the ward. EIT measurements are stored on the EIT monitor. Data will be handled confidentially, in accordance with the Dutch Personal Data Protection Act.
All EIT data will be extracted and will be coded. All patients will be provided with a unique code, only known to the principal investigator and co-investigators. Data cannot be linked to an individual patient. Only on special request the coded data can be unlocked by the principal investigator and/or co-investigators.

12.2 Monitoring and Quality Assurance

Not applicable

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

Data and outcome of the study will be disclosed unreservedly, in accordance with de CCMO statement on publication policy.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

The mechanism of EIT is well known and has been developed over decades since its invention in 1984. The technology is considered non-invasive and is safe.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

The EIT system that will be used in this study is specifically developed for the preterm population, and has been used in many patients before (section 7.3).

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable

e. Analysis of potential effect

There is no potential benefit for subjects in this study, due to the observational setup. Routine care is provided to the patients during measurements. One minor risk can be identified. In a previous study the belt caused minor redness of the skin. In all of the identified cases the skin redness was harmless and disappeared quickly after removal of the belt.

f. Pharmacokinetic considerations

Not applicable

g. Study population

The study is performed in the premature neonatal population due to the reason for intubation in these patients. The premature patients are intubated due to their underdeveloped lungs. As their lungs mature, the need for invasive ventilation decreases. In order to remove the endotracheal tube as soon as possible, non-invasive support needs to be provided after extubation.
In the pediatric and adult population patients generally do not receive ventilation support after extubation.

h. Interaction with other products

Not applicable

i. Predictability of effect

If skin irritation occurs due to the electrode belt, the effect can quickly be observed by attending staff.

j. Can effects be managed?

Minor redness is considered harmless. To ensure that there is no harmful irritation occurs, the patient's skin is checked every eight hours. The measurement can be stopped at all times by the attending physician.

13.2 Synthesis

The observational nature of the study ensures that routine care is provided to the included subjects.
The non-investigational product that will be used in this study has proven to be save in this population, because it has been used in at least 230 premature patients before. The CE approval of the electrode belt confirms its safety.

14. REFERENCES

[1] B. J. Stoll *et al.*, "Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012," *JAMA,* vol. 314, no. 10, pp. 1039-51, Sep 8 2015.
[2] V. Venkatesh *et al.*, "Endotracheal intubation in a neonatal population remains associated with a high risk of adverse events," *Eur J Pediatr,* vol. 170, no. 2, pp. 223-7, Feb 2011.
[3] J. S. Garland, "Strategies to prevent ventilator-associated pneumonia in neonates," *Clin Perinatol,* vol. 37, no. 3, pp. 629-43, Sep 2010.
[4] G. M. Sant'Anna and M. Keszler, "Weaning Infants from Mechanical Ventilation," *Clinics in Perinatology,* vol. 39, no. 3, pp. 543-562, 2012.
[5] G. Schmalisch, H. Fischer, C. C. Roehr, and H. Proquitté, "Comparison of different techniques to measure air leaks during CPAP treatment in neonates," *Medical Engineering & Physics,* vol. 31, no. 1, pp. 124-130, 2009/01/01/ 2009.
[6] M. Cheney, D. Isaacson, and J. Newell, "Electrical Impedance Tomography," *SIAM Review,* vol. 41, no. 1, pp. 85-101, 1999/01/01 1999.
[7] I. Frerichs *et al.*, "Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the TRanslational EIT developmeNt stuDy group," *Thorax,* vol. 72, no. 1, pp. 83-93, 2017.
[8] L. Sophocleous *et al.*, "Clinical performance of a novel textile interface for neonatal chest electrical impedance tomography," *Physiological measurement,* vol. 39, no. 4, p. 044004, 2018.
[9] I. Frerichs. (2016). *Continuous Regional Analysis Device for Neonate Lung (CRADL)*. https://clinicaltrials.gov/ct2/show/NCT02962505, accessed: 22-05-2019