Electrical impedance tomography in high frequency ventilated preterm infants: the search for the Holy Grail

Miedema, M.

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General introduction

Aetiology, assessment and management of low lung volume in preterm infants

Martijn Miedema¹, Frans H. de Jongh¹, Anton H. van Kaam¹

¹Department of Neonatology, Emma Children’s Hospital AMC, Amsterdam, The Netherlands
Introduction

Lung function in preterm infants (gestational age < 37 weeks) is often compromised due to structural immaturity and a loss of lung volume. This loss of lung volume may also injure the newborn lung and lead to long-term respiratory morbidity. In this chapter we will discuss the etiology and management of this loss of lung volume in preterm infants and the currently available options to monitor lung volume in preterm infants.

Basic lung volumes parameters

Before discussing the changes in lung volume in preterm infants a quick insight in the basic lung volume parameters can be helpful. Figure 1 shows several lung volume entities which can be determined during spontaneous breathing and mechanical ventilation and are usually expressed as ml or ml/kg in newborn infants. The volume entering the lung during a normal unforced spontaneous breath or a controlled mechanical breath is called the tidal volume (Vt). The volume that remains in the lungs at the end of a passive expiration is called the functional residual capacity (FRC) or end-expiration lung volume (EELV), while the residual volume (RV) is the volume remaining in the lung after a (forced)

![Figure 1 Standard lung volumes and lung capacities](image)

Definition of abbreviations: ERV = expiratory reserve volume, FRC = functional residual capacity, IC = inspiratory capacity, IRV = inspiratory reserve volume, RV = residual volume, TLC = total lung capacity, VC = vital capacity, Vt = tidal volume

maximal expiration. The volume entering the lung after a (forced) maximal inspiration starting at FRC is called the inspiratory capacity (IC), and the sum of the IC and FRC is the total lung capacity (TLC). TLC minus RV is the vital capacity (VC). The difference between end-tidal inspiration and TLC is known as the inspiratory reserve volume (IRV) while the expiratory reserve volume (ERV) consists of the volume between FRC and RV.
Lung volume is sometimes also displayed as a function of airway pressure, a relationship also known as the pressure-volume curve (Figure 2). This curve can be constructed by either stepwise changing lung volume and measuring the pressure at the airway opening or by stepwise changing the airway pressure and measuring the concomitant change in lung volume. The inflation limb of the pressure volume curve shows a sigmoid change in lung volume when pressures are increased from RV to TLC. If pressure passes the lower inflection point (LIP), lung volume will increase rapidly due to recruitment of alveoli, while minimal change in lung volume can be expected after passing the upper inflection point (UIP), because lung volume reaches TLC (Figure 2). Another characterizing feature is the pressure at maximal respiratory compliance, i.e. the part of the inflation limb corresponding with the largest volume change per unit pressure. Reducing the airway pressure from TLC will provide the deflation limb of the pressure volume curve. Under normal conditions, lung volume can be maintained at lower pressures (P) due to the increased radius (R) of the opened alveoli (Laplace’s law $P = \frac{2 \times ST}{R}$, where ST = surface tension). The difference in lung volume at identical airway pressures between the inflation- and deflation limb is called lung hysteresis. The UIP of the deflation limb marks the pressure after which lung volume rapidly decreases due to increased derecruitment or alveolar collapse (Figure 2).

Figure 2 The pressure-volume relationship of the lung with the different characteristics of the inflation limb (solid-line) and the deflation limb (dashed-line)

The inflation limb is sigmoid shaped and when pressure passes the lower inflection point lung volume will increase. At the pressure of maximal compliance the change in lung volume is maximal per pressure unit, i.e. maximal compliance, and the curve flattens if the upper inflection point is passed. The deflation limb is characterized by the presence of hysteresis, i.e. the difference in lung volume at similar airway pressures between the inflation- and deflation limb, and lung volume will be lost if pressure is decreased below the upper inflection point.
Why are newborns at risk for low lung volumes?

Optimal lung volume or FRC is often threatened in preterm infants. Important factors in this process are the anatomic disadvantages of a more cylindrical shaped thorax and horizontal inserted ribs in combination with a high chest wall compliance, the latter being inversely related to the gestational age \(^1\). A third important factor is the deficiency of intrapulmonary surfactant. Surfactant is a mixture of phospholipids and proteins produced by alveolar type II cells, which lowers the alveolar surface. In preterm infants with respiratory distress syndrome (RDS), which is characterized by primary surfactant deficiency, the increased surface tension makes the alveoli/sacculi prone for collapse resulting in low lung volumes as also shown by the deprived pressure-volume relationship (Figure 3).

**Figure 3** The pressure-volume curve of a healthy newborn lung (solid lines) and a (preterm) newborn (dashed lines) with respiratory distress syndrome (RDS)

![Pressure-volume curve](image)

Observe the difference in hysteresis between the inflation- (grey lines) and deflation limbs (black lines) of the healthy lung and the surfactant deficient RDS lung. Also due to the lower compliance a larger pressure difference is needed to produce a similar tidal volume, as indicated by the two respiration circles in the figure, in RDS lungs.

In addition to these physiological disadvantages, there are also iatrogenic factors that may compromise lung volumes. If infants are intubated because of respiratory failure, bypassing the glottis will inhibit endogenous compensation mechanisms aiming to preserve lung volume, such as expiratory breaking. Furthermore, lung volume may be compromised by endotracheal tube (ETT) suctioning to maintain airway patency. Studies in mechanically ventilated preterm infants and animal models have show that ETT suctioning results in a transient hypoxia and cardiovascular instability attributed to loss in lung volume \(^2\text{-}^4\). Although this has been described in conventional and muscle relaxed ventilated preterm infants, evidence is still lacking for unsedated and unparalyzed infants.
or during high frequency oscillatory ventilation (HFOV). Also, it is unknown if this loss in lung volume is homogenously distributed across the lung.

In conclusion, preterm infants with RDS are prone for low lung volumes and the basic treatment goal should be to correct this as much as possible because these low volumes may result in pulmonary adverse effects.

Adverse effects of low lung volume in preterm infants

A decreased FRC may potentially compromise lung function in preterm infants. First, the dynamic compliance is worsened due to the lower position in the pressure-volume envelope (Figure 3) 5. This ineffective position of ventilation in the pressure-volume envelope results in the fact that preterm infants have to increase their pressure difference to generate the same tidal volume. Second, low EELV causes narrowing of the conducting airways, thereby increasing airway resistance exponentially and making it harder to generate adequate flow of air for the preterm infant 6. Third, unaereated collapsed alveoli are still perfused and this increases intra-pulmonary shunt or ventilation-perfusion mismatch leading to hypoxia 7. Fourth, low EELV will increase pulmonary vascular resistance (PVR), which has a U-shaped relationship with lung volume (Figure 4) 8. Finally, all of the above described phenomena contribute to an increased Work of Breathing (WOB) for the preterm infant. WOB is an equivalent of the energy which is needed to overcome the elastic and resistant forces of the respiratory system for gas to move into the lungs.

Based on the above, it is clear that low lung volumes in preterm infants can cause severe deterioration of lung function leading to respiratory failure. In the next paragraph we will discuss the possible treatment options.

**Figure 4** Relationship between pulmonary vascular resistance (PVR) and lung volume.

Extra alveolar vessels (broken grey line) and alveolar vessels (solid grey line) have an opposite behaviour to changes in lung volume. The sum of changes in PVR in response to changes in lung volume is indicated by the black solid line. Note that the lowest PVR is reached at FRC.

Definitions of abbreviations: FRC = functional residual capacity, PVR = pulmonary vascular resistance, RV = residual volume, TLC = total lung capacity
How can low lung volumes in newborn infants be treated?

*Nasal Continuous Positive Airway Pressure (nCPAP)*

nCPAP is a non-invasive mode of respiratory support which is increasingly used in spontaneously breathing preterm infants. nCPAP applies a continuous positive pressure to the respiratory system of the infant, thereby facilitating inspiration and stabilizing lung volume during expiration. nCPAP reduces the need for (re)-intubation and is effective in the treatment of apnea of the preterm. Although the pathophysiological working mechanisms of nCPAP are fascinating and much is still unknown, this review will focus on the effects of mechanical ventilation and surfactant on lung volume in preterm infants.

**Conventional Mechanical Ventilation (CMV)**

CMV is used in the majority of preterm infants with respiratory failure, with time cycled pressure limited (TCPL) ventilation combined with synchronized intermittent mandatory ventilation (SIMV) as the most commonly used mode. During TCPL ventilation the airway pressure is increased during inspiration (peak inspiratory pressure, PIP) and decreased during expiration (positive end-expiratory pressure, PEEP). The difference in PEEP and PIP is the delta pressure, which results in an influx of air in the lung, i.e. the tidal volume. The magnitude of the tidal volume depends on the resistance and compliance of the respiratory system. PEEP has an important function in maintaining EELV or FRC thereby preventing alveolar collapse at end expiration and reopening of alveoli during the inspiration. However, in daily practice the optimal PEEP is difficult to determine and in most patients is set at a relatively (too) low level.

Although mechanical ventilation restores ventilation and oxygenation it also has adverse effects, also known as ventilator induced lung injury (VILI). VILI is considered to be one of the major risk factors for long term respiratory morbidity, i.e. bronchopulmonary dysplasia (BPD). Studies in animal models have shown that the use of high inspiratory pressure during CMV is injurious to the lung. However, Dreyfuss et al. made it clear that it is not the pressures but the resulting (high) tidal volumes that are responsible for this injury. This is why it is more accurate to speak of volutrauma and not barotrauma. Alveoli exposed to excessive high tidal volumes are overdistended resulting in alveolar edema and release of cytokines (biotrauma). Studies in preterm lambs have shown that it takes only five breaths to trigger the process of VILI. A second important risk factor for VILI is the presence of atelectasis, also referred to as atelectrauma. Atelectasis damages the lung in two important ways: (1) repetitive opening and collapsing of alveoli during, respectively, in- and expiration; (2) redistribution of the delivered tidal volume to the open alveoli leading to regional overdistension. Studies in acute lung injury animal models and adults with respiratory distress syndrome (ARDS) have clearly indicated that lung disease is often heterogeneous and that atelectasis is most prominent in the so-called dependent lung regions. These
regions are exposed to the gravitational effect of the lung tissue on top. For example, in the supine position, the dependent lung regions are located in the dorsal parts of the lung. In addition to volutrauma and atelectrauma, VILI can be augmented by several other factors, such as excessive use of oxygen, pre-exposure to inflammation and the presence of surfactant dysfunction 23;24.

To date, it is unclear if RDS is a homogeneous or heterogeneous lung disease. Furthermore, it is unknown if there are also gravitational effects in the preterm lung during mechanical ventilation.

Based on the above, it is clear that both atelectasis and the use of high tidal volumes should be avoided during CMV. In neonatology, intervention studies and clinical practice have mainly focused on avoiding these high tidal volumes by targeting tidal volumes between 4-7 ml/kg 12;25;26. However, reversing atelectasis and stabilizing lung volume with sufficient PEEP during CMV has received little attention in the neonatology. This is in contrast to HFOV which is discussed in the next paragraph.

High-frequency oscillatory ventilation

By design, HFOV uses small tidal volumes approximating the anatomical dead space (1.5-3 ml/kg) combined with supra-normal frequencies usually varying between 8 and 20 Hz. The generated continuous distending pressure (CDP) or mean airway pressure controls lung inflation (i.e. volume) and together with the fractional inspiratory oxygen level (FiO2) governs adequate oxygenation. The driving pressure, also referred to as pressure amplitude or delta pressure, and the frequency control ventilation (i.e. carbon dioxide clearance (\( \dot{V}_{\text{CO}_2} \)) according to the following equation: 
\[
\dot{V}_{\text{CO}_2} = f \times V_{\text{osc}}^2
\]
in which \( f \) is frequency and \( V_{\text{osc}} \) = oscillatory volume.

Textbooks, manuals and some animal studies have suggested that oxygenation (CDP and FiO2) and ventilation (pressure amplitude and frequency) are controlled independently 27-31. However, this assumption has so far not been confirmed in humans. From a physiological point of view it seems unlikely that control of oxygenation and ventilation during HFOV is truly independent.

Open Lung ventilation strategy

Animal studies have indicated that the low tidal volumes applied during HFOV are not sufficient to attenuate VILI 32-34. HFOV needs to be combined with a ventilation strategy that aims to reverse atelectasis via a recruitment manoeuvre and subsequently stabilize lung volume with sufficient airway pressures. This strategy is also referred to as the optimal lung volume or open lung ventilation (OLV) strategy 34;35. The OLV strategy uses the physiological behavior of the lung to recruit and stabilize collapsed lung tissue, aiming to place ventilation on the more compliant part of the deflation limb, thereby reducing intrapulmonary shunt, improving oxygenation and minimizing lung injury 7;34-38.
The clinical application of OLV during HFOV has mainly been studies in preterm infants with RDS. Due to the lack of non-invasive bedside tools to monitor lung volume, lung recruitment in daily clinical practice is usually guided by changes in oxygenation. This is based on the assumption that alveolar recruitment will decrease the intrapulmonary shunt fraction which in turn will improve oxygenation. The individual recruitment procedure used in the Emma Children’s Hospital in Amsterdam can be described as follows (Figure 5):

**Figure 5** Graphical representation of the individual open lung ventilation strategy used at the Emma Children’s Hospital.

The first phase aims to recruit alveoli and improve oxygenation by incremental pressure steps (1-2 cmH2O) taken every 2-3 minutes until the FiO2 is ≤ 0.25 or oxygenation no longer improves at higher FiO2. Assuming the presence of hysteresis, the pressure is then stepwise decreased until oxygenation deteriorates, indicating alveolar collapse. During the last stage the lung is once again opened and the optimal CDP is set 2 cmH2O above closing pressure.

1 Recruiting phase (inflation limb)

The preterm infants are unsedated, unparalyzed and ventilated in supine position. Following intubation, HFOV is started at a low continuous distending pressure (CDPst) of 6-8 cmH2O. The pressure amplitude is set at a level that results in visible oscillation of the chest, with a frequency of 10 Hz and inspiration time of 33%. The FiO2 is dynamically adjusted to keep the transcutaneous oxygen saturation (SpO2) between 86%-94%. The CDP is then stepwise increased with 1-2 cmH2O, aiming to recruit collapsed alveoli/sacculi, in which case intrapulmonary shunt will decrease, oxygenation will improve and the FiO2 will be reduced in steps of 0.05-0.10 if SpO2 exceeds the upper limit of the target range (Figure 2 and 6). After each pressure steps the clinician waits at least 2 – 3 minutes to determine if there is a change in oxygenation. The CDP
is stepwise increased until the FiO2 is ≤ 0.25 or oxygenation no longer improves after three consecutive pressure steps (the opening pressure or CDPo).

2 Derecruitment phase (deflation limb)
Assuming the presence of lung hysteresis, the CDP is decreased with similar 1-2 cmH2O steps, while keeping the FiO2 constant. Again, the clinician will wait at least 2-3 minutes to detect a possible deterioration in oxygenation indicating alveolar/saccular collapse. The pressure at which this occurs is called the closing pressure or CDPc.

3 Re-Opening and optimizing lung volume
Following derecruitment, the lung is once more opened with the know CDPo for 5 minutes and then stabilized at an optimal CDP (CDPopt) which is set 2 cmH2O above CDPc.

In the presented recruitment procedure some assumptions are done which have not been validated or verified. First, one of the principles OLV is based on is the presence of lung hysteresis 40;41. However, it is unknown if this hysteresis is indeed present in preterm infants with RDS. Second, in adults differences in hysteresis are seen in the dependent and non-dependent lung regions due to gravity and the heterogeneity of the underlying lung diseases 20. It is unknown if these regional differences are present during OLV in HFOV preterm infants with RDS. Third, in daily clinical practice changes in lung volume are guided at the bedside by changes oxygenation. However, oxygenation (SpO2) is not only affected by lung aeration but also pulmonary perfusion. Especially in preterm infants pulmonary hypertension may result in an increased extra-pulmonary right to left shunt across the open duct of Botalli or open foramen ovale, causing changes in oxygenation independent of lung aeration. Finally, it is unclear how quickly lung volume stabilizes after each pressure step in preterm infants with RDS and if this stabilization time is dependent on the position in the pressure-volume envelope or the surfactant status of the lung. This information is important when optimizing the time and applied pressure during lung recruitment.

Surfactant therapy
Surfactant is a complex mixture of phospholipids, neutral lipids and four proteins (surfactant protein A, B, C and D) and is the corner stone in the treatment of preterm infants with RDS. Exogenous natural surfactant reduces the surface tension of the alveoli and has an important role in the pulmonary immune response. Surfactant has proven to be beneficial in reducing barotraumas and mortality in preterm infants. Studies exploring the effect of exogenous surfactant on the lung function have mainly focused on conventionally ventilated preterm infants with RDS, showing an increase
in FRC by 20-100% \textsuperscript{42-44}. Findings on changes in lung compliance were much less consistent with some studies reporting a reduction, some no change and others an increase in lung compliance after surfactant administration \textsuperscript{45-50}. A possible explanation for this discrepancy is the time at which compliance was assessed, which varied from 15 minutes to several days after surfactant treatment. To date, no study measured the direct or immediate effect of surfactant on lung volume. Another important gap in the available literature is the regional effect of surfactant on lung volume and ventilation. Studies using radio-active labeled surfactant in preterm animal models have shown that deposition of surfactant depends on the duration, chest position, nebulization and volume of the bolus \textsuperscript{51-55}. To our knowledge there are no data available in preterm infants with RDS.

Lung volume assessment techniques
Measuring changes in lung volume non-invasively at the bedside in newborn infants has been a challenge for many years now. This chapter will review all the available tools including their advantages and disadvantages.
Oxygenation

As previously reported in this review, oxygenation is the most widely used bedside tool to monitor changes in lung volume in preterm infants. The variables that are mainly used to assess oxygenation at the bedside are pulse oximetry and transcutaneous partial oxygen pressure (TcPO2).

Despite its wide use there are some important limitations that have to be addressed. It is important to acknowledge that oxygenation is an indirect marker of lung volume that is based on changes in intrapulmonary shunt fraction 7. This means that oxygenation will only detect lung volume changes that also change intrapulmonary shunt, i.e. alveolar recruitment but not distension. Furthermore, oxygenation does not provide information on regional lung volume changes. Oxygenation will fail to provide accurate information on lung volume changes in case of extra-pulmonary right-left shunt, as sometimes seen in preterm infants with RDS who also have some degree of pulmonary hypertension.

Chest X-Ray (CXR)

CXR has been used to assess lung aeration for several decades 56;57. In preterm infants with RDS a CXR can determine the degree of lung disease and also assess the level of inspiration 58. The degree of inspiration can be estimated by the level of the diaphragm in relation to the ribs and the configuration of lung tissue in the intercostal space. Bulging of lung tissue in the intercostal space and the presence of air under the heart are considered signs of lung overdistension 59;60. Important limitations of CXR are the poor correlation between lung volume assessment by CXR and the sulfur hexafluoride dilution methods, the lack of regional information, and the lack of continuous information on lung volume changes.

Whole body plethysmography

Whole body plethysmography uses a rigid isolated closed chamber in which infants, in supine position, breath through a facemask measuring tidal flow and volume 61;62. Intra-thoracic lung volume is assessed by occlusion of the airway opening, keeping lung volume constant, resulting in respiratory efforts of the infant changing volume and pressure in the box. By applying Boyle’s law \( P_1 \times V_1 = P_2 \times V_2 \), in relation to the initial state, the thoracic gas volume (TGV) can be derived non-invasively. In the absence of air trapping, TGV equals FRC. After its introduction this technique has been successfully used in multiple studies including spontaneous breathing (preterm) infants 63;64. However, whole body plethysmography has not gained much popularity among researchers/clinicians due to its limitation that include the inability to monitor lung volume changes during mechanical ventilation and the practical difficulties (air tight box, bedside, expenses etc).
Gas wash-in/wash-out techniques

Measuring lung volume changes with tracer gases has been explored for several decades. Basically there are two different modalities, the washout and the dilution techniques. Sivan et al described an open circuit nitrogen (N₂) washout technique for assessing FRC in mechanically ventilated infants and children. In a standard situation the lung is filled with air consisting of 80% N₂, 15% O₂ and 5% CO₂. The basis of this technique is replacing all N₂ by O₂ and measuring the quantity of the N₂ which is washed out of the lung using a second ventilator which delivers 100% of O₂. In case the subject is on higher FiO₂ levels than the technique remains the same but the quantity of N₂ is lower making the technique less accurate.

The biggest advantages of the N₂-washout technique is that it can be applied in sick and ventilated infants. However, there are also several disadvantages. First, to use a FiO₂ of 100% is potentially toxic in newborns. Second, N₂ washout techniques can underestimate FRC because only lung volume communicating with the larger airways can be assessed. Third, a washout technique needs tidal ventilation and is therefore not applicable during HFOV. Finally, washout techniques can not differentiate between alveolar recruitment and distension, because there is no information on the regional distribution of FRC changes.

A dilution technique differs from a (N₂) washout method in that it uses a known tracer gas concentration in the second ventilator, usually helium (He) or sulphur hexafluoride (SF₆), which is allowed to equilibrate with the lung. At end expiration ventilation is switched to the closed circuit and the gas of interest will distribute in 1-2 minutes across the two compartments (the known volume of the equipment and the unknown lung volume or FRC of the subject). Using the old and new gas concentration the FRC can be calculated. If an adequate and rapid closed circuit is achieved the time of equilibration can be interpreted as a proportion of (in) homogeneity of ventilation of the lungs.

As with N₂ washout, dilution techniques can be used in both spontaneous breathing and mechanically ventilated infants, but the later is easier to perform at the bedside, requires less equipment and therefore costs, requires less time for equilibration and, most importantly, does not require the use of 100% O₂. Most of the other limitations summarized in the N₂-washout section also apply to the dilution techniques.

Respiratory Inductive Plethysmography

RIP is a non-invasive measurement technique that uses two elastic bands insulated with Teflon-coated wires which encircled the rib cage (RC) and abdomen (AB). The wires are excited by a low current high frequency electrical oscillator circuit. Repetitive expansion of the wires during spontaneous breathing or mechanical ventilation will cause a change in the self-inductance and alter the oscillatory frequency. This frequency modification is demodulated to a change in voltage and when the summed signal is calibrated to a
known gas volume a measure for changes in lung volume in the entire lung is originated. Calibration uses the assumption that the respiratory system is a two compartment model and can be performed with the qualitative diagnostic calibration method when no external volume device is present. A regression method can compute with an equivalence coefficient the RC and AB gains to a simultaneous recorded integrated pneumotachography or spirometry. In clinical practice RIP is used for monitoring breathing patterns in (ex-preterm) infants and in research hands it is used to assess FRC, tidal volume, in- and expiration time and RC-AB (a)synchrony. Although RIP is a very useful monitoring device for measuring tidal volume changes in preterm infants its ability to assess FRC is often hampered by movement artifacts in non-sedated and non-paralyzed infants. Other limitations are the inability to distinguish lung volume changes caused by alveolar recruitment and distension and the fact RIP provides no regional information which is important in heterogeneous lung disease.

Electrical Impedance Tomography (EIT)

EIT is a relatively new non-invasive, radiation-free imaging technique extremely suitable for monitoring lung volume changes at the bedside. In this paragraph we will discuss the basic principles, validation studies, animal- and clinical data and the limitations of this promising tool.

Basic principles of EIT

In the early 1980's Barber and Brown developed the first tomography system that produced anatomical images based on differences in electrical resistance of various tissues within the body. Human tissues with a high number of ion channels (blood, muscles) conduct electrical currents easily and therefore have a low resistance, while tissue with limited ion channels (bone, fat) results in a poor conductivity or high resistance. In 1985 the first report was published that showed a cross-sectional image of a human chest. EIT proved to be extremely useful in detecting changes in aeration during the respiratory cycle, because changes in air, which has poor conductive properties, results in major change in resistivity for electrical currents over time. In the next three decades EIT took a big leap forward with the introduction of personal computers and more sophisticated software and hardware. Nowadays, EIT uses the characteristics of internal distribution of electrical impedances, i.e. resistance to alternating electrical currents, to generate cross sectional images of the human thorax. Presently the single frequency EIT devices are mainly used for respiratory monitoring in contrast to the less popular multi-frequency EIT techniques (MFEIT). MFEIT systems probe the body by excitation currents of different frequencies and generate frequency-different images of impedance distribution and images based on the parameters of the Cole’s tissue model (so-called parametric images). Because the electrical properties of biological tissue are related to the current frequencies it is expected that MFEIT might
provide useful information on body tissue composition with relatively good anatomical resolution \(^{80}\). The most important limitation of MFEIT is that the hardware and software are more complex and sophisticated making it a more expensive technique. Besides, novel lung tissue models are needed to improve the parametric imaging. However, this is currently not outweighing the benefits for pulmonary monitoring.

The single EIT systems usually work with sixteen electrodes equidistantly attached to the patients’ chest circumference. Through one electrode pair a 5mA current is injected and distributes through the chest of the patient (Figure 6). All other passive electrode pairs measure the resulting voltage or potential difference of the current at the surface. The fixed injection frequency of the current can be varied between 25 kHz to 1 MHz. Next, the consecutive electrode pair is used for current injection and the other pairs measure the voltage differences. This process is repeated until all pairs of electrodes have served as injection pairs thereby creating a total of 208 voltage potentials. Sample frequencies in which a new cycle of readings is generated started in the early devices at 1 Hz, but more recent software and hardware makes it possible to go up to 60 cycles per second. The voltage potentials measured at the surface are then used for image reconstruction using a mathematical “back projection” algorithm. The algorithm generates a cross-sectional matrix of 32 x 32 pixels of the chest, calculating for each pixel the local relative impedance changes in relation to a reference state. The created relative impedance changes are expressed in arbitrary units because all impedance changes are in relation to the reference state and no actual lung volumes are determined. Some research groups have tried to generate absolute impedance values but have so far been unsuccessful in producing accurate and reproducible data. The thickness of the cross-sectional “slice” of the thorax is around the 15 cm in adults and estimated at a few cm’s in preterm infants depending on the electrodes used \(^{81}\). Conventional hand trimmed self adhesive radiolucent ECG electrodes are very suitable when using EIT in preterm infants because of the limited space on chest circumference and the ability to take a CXR with the electrodes in place.

Validation

In the late 1990’s and early 2000 several studies in animals and adults investigated the accuracy of EIT to detect intrapulmonary changes in aeration. Frerichs et al showed a good correlation between changes in air content measured by EIT and electron beam computed tomography (CT) during different levels of PEEP and tidal volumes in mechanically ventilated pigs \(^{82}\). Hinz et al validated the ability of EIT to measure changes in regional air content in mechanically ventilated pigs using single photon emission CT \(^{83}\). More recently, two studies in piglets confirmed the high correlation between EIT and CT or positron emission tomography when measuring changes in EELV and tidal volumes during a PEEP trial \(^{84};^{85}\). Human studies in spontaneous breathing subjects showed a high correlation between spirometry and EIT in the assessment of global lung volume changes \(^{86}\). Kunst et
al was one of the first to report a similar changes in regional ventilation measured by EIT and scintigraphy in fourteen mechanically ventilated adult subjects. Finally, studies in mechanically ventilated adults showed an excellent correlation between dynamic CT and EIT in detecting right to left differences in ventilation. Due to the inability to use CT or scintigraphy, no validation studies have been performed in preterm infants. However, it is very likely that EIT will provide similar results as found in animal and adults studies.

Analyzing techniques and available literature

Analysis of EIT data is presently done off-line and can be described in three main categories: 1) estimation of end expiratory impedance changes; 2) analysis of tidal- and oscillation related impedance changes; 3) distribution of ventilation. An important advantage of EIT is that all above described analysis can be performed in the 32 x 32 matrix which also provides information on a regional level. These three analyzing techniques will be discussed further in the next subheading in combination with the already available evidence.

Determination of end-expiratory impedance level or FRC

In order to detect changes in EELV or FRC, impedance changes after an intervention need to be referenced to a period before this intervention. The duration of the reference period can be determined by the investigator. Usually all impedance data in this period are averaged (HFOV), but it is also possible to average a selection of impedance data, for instance the troughs of a tidal breathing signal (CMV). In case of a stepwise intervention, such as a recruitment procedure, the same reference period is used for all steps. Using the sequential pressure-impedance pairs, the inflation and deflation limb can be constructed.

Studies in animals and humans have shown that EIT can detect changes in FRC in response to endotracheal suctioning, changes in PEEP level during CMV and changes in CDP during HFOV.

As previously stated, the raw impedance data in the matrix can easily be divided in different regions of interest, such as ventral vs dorsal or right vs left.

Analysis of tidal- and oscillation related impedance changes

A second important variable that can be analyzed with EIT is tidal (spontaneous breathing or CMV) or oscillatory (HFOV) changes in aeration during the respiratory cycle. The first step in this off-line analysis is to determine the frequency distribution of the impedance changes using a Fast Fourier Transformation. This analysis will detect the most prominent frequencies at which impedance changes occur. For instance, in case of spontaneous breathing there will be a frequency peak at 20-70/minute and in case of HFOV at 600/minute or 10 Hz. Using band-pass filtering, the frequency of interest is selected, resulting in a trace showing only the impedance changes in the selected frequency. To determine the impedance related tidal or oscillatory amplitudes, the signal
is referenced to the average impedance over the same period. The peaks and troughs of the signal are used to assess the impedance amplitude, i.e. the tidal or oscillatory impedance changes.

Studies in animals and humans have shown that this analysis is indeed useful in detecting changes in tidal and oscillatory ventilation in response to different interventions, such as spontaneous (rapid) breathing in different body positions, during lung recruitment procedures or in three different transverse thoracic planes\(^91,94-98\). However, caution is needed because, as stated previously, the impedance changes in tidal- and oscillation volume are not actual absolute lung volumes. Secondly, the measured changes are only determined in the thoracic cross-section and it is unknown how representative these changes are for the entire lung.

**Distribution of ventilation and perfusion**

Hahn et al described for the first time an analyzing technique using the acquisition of multiple consecutive EIT scans\(^99\). The derived functional EIT (f-EIT) images are determined by the standard deviation (SD) or amplitude of the signal in each individual pixel during a certain period of time (Figure 7). These individual pixel values of SD or amplitude are then codexed, depending on the chosen setting, in black (low values = small changes in impedance over the selected time period) and white (high values = larger changes in impedance over the selected time period) or in a color spectrum (blue: low values or red high values) resulting in a temporal depend image (Figure 8). This application has, since its introduction, been used to assess the ventilation distribution of mechanical ventilation or spontaneous breathing. However, newer papers have tried to use an advanced filtering technique combining the ventilation and cardiac related (heart

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**Figure 7** Simplified graphic of the analyzing process generating functional electrical impedance images (f-EIT)

At the left side of the figure the start and the end of a time course of simple EIT images is seen which is the first step of the analyzing process constructing f-EIT images. Next, the impedance EIT data are analyzed pixel by pixel calculating the time course related impedance change. These data are used to determine the regional variation (SD) or average values of end-inspiration to end-expiration difference and indexed by colour or in a black-and-white scale to generate new f-EIT image (right side of the scheme). Light area’s indicate a high variation and black a low variation in impedance values\(^99,117\).
and lung perfusion) f-EIT images to assess pulmonary perfusion or even ventilation-perfusion (miss-) match. The first data and validation studies look very promising. f-EIT imaging analysis can be used to select the regional of interest (ROI) based on a cut off of the maximal value of SD or amplitude. In the literature cut off values between 20-30% are described (Figure 8). It has been suggested that f-EIT selection of ROIs provides a better anatomical position of the lungs and therefore more accurate results on regional changes in ventilation than simply dividing the 32x32 matrix in different regions, as previously described.

In animal and human studies, f-EIT have mainly been used to detect regional ventilation differences during the induction of pneumothoraces, one-lung ventilation, parabolic flights or gravity-(in)dependency, ETT suctioning, surfactant administration or different ventilation modes. The application of f-EIT makes it is also possible to qualify the regional dynamic behavior of lungs resulting in establishment of filling and emptying characteristics of regional lung regions (dependent vs non-dependent lung region) but has not been validated.

In summary, EIT is a non-invasive easy to use bedside tool capable of continuously recording changes in aeration which can provide useful information on regional changes in end expiratory impedance levels (EELV or FRC), tidal impedance (tidal volume), and ventilation distribution in response to standardized intensive care procedures. This makes EIT a promising tool for monitoring changes in aeration in preterm infants subjected to intensive care treatment.

**Figure 8** Functional electrical impedance images of a preterm infant on high frequency ventilation.

The left panel and the middle panel represent a f-EIT image based on the standard deviation using either a color or black and white scale. Red or light areas indicate larger variation over time while blue or black areas have little variation in impedance. The right panel shows determination of a region of interest (area within the black lines) using a cut off of 20% of the maximal value.

*Definition of abbreviation*: D = dorsal, L =left, R = right, V = ventral

**Limitations of EIT**

Although EIT is a promising tool for online bedside monitoring of regional changes in lung volume there are certain limitations which need to be addressed. First, the resolution of EIT images is limited to the 32 x 32 matrix and therefore unsuitable for anatomical...
imaging. Increasing the number of electrodes, which will be cumbersome in preterm infants, could increase the number of pixels but would still produce an image inferior to established imaging tools such as CT. Second, proper attachment of the 16 electrodes is quite a challenge in preterm infants and has so far only been done by experienced researchers. This part of EIT monitoring has to be improved before introducing this tool in daily clinical practice. Third, EIT can easily pick up electrical environmental noise in intensive care units or the operating rooms which can potentially disturb the EIT recording. Future hardware should focus on improving isolation of the electrodes and cables. Fourth, intersubject comparison of EIT data is difficult because data are expressed as relative (arbitrary units) and not absolute impedance values. Calibration of tidal impedance changes with a known tidal volume changes have been described in recent publications but have to be interpreted with caution. Changes in volume measured at the airway opening reflect the entire lung while impedance changes only reflect changes in a slice of the thorax. Finally, registered changes in regional impedance may be the result of different physiological or pathophysiological processes. For instance, a drop in local impedance can be a result of decreased air content but can just as well be caused by local fluid accumulation.

The challenges for the future are to overcome these limitations by developing newer electrode belts, EIT hardware capable of measuring absolute impedance levels and software upgrades with algorithms that are more sensitive and accurate. The recently developed Graz consensus Reconstruction algorithm for EIT (GREIT) is an important first step in this process.\textsuperscript{116}
Reference List


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