Regional Lung Perfusion estimated by Electrical Impedance Tomography in a piglet model of lung collapse

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ABSTRACT

The assessment of the regional match between alveolar ventilation and perfusion in critically ill patients requires simultaneous measurements of both parameters. Ideally, assessment of lung perfusion should be performed in real-time with an imaging technology which provides, through fast acquisition of sequential images, information about the regional dynamics or regional kinetics of an appropriate tracer. We present a novel electrical impedance tomography (EIT) based method that quantitatively estimates regional lung perfusion based on first-pass kinetics of a bolus of hypertonic saline contrast. Pulmonary blood flow was measured in six piglets during control and unilateral or bilateral lung collapse conditions. The first-pass kinetics method showed good agreement with the estimates obtained by single-photon-emission computerized tomography (SPECT). The mean difference (SPECT minus EIT) between fractional blood flow to lung areas suffering atelectasis was -0.6 %, with a standard deviation of 2.9 %. This method outperformed the estimates of lung perfusion based on impedance-pulsatility. In conclusion, we describe a novel method based on Electrical Impedance Tomography for estimating regional lung perfusion at the bedside. In both, healthy and injured lung conditions, the distribution of pulmonary blood flow as assessed by EIT agreed well with the one obtained by SPECT. The method proposed in this paper has the potential to contribute to a better understanding of the behavior of regional perfusion under different lung and therapeutic conditions.

Keywords: electrical impedance tomography; first-pass kinetics; pulmonary blood flow distribution
INTRODUCTION

Efficient gas exchange, the primary function of the lung, is the result of an intimate matching of regional ventilation and perfusion across alveoli. Critically ill patients under mechanical ventilation often present gross disturbances of pulmonary gas exchange. To determine the regional matching of alveolar ventilation and perfusion during pathologic conditions a method capable of measuring ventilation and perfusion, both globally and regionally, is needed. Such measurements go beyond the structural and anatomical information provided by classical imaging technologies and require functional information like regional blood flow or the regional kinetics of a convenient tracer at the bedside. In recent publications the determination of regional perfusion through atelectatic lung units has been repeatedly pointed out as an important missing link in the assessment of the consequences of mechanical ventilation (15, 16).

New developments in functional imaging methods such as magnetic resonance imaging (MRI) (50), X-ray computerized tomography (CT) (5, 6, 23, 32), single-photon-emission computerized tomography (SPECT) (29) and positron emission tomography (PET) have provided, to various degrees, interesting insights into the heterogeneity of lung aeration and the distribution of ventilation and perfusion. From these methods, PET has established a quantitative relationship between regional ventilation and perfusion and gas exchange (52). However, the above methods lack the ability to track the frequent changes in the lung structure and function that occur in the critically ill, because they do not allow for continuous monitoring at the bedside. Novel methods capable of repeated data acquisition and interpretation in real time are welcome.

Electrical impedance tomography (EIT) has emerged as a new functional imaging method potentially meeting many clinical needs (1-3, 8, 25, 51). Subjecting the chest to minute electrical currents this radiation-free, noninvasive technique measures the electric
potentials at the chest wall surface to produce two-dimensional images which reflect the impedance distribution within the thorax. Cyclic variations in pulmonary air and blood content are the major determinants for the changes in thoracic impedance, the former usually of much larger magnitude. Because cyclic changes in local impedance mainly correspond to changes in lung aeration, recent studies have shown that EIT can reliably assess imbalances in the distribution of regional ventilation in critically ill patients (22, 27, 40, 51, 56). Besides other features like portability and the possibility of around-the-clock monitoring, the high temporal resolution is an important aspect of bedside imaging that allows for the study not only of ventilation but also of faster physiological phenomena, such as the pulsatility of the lung during the cardiac cycle (7, 9, 17-20, 30, 37, 45, 53, 55). The measurement of lung pulsatility has been the principal method for assessing perfusion by EIT as it correlates well with stroke volume measured by thermodilution (53). The pulsatility method measures the amplitude of the cyclic perturbations in local lung impedance caused by the passage of the stroke-volume through the lung (7, 17-19, 30, 37, 45, 53, 55). Lung pulsatility, however, is also influenced to a significant degree by the distensibility of the pulmonary vessels as well as the size and patency of the pulmonary microvascular bed (42). Therefore, pulsatility-based methods might be misleading as a measure of pulmonary perfusion should collapse of small pulmonary vessels occur, as well as during any important change in parenchyma architecture.

The concept of using hypertonic solutions as an EIT contrast agent to measure perfusion was proposed a long time ago (9). More recently, lung perfusion estimated by such method has been compared to regional static CT images (20). We herein present a modified version of the EIT-based method to estimate regional lung perfusion based on the first-pass kinetics of a bolus of hypertonic contrast. While the theoretical framework of such first-pass kinetics has been validated for CT and MRI technology (26, 28, 34, 35,
41), it requires adaptations to meet the particularities of EIT like the nature and timing of the perturbations caused by the hypertonic bolus as well as the absence of precise information about the slice thickness of the EIT image, which encompasses large portions of the lung and heart. Our hypothesis was that the novel indicator dilution method should outperform lung pulsatility as a surrogate for regional lung perfusion.
METHODS

Electrical impedance tomography

EIT data were acquired using the ENLIGHT platform for impedance tomography, developed by the Experimental Pulmonology Laboratory and Polytechnic Institute of the University of São Paulo, in a partnership with Dixtal Biomédica Ltda., São Paulo, Brazil (12-14). The prototype is capable of producing 50 real time images per second. After measuring the thoracic perimeter, 32 adhesive electrodes were placed equidistantly around the circumference of the thorax just below the level of the axilla. Small electrical currents (5–12 mA; 125 kHz) were injected in a rotating sequence through pairs of electrodes, with one non-injecting electrode interposed between two injecting electrodes. During an injection pattern, the non-injecting electrodes were used to measure 29 differential voltages between interleaved electrode pairs in parallel. One complete acquisition cycle of 32 current patterns produced 928 voltage measurements comprising one “raw voltage frame” used as an input to construct a relative EIT image. These images were generated by a reconstruction algorithm for a cross section of the thorax, which is based on a sensitivity matrix derived from a three-dimensional finite element model with approximately 6000 elements, 6 cm thick, and with the approximate dimensions of a piglet’s thorax (21x22 cm). The relative impedance changes estimated for the mid layer of the finite element mesh (midway along the cranio-caudal axis) was plotted in a matrix containing 860 valid pixels from a total of 1024 (32 by 32). Thus, the size of each pixel corresponded to approximately 0.7 x 0.7 cm in the axial plane. A “primary relative image” was created by comparing the most recent raw voltage frame with a reference frame recorded at the beginning of each data acquisition or at any other selected moment. Output pixel values represented percent changes in local impedance as compared to such reference. For the present analysis, the reference was taken either at the beginning of each
ECG-triggered data acquisition, or at the beginning of inspiration for mechanical ventilation-gated images. In the case of our novel perfusion analysis, however, the reference frame was always taken at apnea during a preceding expiratory pause. For further details on the technical aspects of EIT technology, see references (4, 12-14). The average or simple sum of all pixel values within each output image was plotted against time, producing a global EIT signal. Such signal is linearly related to changes in parenchymal air content (39, 51). This concept was applied regionally within regions of interest (ROIs) producing regional EIT signals.

Concept of estimating regional lung perfusion by EIT

Due to its high conductivity NaCl-20% acts as an EIT contrast agent (9, 20, 49) which after injection into the right atrium, during apnea, passes through the pulmonary circulation thereby producing a dilution curve that follows typical first-pass kinetics. The resulting regional time-impedance curves are then analyzed to quantitatively assess regional perfusion. After inverting these curves (multiplying by -1) an appropriate time window lasting from the moment of bolus infusion until just before some impedance rebound was detected (usually at the mid decay of the curve) was selected to avoid recirculation artifacts. This window was restricted further by using data points from the beginning of the perturbation until its peak (48), thereby making recirculation artifacts even more unlikely. The resulting curve was then fitted on a pixel by pixel basis by a corresponding gamma variate function. (33, 48)

Before using such routine, however, the following additional signal processing at the pixel level had to be performed:

Subtraction of the right cardiac phase
During contrast bolus injection, some EIT pixels, especially those in the right heart region, typically show a two valley-behavior in which the earlier local minimum is related to the passage of the bolus through the right heart, and the later one, to its passage through the lung parenchyma – with both phenomena represented within the same pixel (Figure 1). Such behavior, known as partial volume effect, is well described for CT technology. Given the relatively large pixels and comparatively poor spatial resolution of EIT, especially along the Z axis (craniocaudal), this effect requires proper treatment.

We assumed that each pixel in the image was composed of a double compartment, an earlier and faster one related to the right heart, and a later and slower one to the lung. Each compartment exhibited its own first-pass kinetics and a respective gamma function. The fitting process was then performed in such a way that the sum of the two independent gamma functions had to best fit the raw curve for each pixel, allowing a certain temporal overlap between both curves. We then discarded the right heart component and continued the analysis with the net lung-perfusion signal corresponding to the expected behavior of the slow compartment and its respective gamma function (Figure 1).

**Left cardiac phase and recirculation**

Perfusion of the bronchial arteries and systemic recirculation cause a typical and late (8 to 12 seconds after bolus injection) rebound of impedance perturbation of very low magnitude. For most measurements it was easy to select a time window long enough to obtain an adequate curve fitting but short enough to avoid contamination by the above phenomena. In addition, a transient and localized impedance rebound was sometimes observed due to accumulation of contrast within the left cardiac chambers. This effect happened before recirculation and just a few frames (0.5 to 1.0 s) after the main lung-perfusion phase. Although causing impedance perturbations of much lower magnitude than the right heart, we reasoned that such phenomenon could also cause
partial volume artifacts in the few pixels corresponding to the left heart region leading to an overestimation of the net lung-perfusion components. Therefore, especially because of those pixels with a very slow perfusion and those showing an early left heart perturbation, we used a method to estimate regional blood-flow which relies solely on the part of the dilution curve before its peak. For details see below and Appendix.

Calculating regional flow

After extracting the net contrast curve representing lung perfusion within each pixel the following parameters were derived from the fitted gamma function: peak-value, time-to-peak, area above the curve (i.e. integral of the corresponding gamma function curve over time - also called \( \text{gamma-area} \) (48)), and maximum-slope within the time interval from time-to-appear to the time-to-peak.

The most widely described method for calculating regional blood flow in CT analysis, MRI, or focal angiograms is based on the Central Volume Theorem (57), according to which the regional perfusion of a parenchymal organ is expressed by the following formula:

\[
\text{Relative Blood Flow}_{\text{pixel}} = \frac{\text{Relative Blood Volume}_{\text{pixel}}}{\text{Mean Transit Time}_{\text{pixel}}},
\]

where the \( \text{Relative Blood Volume}_{\text{pixel}} \) is directly estimated from the fitted \( \text{gamma-area} \) for each pixel.

In our calculations, however, the accurate estimation for the \( \text{Mean-Transit-Time} \) would require not only the removal of the signal-components related to recirculation and left cardiac phase, but also the simultaneous measurement of the time-impedance curves of the feeding pulmonary artery (to be used in a deconvolution process, in order to correct for the fact that the bolus is not fast enough).
Due to such practical difficulties, we opted for an adaptation of an older and less frequently used method for measuring regional perfusion, called the maximal slope method (28, 34). The method is based on Fick principle of the conservation of mass to a given region of interest (28, 36). Assuming there is no venous drainage of contrast before the peak of the pulmonary artery input function, the accumulated mass of the contrast within a pixel can be calculated as the product of regional blood flow and the time integral of the pulmonary artery contrast concentration:

\[ m(t)_{\text{pixel}} = \text{blood flow}_{\text{pixel}} \cdot \int_0^\infty \text{pulmonary artery concentration}(\tau) \, d\tau \]  

(1)

Differentiating equation (1) leads to an expression of the slope or \( \frac{dm(t)}{dt} \):

\[ \frac{dm(t)}{dt} = \text{blood flow}_{\text{pixel}} \cdot \text{pulmonary artery concentration}(t) \]  

(2)

Consequently, the slope will be maximal when the pulmonary artery concentration is maximal. Regional blood flow can then be calculated as:

\[ \text{blood flow}_{\text{pixel}} = \frac{\left[ \frac{dm(t)}{dt} \right]_{\text{max}}}{\text{pulmonary artery concentration}(t)_{\text{max}}} \]  

(3)

The maximal slope method is thus based on the concept that the speed of accumulation of contrast within a pixel - represented by the initial slope of the gamma-curve - reflects perfusion as the flow of blood into that pixel, or the wash-in function to that compartment. An assumption of this method is that there is no venous outflow of contrast during the period used for estimating the slope, thus requiring a high rate of contrast injection in relation to the transit-times found in the lung. Another assumption is that we are assuming that the blood flow is constant, instead of pulsatile.

For EIT, this method is especially convenient for several reasons: a) the high temporal resolution of EIT delivers up to 50 points per second with a signal-to-noise ratio higher than in CT or MRI imaging at their common resolutions, making the curve fittings and
slope determinations more reliable; b) the bolus of hypertonic contrast is relatively small (5 ml) and can be infused in less than 1 second; c) we observed that pixel perturbations caused by the given amount of hypertonic contrast were well above background noise (the signal to noise ratio per pixel is higher than in CT studies of lung perfusion, for instance) d) there was no need to measure the input function as we were not interested in absolute values of perfusion, (it was enough to compare pixels within the image); and e) we could focus on the very initial part of the gamma-curve for each pixel thereby avoiding recirculation and left-heart artifacts. These artifacts can markedly affect the gamma-area calculations but their effect on the initial slope of such gamma-curve is negligible. For each pixel, we searched for the maximum slope of the gamma-function from the time-to-appear to the time-to-peak of the fastest pixel (i.e., after removing the right heart perturbations, we identified the first pixel in the image to reach its peak and assumed that it represented the compartment with the fastest transit time within the lung). The relative proportion of this fastest slope, against the slopes for all other pixels, represented the relative perfusion to each lung region.

In order to evaluate the predicted performance of such adapted algorithm, we performed heuristic mathematical simulations (see Appendix I).

EIT-perfusion analysis based on local lung pulsatility

At each protocol condition an EIT perfusion analysis based on local lung pulsatility (ΔZ) (7, 17-19, 30, 37, 45, 53, 55) was performed and compared with the hypertonic saline bolus first pass kinetics method.

Briefly, this method is based on the fact that the ejection of the stroke volume from the right heart during systole causes an increase in intravascular pulmonary blood volume and pressures, which leads to the distension of the elastic pulmonary vascular bed; such
bulging of blood within septa purportedly causes a decrease in local electrical impedance. It is assumed that such cyclic changes in regional impedance reflect the proportion of the stroke volume directed to such regions. Thus, by measuring the amplitude of the cyclic changes in lung impedance for each pixel, one can estimate the local distribution of right ventricular stroke volume or the local distribution of pulmonary blood flow. The pulsatility measurement did not require a contrast agent and was made using an ECG-gated acquisition comprising 50 consecutive cardiac cycles during a 20 second apnea. Additionally, the resulting gated signal was low-pass filtered at a frequency of 15Hz to avoid overestimation in the ΔZ due to noise (24).
Experimental protocol

The study was approved by the Animal Ethics Committee of Uppsala University (Sweden). Six piglets (2-3 months old weighing 28.4 ± 2.6 kg) of mixed Hampshire, Yorkshire, and Swedish country breeds obtained from a local breeder were used and studied during various experimental conditions. All animals underwent the same routine instrumentation, intravenous anesthesia using a combination of fentanyl, ketamine and midazolam, and monitoring as previously described (46). Animals were tracheotomized and mechanically ventilated using a cuffed 7 mm ID endotracheal tube (Mallinckrodt, Athlone, Ireland). Baseline ventilation was delivered in a volume controlled mode using a Servo-i ventilator (Maquet Critical Care, Solna, Sweden) with the following settings: tidal volume ($V_T$) of 6 ml/kg, respiratory rate (RR) 30 breaths/min, positive end-expiratory pressure (PEEP) 10 cmH$_2$O, inspiratory to expiratory ratio (I:E) 1:2 and fraction of inspired oxygen ($F_{IO2}$) of 1. All protocol steps were performed with the animals lying in the supine position. After preparation, two major experimental conditions were studied:

1 - Unilateral lung collapse in healthy animals

Using healthy animals, the following conditions were sequentially applied: 1) bilateral lung ventilation, 2) unilateral lung ventilation due to complete contralateral lung collapse after selective intubation of the main bronchus of the ventilated lung, 3) unilateral lung ventilation with sodium nitroprusside infusion to attenuate hypoxic pulmonary vasoconstriction.
Lung injury was induced by repeated lung lavages as previously described (31). After establishing the lung injury, three situations were monitored sequentially during bilateral lung ventilation: 1) Ventilation using baseline settings, 2) after sodium nitroprusside infusion, and 3) after an effective lung re-expansion maintaining an “open lung condition” by a PEEP of approximately 16 cmH₂O (46). Each experimental condition lasted 45 min and measurements were made at the end of each one. EIT measurements of perfusion based on first-pass kinetics were performed after switching the ventilator to continuous positive airway pressure (CPAP) maintaining the same level of expiratory pressure but eliminating tidal ventilation. A NaCl 20% bolus was injected within less than one second through a central venous line into the right atrium 5 seconds after starting CPAP.

SPECT Imaging

Pulmonary blood flow distribution was assessed by i.v. injection of ⁹⁹ᵐTc-Technetium-labelled macro-aggregated albumin (⁹⁹ᵐTc-MAA, Pulmocis; CISbiointernational, Gif sur Yvette, France). At the beginning of each phase, a reference SPECT was performed prior to each new injection of ⁹⁹ᵐTc-MAA in order to subtract the remaining Technetium activity from the previous scan. A CT scan (covering the same volume as the SPECT) was taken immediately after each SPECT and used for attenuation correction. Images were acquired using a SPECT/CT dual-head gamma camera (Millennium; General Electric Systems, Milwaukee, WI, USA) with an all-purpose medium-energy collimator. SPECT acquisition was made in 60 projections (30 per head) and stored in a 128 by 128 matrix, resulting in a pixel size of 4.42 mm. The overall scan time for SPECT and CT was approximately 45 min. Data were reconstructed first on an
eNTEGRA workstation and later on a Xeleris workstation (Millennium; General Electric Systems). The reconstruction was performed with an iterative model (OSEM, four iterations and eight subsets) and a Hann filter (cut-off 0.85) for the post-reconstruction filtering on both workstations. The 128 transverse slices, each of thickness 4.42 mm, were corrected for radiation spill-over and for baseline subtraction using a HERMES workstation (Hermes Medical Solution, Stockholm, Sweden). For each reconstructed slice the contents were analyzed by custom-made software. Before calculating activity distribution, a background subtraction of 10% of the global maximum was performed.

As opposed to EIT, SPECT measurements had to be performed along the entire experimental condition for 45 min in order to improve signal to noise ratio. The initial bolus of labeled albumin, however, was injected after switching the ventilator to CPAP maintaining the same level of expiratory pressure but eliminating tidal ventilation, similarly to the injection of hypertonic saline during EIT acquisitions.

### Regions of interest

For EIT and SPECT image comparisons at the different experimental conditions we analyzed pulmonary blood perfusion in different ROIs:

- During unilateral lung collapse in healthy animals the lung was divided by a vertical line into two ROIs: the left and the right lung (Figure 2).
- During bilateral dependent lung collapse in injured lungs, the lung was divided by a horizontal line into two ROIs delimiting a superior (nondependent and aerated) from an inferior (dependent and collapsed) one. Based on the corresponding CT images, we identified the horizontal plane that best separated a nondependent region encompassing an open lung region from a fixed dependent one encompassing most of atelectatic tissue (Figure 3).
Finally, for both healthy and injured lungs, we analyzed four symmetrically delimited quadrants of the lung.

Images Analysis

The perfusion of each ROI was calculated as its respective percentage of total blood flow.

For SPECT (using $^{99m}$Tc-MAA – SPECT):

$$\text{ROI}_a \% = \frac{\text{ROI}_a \text{ counts}}{\text{total counts}},$$

Where:

- $\text{ROI}_a \% = \text{percentage of total pulmonary blood flow directed to ROI}_a$
- $\text{ROI}_a \text{ counts} = \text{sum of absolute values of counts of all pixels encompassed in ROI}_a$
- $\text{total counts} = \text{sum of absolute values of counts of all pixels encompassed in all ROIs}$

To obtain the corrected SPECT count values used in the calculations above a reference SPECT was taken prior to each new injection of $^{99m}$Tc-MAA in order to subtract the remaining technetium activity from the previous scan.

For EIT-gamma variate modeling:

$$\text{ROI}_a \% = \frac{\text{ROI}_a \text{ (maximal slope)}}{\text{total (maximal slope)}},$$

Where:

- $\text{ROI}_a \% = \text{percentage of total pulmonary blood flow directed to ROI}_a$ estimated by EIT-gamma variate modeling, maximal slope = pixel by pixel maximal slope of the gamma-function of the net lung perfusion component from the time-to-appear to half the time-to-peak of the fastest pixel, $\text{ROI}_a \text{ (maximal slope)} = \text{sum of (maximal slope) values of all pixels encompassed in ROI}_a$, total (maximal slope) = sum of (maximal slope) values of all pixels encompassed in all ROIs.
For EIT-pulsatility modeling:

\[ \text{ROI}_a \% = \frac{\text{ROI}_a (\Delta Z_{\text{pulsatile}})}{\text{total} (\Delta Z_{\text{pulsatile}})} \]

Where:

\( \text{ROI}_a \% \) = percentage of total pulmonary blood flow directed to ROI\(_a\) estimated by EIT-pulsatility, \( \Delta Z_{\text{pulsatile}} \) = amplitude (difference between maximum and minimum values) of \( \Delta Z \) cardiac oscillations for each pixel, observed in ECG-gated measurements, \( \text{ROI}_a (\Delta Z_{\text{pulsatile}}) \) = sum of \( \Delta Z_{\text{pulsatile}} \) values of all pixels encompassed in ROI\(_a\), total \( (\Delta Z_{\text{pulsatile}}) \) = sum of \( \Delta Z_{\text{pulsatile}} \) values of all pixels encompassed in all ROIs.

For EIT pulsatility analysis, all pixels corresponding to the heart region were previously removed. The selection of such pixels was based on a phase analysis: pixels presenting a predominant positive variation in \( \Delta Z \) between two consecutive QRS complexes were considered “heart” pixels (21, 47) (Figure 4).
RESULTS

A total of six animals are included in this analysis: three in the unilateral lung collapse protocol (complete left lung collapse in two and right lung collapse in one) and three in the bilateral dependent lung collapse protocol.

EIT-perfusion analysis based on the first-pass kinetics

The distributions of pulmonary blood flow assessed by SPECT and EIT (first-pass kinetics) showed good agreement, as exemplified by the qualitative inspection of the images (Figures 2 and 3) and also by the quantitative analysis using two ROIs (Figure 5), one of them always representing the collapsed part of the lung. This was true for both, healthy and injured piglets. After induction of atelectasis, both techniques consistently demonstrated an initial redistribution of blood flow to non collapsed lung areas, especially in the healthy lung preparations. For instance, in one of the healthy animals, the fractional pulmonary blood flow directed to the left lung decreased from ~50 % down to ~20 % after complete atelectasis of this lung (Figures 2 and 5). This redirection of blood flow was attributed to hypoxic pulmonary vasoconstriction (HPV), which was later attenuated by nitroprusside infusion. We also observed an immediate increment in regional flow to dependent lung regions after recruitment of the collapsed areas in injured lungs. This increment exceeded the increment caused by nitroprusside in all animals, as demonstrated by both, EIT and SPECT analysis (see Figure 5).

Altogether, the mean difference (bias) between the estimates for the blood flow towards the atelectatic ROI in relation to the blood flow to the whole lung (henceforth called fractional blood flow), as measured by SPECT versus EIT, was - 0.6% with a SD of 2.9% (range: -6.7% to + 3.8%).
Figure 6 shows the Bland-Altman plots of the SPECT versus EIT measurements of fractional blood flow to four lung quadrants of the transverse images. The overall agreement was good (limits of agreement = -10.9% to +10.5%) although a systematic overestimation of perfusion to the upper-left quadrant was observed in EIT measurements ($P < 0.05$). We did not observe any dependence between the difference seen in SPECT and EIT-NaCl measurements and their average magnitude ($P = 0.14$).

**EIT-perfusion analysis based on local lung pulsatility ($\Delta Z$)**

Significant differences between the estimates of pulmonary blood flow distribution by SPECT and the corresponding estimates based on EIT-pulsatility were observed (Figures 5 and 6).

The discrepancy was especially magnified in the presence of whole lung atelectasis, or after the infusion of nitroprusside. In all animals, SPECT analysis indicated that atelectasis caused a systematic decrease in local perfusion (mean decrease = -23% of total pulmonary blood flow; range: -14% to -29%; $P = 0.028$, Wilcoxon rank test). The pulsatility analysis, however, showed contradictory results: atelectasis of the injured, dependent lung zones caused some decrease in $\Delta Z$ pulsatility, but atelectasis of one whole lung caused a marked increase in local $\Delta Z$ pulsatility in two animals. In Figures 4B and 5, we show one extreme example in which EIT’s local pulsatility estimated a fractional perfusion of 74% to the atelectatic left lung, whereas the SPECT indicated just 19%.

The infusion of nitroprusside increased the blood flow through atelectatic areas in all animals. The pulsatility analysis, however, systematically suggested a decreased blood flow through atelectatic areas after nitroprusside.

Figure 6 shows the Bland-Altman plots of the SPECT versus EIT pulsatility measurements of fractional blood flow to four lung quadrants (of axial images).
was a systematic overestimation of perfusion to the upper left quadrant ($P < 0.001$), and a systematic underestimation of perfusion to the lower right quadrant ($P < 0.01$). There was no dependence of the difference between SPECT and EIT-pulsatility in relation to their average magnitude ($P = 0.16$).
DISCUSSION

We herein report a novel EIT-based method for estimating regional lung perfusion at the bedside. The proposed approach is based on first-pass kinetics of an EIT-indicator dilution curve, using hypertonic saline bolus, and overcoming major limitations of a pulsatility-based method. This method showed a good agreement with estimates of lung regional perfusion obtained by SPECT. Our findings also support the notion that EIT-pulsatility may be a less suited method for estimating pulmonary perfusion.

A fundamental reason for the poorer performance of the EIT-pulsatility, as evidenced in Figure 4, is probably related to the fact that such method basically measures the pulsatile changes in pulmonary blood volume instead of real forward flow of blood. Changes in vascular tone and synchronous changes in air content (in opposite phase) as previously described (44, 54) might potentially affect the relationship between the cyclic pulsatile changes in regional impedance and the proportion of the stroke volume directed to those regions. Our results suggest that EIT-pulsatility data may be strongly influenced by the downstream pulmonary vascular resistance and by the distensibility of the small pulmonary vessels (19, 43). Probably, different lung conditions and airway pressures also modulated the pulsatility behavior of small pulmonary vessels. Another potential reason for the poor performance of the pulsatility method would be the inclusion of the heart region in the measurements, which we tried to avoid by identifying the heart region and excluding it from the analyses. However, the identification of pixels corresponding to the heart region might have been less than ideal in some cases which could partially explain the overestimation of perfusion to the upper left quadrant by the pulsatility method. The review of individual cases suggested that it is hard to completely exclude residual components of left atrium from the images. The phases of the left atrium and lungs are
similar enough to preclude the exclusion of the former based on phase analysis. More sophisticated methods would be required.

The biggest difference between local blood flow measured by SPECT and EIT-pulsatility images was found during unilateral collapse. Stronger pulsatile changes in impedance were found within the collapsed lung, while the amount of blood flowing to this region was significantly reduced according to both, SPECT and EIT-first-pass-kinetics (Figures 4B and 5). Our data are in agreement with the findings of Newell et al (38), who reported a retrograde flow from atelectatic lung zones to healthy ones during the diastolic phase. Within the atelectatic lung, the elastic compartment represented by small pulmonary vessels seems to accumulate great part of the stroke volume at the end of systole, expelling it back to the contralateral lung during diastole. The much later nadir of EIT signal oscillations in the healthy lung (suggesting a later surge in local blood volume), as compared to the atelectatic one (Figure 4C), suggested this redistribution of perfusion (“pendelblut” in analogy with the German term “pendelluft”) between both lungs. This “pendelblut” was not present during bilateral ventilation. We hypothesize that, in the presence of massive atelectasis, the “pendelblut” effect could be so marked and prolonged that the normal diastolic emptying of pulmonary vessels might be attenuated, decreasing the magnitude of ΔZ-pulsatility in the healthy areas. It works as if the healthy lung was receiving an almost constant flow rather than a pulsatile, variable flow. Thus, despite a higher flow rate (as evidenced by SPECT and EIT-first-pass kinetics) the healthy lung had lower pulsatility.

Interestingly, nitroprusside infusion always attenuated the relative pulsatility within the collapsed lung (Figures 4C and 5), although systematically increasing the amount of blood shunting through these areas. This seemed to be associated with an increased
pulsatility within the remaining open lung areas, rather than a true attenuation within collapsed areas.

It is important to keep in mind that, although the pulsatility method has been appealing because of its ease, it does not rely on solid mathematical foundation to really represent perfusion in a quantitative manner. In contrast, the theory behind the first-pass kinetics of a tracer and the maximum-slope approach described in this study are concepts that relate to classic physiological studies (11, 28, 34, 57) about parenchymal perfusion, having also a proven mathematical justification (see the mathematical model described in the Appendix 1). The present data may unravel a potential limitation of the pulsatility method, especially in conditions where atelectasis may play an important role, which will have to be confirmed in further studies.

Besides the small number of animals, which prevented us from presenting definitive statistics, but rather a descriptive proof of concepts, some other limitations of this study deserve mentioning. First, due to technical reasons, SPECT and EIT image acquisitions could not be done simultaneously, but sequentially. In order to circumvent this limitation, we always waited for steady-state conditions, including the effects of nitroprusside, whereby a continuous monitoring of arterial blood gases was essential. A second limitation comes from the fact that SPECT is essentially a 3D imaging procedure, while EIT analysis is something between 2D and 3D (although the finite mesh is 3-D, the electrodes were placed within a single plane). Although reasonably large, the effective thickness of the EIT cross-sectional slice (~5-10 cm), varies with the size and shape of the animal (14), and one could never guarantee that most of the lung is being represented in all animals. Clinically, this limitation has to be balanced against the 20-seconds acquisition in EIT versus the 45-minutes acquisition in SPECT. The subtraction of the cardiac component of perfusion from mixed pixels while maintaining the net lung component (Figure 1) by using the EIT-gamma variate algorithm was an essential feature
of this method. However, at the edges of the heart, some challenging overlap between the
behavior of lung and heart tissue may have remained, sometimes causing uncertainties in
the double-function fitting process. This phenomenon may be responsible for the lower
agreement between SPECT and EIT in the upper left quadrant. Although the location of
the cardiac chambers in humans could make this differentiation easier in the clinical
setting, more studies on this subject are needed. Fourth, the assumption of the maximal
slope method that no tracer leaves the ROI before the peak artery concentration is reached
could be violated in the presence of the combination of high blood flow and low blood
volume. As discussed in the appendix 1, however, such violations in the assumption
would lead to small estimation errors, provided that blood volume decreases by no more
than one order of magnitude. Another potential limitation of the proposed method is the
possibility of some diffusion of sodium chloride to the outside of the vessels in the lungs.
In this situation, the solute that remains in the vessel will leave the lungs through the
venous drainage, while the diffused solute will tend to stay in the lungs, violating the
conservation of mass principle (unless an extravascular compartment is accounted for).
For the calculations of the maximal slope, however, the conservation of mass could still
be applied correctly, since one of the assumptions is that there is no outflow of hypertonic
saline before the peak of the pulmonary artery input function. In this case, what the
conservation of mass implies is that all the solute that reaches the ROI (feeding vessel and
extravascular compartment lumped together), irrespective of whether it remains inside
the vessels or not, came through the feeding artery. Finally, one last important theoretical
concern is that, due to the low spatial resolution of EIT, the maximum slope time-point
might be slightly displaced (in time) among sub-regions within the ROI, likely causing
wrong estimates of spatially-averaged maximum-slopes. The extent of this potential
limitation deserves future studies.
In conclusion, we describe a novel method based on Electrical Impedance Tomography for estimating regional lung perfusion at the bedside. In both, healthy and injured lung conditions, the distribution of pulmonary blood flow as assessed by EIT agreed well with the one obtained by SPECT. The method proposed in this paper has the potential to contribute to a better understanding of the behavior of regional perfusion under different lung and therapeutic conditions.
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DISCLOSURES

Conflict of Interest Statement: Stephan H Bohm has been consultant for Dixtal Biomedica and is the inventor and owner of patents for EIT technology. Alexandre Melo received honoraria for supporting the EIT project as an expert electronic engineer. In addition to financial support from FAPESP and FINEP, Marcelo Amato received grant support from Dixtal Biomedica. The remaining authors have not disclosed any potential conflicts of interest.
Heuristic model for regional blood flow

A mathematical model representing 3 compartments, the right heart in series with two lung compartments in parallel (compartments A and B), was simulated, using reference conditions found in normal physiology: right heart chamber volume ~150 ml; infusion time ~2 s; baseline blood-volume for each lung compartment ~150 ml; total cardiac output ~5 l/min. Each lung compartment had an inflow equal to its outflow, adjusted independently from other compartments, and thus a fixed blood-volume over time. This fixed blood-volume could be different among compartments, depending on simulations.

Equations simulating mass balance and concentration curves inside each compartment were solved numerically, by assuming that: a) the contrast was infused at the right heart chamber, in a short bolus (2s); b) the bolus suffered immediate and ideal dispersion; c) blood flow was constant and non-pulsatile.

We calculated the regional percentage change in resistivity according to a modification of the formula proposed by Brown et al (9) based on the volume fraction (V) of the indicator (the hypertonic saline) contained within the compartment, at that particular moment, the conductivity of blood (\(\sigma_1 = 0.62 \text{ Sm.m}^{-1}\)), and the conductivity of the hypertonic saline (\(\sigma_2 = 32 \text{ Sm.m}^{-1}\)).

\[
\frac{\rho - \rho_0}{\rho_0} = \frac{3 \cdot V \cdot (\sigma_2 - \sigma_1)}{2 \cdot \sigma_1 + \sigma_2 + 2 \cdot V \cdot (\sigma_2 - \sigma_1)}
\]

This means that the instantaneous intensity of the EIT signal represented both, the volume of the compartment and its final concentration of sodium.

The estimated regional lung flow was calculated as the maximal slope derived from the fitted gamma-curve (34). As in our experiments, we searched for the maximal slope from...
the start to the time-to-peak perturbation. Percent flow directed to compartment A was calculated as the maximal slope of that compartment A divided by the sum of the slopes of compartments A and B.

We simulated changes in the perfusion to compartment A from 100% down to a minimum of 10% of the value in compartment B, which was kept constant (Appendix Figure, left). The maximal slope of the perturbation found in compartment A (derived from the gamma-fitted curve) showed a strong linear correlation with the true perfusion simulated in the model ($R^2 = 1.00$). Additionally, we varied the volume of blood contained in compartment A from 100% down to 10% of the value found in compartment B, while keeping the perfusion (input flow) fixed in both compartments, in order to assess if the estimation of the perfusion was affected by changes in the residing blood volume (Appendix Figure, right). For values of blood volume above 30% of the initial value, the maximal slope measurement was not affected by the decrease in blood volume. For greater decreases in blood volume (below 30% of the initial value), perfusion was underestimated, albeit to an error of less than 10%.

Therefore, we concluded that the maximum slope was a robust estimate of perfusion even in the presence of changes in blood volume, provided that those changes are not greater than one order of magnitude. Previous studies on blood pooling at dorsal, gravity-dependent lung regions have revealed that a difference of 10 times in blood volume can be found in normal lungs, when comparing the two most extreme lung regions along the gravity axis. Under such conditions, the maximum slope approach would underestimate the perfusion of these lung regions with very low blood volume by approximately 10%.
The new dilution curve fitting method

We developed an automatic/heuristic solution that ran for every pixel in the figure in a batch process. Before the gamma fitting, we used a finite-impulse response filter in the time domain to reduce the high-frequency noise. To the filtered signal, we applied the fitting process, described in detail elsewhere (48). Of note, the fitting was non-iterative and made use of only 3 relevant data points: the time to appear, the middle-height point, and the peak point. If the curve had two peaks, as in Figure 1B, we localized the two peaks, even when the first one was smaller than the second one (by using the second and third derivatives), and applied this gamma fitting to the 3 data points obtained till the first peak. This procedure intrinsically assumed that no contrast entered the lung before the first peak in the right heart. Then we calculated the subtraction between the raw contrast curve and the gamma-fitted curve of the right heart. We subsequently performed a second gamma fitting to this subtracted curve, obtaining the gamma-fitted curve related to the lung. This procedure was performed on a pixel-by-pixel basis. Bad fittings occurred in 5-10% of the cases and could be detected as pixels to which there was either zero or abnormally high perfusion (outliers). When this happened, we visually detected the right heart area as well as the typical-lung areas - using videos of the saline passage through the heart and lungs - and used the time to peak information of each of these two regions to establish boundaries for fitting. For instance, if the first peak of a two-peaked curve occurred close to the time to peak of the typical-lung pixel, the second peak would be ignored, as opposed to considering the first and second peaks as related to the right heart and lung, respectively.

Limitations
In our images, due to the low spatial resolution, it was very difficult to separate the lung parenchyma from the pulmonary vessels of second or third generation. Thus, our perfusion data was likely contaminated by the perfusion of the large pulmonary arteries. This is a limitation when analyzing very small regions of interest, since the inclusion or not of an artery can cause large differences in the estimates (especially if the cross section of the artery belongs to one region of interest but its feeding territory belongs to another one). However, when analyzing large regions of interest, as in our study, it is very likely that the perfusion of big arteries is mixed up with the surrounding parenchyma perfusion, and both are strongly related to the perfusion of the respective region of interest.

In theory, there might be to some extent diffusion of sodium chloride to the outside of the vessels in the lungs (characterizing the system as “open” instead of closed). In this situation, the diffused solute would tend to stay in the lungs, while the solute that remained in the vessel would leave the lungs through the venous drainage. In order to apply the principle of conservation of mass, we would need to consider a closed system and, therefore, we should consider the three compartments: the arterial (input), the interstitial (diffused solute), and the venous (output). Since the calculation of the maximal slope assumes that there was no outflow of hypertonic before the peak of the pulmonary artery input function, the conservation of mass would still be applied correctly if we only consider a system with two compartments. In this case, what the conservation of mass implies is that all the solute that has reached the lungs came through the feeding artery, irrespective of whether the solute has remained inside the vessels or not.

REFERENCES


FIGURES LEGENDS

Figure 1: Behaviors of a lung and a heart/lung pixel dilution curves after NaCl 20% injection

Typical behaviors of the signal in a lung and a heart/lung pixel observed after injection of a bolus of hypertonic saline. In panel A, a typical lung pixel shows one visible valley only, representing the passage of the contrast through the lung. The fitting of the early cardiac component was negligible and cannot be seen in this panel. Note that the nadir of the curve occurs around 3-4 s after bolus injection. In contrast, panel B shows a typical pixel behavior at thoracic regions close to the heart, exhibiting a two-valley shape. Note that the first and steeper valley occurs earlier, immediately after the bolus of contrast (arrow), corresponding to the passage of the bolus through the cardiac chambers (right atrium and ventricle). A second valley can be observed later along this same pixel tracing (4-5 s after bolus injection), corresponding to the later passage of the contrast through lung regions also represented within this same pixel. Such lung regions are probably located at a different position along the craniocaudal Z-axis, but at similar location in the X-Y plane. Although fitting and integral calculations were performed after inverting the curves above, we presented the negative curves directly derived from EIT images, illustrating the negative perturbation in impedance caused by the hypertonic bolus. For both pixels, the estimates for net lung-perfusion (i.e. the maximum slope of the initial moment of lung perturbation) were calculated from the fitted gray curve.

Figure 2: Regions of interest in healthy lungs

Regions of interest in healthy lungs for the perfusion analysis. Three situations were studied sequentially: (A) bilateral lung ventilation; (B) unilateral lung collapse (left lung atelectasis); and (C) unilateral lung collapse with sodium nitroprusside infusion. After
determining the lung borders by the CT scan, the left and the right lungs were separated by a vertical line, drawn from the sternum to the spinal column. The corresponding vertical line was also drawn in the EIT images after identifying the corresponding positions of electrodes on CT and within EIT finite-element mesh. Note the decreased intensity of the signal in the left lung after atelectasis (B), representing a decreased perfusion, which was partially recovered during the infusion of nitroprusside.

Figure 3: Regions of interest in injured lungs

Regions of interest in the piglets with acute lung injury. Three situations are represented sequentially: (A) lung injury condition (dependent lung atelectasis); (B) lung injury in conjunction with sodium nitroprusside infusion; and (C) open lung condition after lung recruitment. One superior and one inferior region of interest were separated by a horizontal line based on the corresponding CT images, where the dependent region encompassed nearly all atelectatic tissue in condition (A). The corresponding horizontal line was also drawn in the EIT images after objectively identifying and matching the positions of electrodes on CT images and within the EIT finite-element mesh. Note the zones of maximum intensity of perfusion, which are above the horizontal line in situation A. This was evident on both, EIT (first-pass kinetics) and SPECT images. Such zones of maximum intensity were displaced downward in situations B and C, where the highest intensity can be detected in dependent lung zones.

Figure 4: EIT-pulsatility images of one healthy animal before removing pixels corresponding to the heart region

EIT-pulsatility (ECG gated) images of one non-injured animal, before removing pixels corresponding to the heart region, during three conditions: (A) bilateral lung ventilation; (B) unilateral lung collapse (left lung atelectasis); and (C) unilateral lung collapse plus...
sodium nitroprusside infusion. A gray scale was applied, with lighter color corresponding to higher pulsatility signal. Time-synchronized ECG plus impedance waveforms of three representative pixels are shown, with equivalent scales for both lungs (but halved for heart region). The orange pixel represents the left lung, the gray represents heart, and the yellow represents the right lung. After creation of atelectasis, note the global decrease in pulsatility, but especially in the right (open) lung (B), where the fractional blood flow at this moment, according to SPECT and EIT-first-pass kinetics, was maximal. Concomitantly, the left atelectatic lung gets relatively “brighter” (because of the auto-scaling of the gray images) producing the false impression of an increased perfusion. As explained in the discussion, this phenomenon may be caused by a diastolic redistribution of blood flow (“pendelblut”) from the left to the right pulmonary artery. By adding nitroprusside infusion (C) a marked attenuation of the difference between the open and collapsed lung becomes evident, approaching the normal lung pattern with bilateral ventilation (A).

The diastolic emptying of the pulmonary vessels toward the left atrium is characterized by a marked rise in ΔZ signals (amplitude = difference between maximum and minimum values of EIT signal oscillations), before the next QRS complex. Note the delay of such process within the right lung in situation (C), which is absent in (A) (arrows). Note also the complete opposition of phases between the heart and the lungs waveforms.

Figure 5: Distribution of pulmonary blood flow in healthy lungs and in lungs with acute lung injury

Percentage of total pulmonary blood flow flowing through the left atelectatic lung as measured by EIT and SPECT. All animals are shown. Each panel refers to one studied animal. The EIT perfusion according to the first-pass kinetics was based on the maximum slope of the first-pass of contrast through the lung. The EIT-pulsatility represents the
local amplitude of impedance swings during ECG-gated acquisition (see methods for details).

Three sequential conditions in three non-injured lung preparations are shown: bilateral lung ventilation, unilateral lung collapse, and unilateral lung collapse with sodium nitroprusside infusion. And three sequential conditions in three injured lung preparations are shown: lung injury (bilateral, dependent lung atelectasis), lung injury plus sodium nitroprusside infusion, and open lung condition after lung recruitment (total reversal of atelectasis). Note the good match between the first-pass kinetics method and SPECT. Note also the opposite, artifactual changes in EIT-pulsatility observed during atelectasis and after the infusion of nitroprusside.

Figure 6: Bland-Altman plots of perfusion for EIT and SPECT

The figure shows the Bland-Altman plots of the SPECT versus EIT measurements based on the first-pass kinetics and pulsatility method. For both healthy and injured lungs we analyzed four symmetrically delimited quadrants of the lung.

Right: the Bland-Altman plots of the SPECT versus EIT pulsatility measurements of fractional blood flow to four lung quadrants (of axial images). There was systematic overestimation of perfusion to the upper left quadrant ($P < 0.001$), and systematic underestimation of perfusion to the lower right quadrant ($P < 0.01$). There was no dependence of the difference between SPECT and EIT-pulsatility in relation to their average magnitude ($P = 0.16$).

Left: the Bland-Altman plots of the SPECT versus EIT measurements based on the first-pass kinetics of fractional blood flow to four lung quadrants of the transverse images. The overall agreement was good (limits of agreement = - 10.9 % to + 10.5%) although a systematic overestimation of perfusion to the upper-left quadrant was observed in EIT measurements ($P < 0.05$). We did not observe dependence between the
difference between SPECT and EIT-NaCl measurements and their average magnitude ($P = 0.14$).

Appendix 1 - Figure: Model simulations for the influence of blood-flow and blood-volume on the estimates of lung perfusion based on the maximum-slope of contrast perturbation

Model simulations for the impedance perturbation caused by changes in instantaneous sodium concentration within two lung compartments (A and B) after hypertonic bolus injection. The timing and amount of sodium chloride infusion (5 ml of 20% sodium chloride infused within 2 seconds - injected directly into a third compartment upstream, with 150 ml, simulating the right heart) was kept constant throughout the simulations.

The situation of compartment B was kept constant (regional blood-flow = 2.5 L/min, and regional blood-volume = 150 ml), while the blood-flow of compartment A changed from 2.5 down to 0.25 L/min (left panel). In the right panel we simulated a reduction in the blood-volume of compartment A, from 150 ml down to 15 ml. As shown, the calculus of the maximum slope in impedance perturbations found in compartment A kept a quasi-linear relationship with the true blood flow (relative perfusion) to this compartment. As also expected, pure changes in blood-volume within this compartment (but with sustained blood-flow) caused only a minor change (~5%) in the maximal slope. Ideally, we should see no changes related to such pure blood-volume variations.
Figure 1A

Typical behavior of a lung pixel

Pixel impedance change (%)

0
-10

0 5 10 15
seconds

fitted gamma function
raw
Figure 1B

Hybrid pixel behavior (heart/lung)

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fitted gamma function for contrast through the heart

fitted gamma function for contrast through the lung (net lung perfusion component)

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Pixel impedance change (%) vs. seconds

- raw
Figure 4B
Left Lung
\( \Delta Z = 8\% \)

Right Lung
\( \Delta Z = 4\% \)

Heart
\( \Delta Z = 4\% \)

ECG

Figure 4C
EIT pulsatility – max. amplitude

EIT hypertonic – max. slope

Quadrants:
- • Upper right
- ▲ Lower right
- ○ Upper left
- △ Lower left
Relative perfusion simulated in compartment A (%)  
Blood-volume kept constant = 150 mL

Relative Blood-volume simulated in compartment A (%)  
Perfusion kept constant at 2.5 L/min

\[ y = 0.04x + 96 \]  
\[ R^2 = 0.19 \]

\[ y = 1.00x + 0.04 \]  
\[ R^2 = 1.00 \]