Research

Electrical impedance tomography compared to positron emission tomography for the measurement of regional lung ventilation: an experimental study

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Abstract

Introduction Electrical impedance tomography (EIT), which can assess regional lung ventilation at the bedside, has never been compared with positron-emission tomography (PET), a gold-standard to quantify regional ventilation. This experiment systematically compared both techniques in injured and non-injured lungs.

Methods The study was performed in six mechanically ventilated female piglets. In normal lungs, tidal volume (VT) was randomly changed to 6, 8, 10 and 15 ml/kg on zero end-expiratory pressure (ZEEP), then, at VT 10 ml/kg, positive end-expiratory pressure (PEEP) was randomly changed to 5, 10 and 15 cmH2O. Afterwards, acute lung injury (ALI) was subsequently created in three animals by injecting 3 ml/kg hydrochloric acid into the trachea. Then at PEEP 5 cmH2O, VT was randomly changed to 8 and 12 ml/kg and PEEP of 10 and 15 cmH2O applied at V T 10 ml/kg. EIT and PET examinations were performed simultaneously. EIT ventilation (VTEIT) and lung volume (VL) were measured in the anterior and posterior area of each lung. On the same regions of interest, ventilation (VPET) and aerated lung volume (VAatten) were determined with PET.

Results On ZEEP, VTEIT and VPET significantly correlated for global (VTEIT = VPET - 2E-13, R2 = 0.95, P < 0.001) and regional (VTEIT = 0.81VPET+7.65, R2 = 0.63, P < 0.001) ventilation over both conditions. For ALI condition, corresponding R2 were 0.91 and 0.73 (P < 0.01). Bias was = 0 and limits of agreement were -37.42 and +37.42 ml/min for global ventilation over both conditions. These values were 0.04 and -29.01 and +29.08 ml/min, respectively, for regional ventilation. Significant correlations were also found between VL and VAatten for global (VL = VAatten-1E-12, R2 = 0.93, P < 0.0001) and regional (VL = 0.99VAatten+0.92, R2 = 0.65, P < 0.001) volume. For ALI condition, corresponding R2 were 0.94 (P < 0.001) and 0.54 (P < 0.05). Bias was = 0 and limits of agreement ranged -38.16 and +38.16 ml for global ventilation over both conditions. These values were -0.24 and -31.96 to +31.48 ml, respectively, for regional ventilation.

Conclusions Regional lung ventilation and volume were accurately measured with EIT in healthy and injured lungs and validated by simultaneous PET imaging.

ALI: acute lung injury; ARDS: acute respiratory distress syndrome; CT: computed tomography; ΔZ: change in thorax electrical impedance; EIT: electrical impedance tomography; FiO2: fraction of inspired oxygen; ICU: intensive care unit; PaO2: partial pressure of arterial oxygen; PCO2: partial pressure of carbon dioxide; PEEP: positive end-expiratory pressure; PEEPt: total positive end-expiratory pressure; PET: positron emission tomography; PO2: partial pressure of oxygen; ROI: region of interest; SD: standard deviation; SPECT: single photon emission computed tomography; VAatten: lung volume measured with PET from density obtained on the transmission scan; VILI: Ventilator-Induced Lung Injury; Vl: change in lung mid-capacity measured with EIT; VTEIT: tidal volume measured with EIT; VL: change in thorax electrical impedance; ZEEP: zero end-expiratory pressure.
Introduction
Electrical impedance tomography (EIT) is a new lung imaging modality. It might become highly relevant to managing patients with acute respiratory distress syndrome (ARDS) in the intensive care unit (ICU) because it can estimate regional lung ventilation at the bedside [1]. An acceptable agreement, namely bias of 0% and limits of agreement of -10 to +10%, has been found between EIT and computed tomography (CT) in detecting right-to-left lung changes in gas volume [2]. However, x-ray CT does not measure lung ventilation directly. Concerns were raised about the ability of EIT to accurately quantify ventilation in an experimental study using single photon emission computed tomography (SPECT) as a reference [3]. However, whether the slight disagreement between the two methods is attributed to EIT or SPECT remains unknown. Positron emission tomography (PET) is a non-invasive and powerful method to quantify alveolar ventilation and volume [4], and alveolar recruitment [5] regionally, and may be considered as a gold standard to quantify regional lung ventilation. No study has compared both techniques and their ability to measure alveolar ventilation and volume so far. Furthermore, the capability of EIT to detect changes over a large range of end expiratory lung volume and delivered tidal volume (VT) has only seldom been studied so far. Therefore, the primary goal of the present study was to compare EIT with PET after changing lung ventilation and volume in anesthetized pigs.

Materials and methods
Animals
The protocol was approved by our Institutional Review Board for the care of animal subjects. The care and handling of the animals were performed in accordance with the National Institutes of Health guidelines for ethical animal research.

Six female piglets (mean ± standard deviation (SD) = 28 ± 3 kg; Table 1) were premedicated with an intramuscular injection of xylazine (20 mg), droperidol (10 mg), and ketamine (500 mg). The animals were tracheotomized and mechanically ventilated (Avea; Viasys Healthcare, Höchberg, Germany) in volume-controlled mode using VT 10 ml/kg, fraction of inspired oxygen (FiO2) 0.21 during the part of the experiment on non-injured lungs, and zero end-expiratory pressure (ZEEP) (Table 1). Right internal jugular vein and carotid artery were cannulated. Anesthesia-analgesia was maintained with intravenous infusion of propofol 200 to 300 mg/hour and fentanyl 2 to 4 mcg/kg/min, and paralysis with pancuronium bromide 3 mg/hour.

Equipment
The experiments were carried out in the experimental research imaging facility of the University of Lyon (CERMEP, Lyon, France).

The EIT device used was the Goettingen Goe-MF II System (Viasys Healthcare, Höchberg, Germany). A single array of 16 electrodes (Blue Sensor, BR-80-K, AMBU, Denmark) was placed on the mid-chest circumference of the animal. Electrical currents (50 kHz, 5 mA) were injected through adjacent pairs of electrodes in a rotating mode. During each electrical current injection, the resulting potential differences were measured at adjacent electrode pairs and the resulting impedance (Z) distribution was calculated. The EIT recordings were sampled at a rate of 13 Hz, that is, 13 scans/second.

The PET study was performed using an ECAT EXACT HR+ scanner (Siemens, CTI, Knoxville, Tennesse, USA).

Piezoresistive pressure transducers (Gabarith 682002, Becton Dickinson, Sandy, UT, USA) were calibrated at the mid-

Table 1
Baseline ventilatory settings of six pigs

| Pig number | Weight (kg) | VT (ml) | Rf (breaths.min) | V' (L/s) | PEEPi (cmH2O) | Pplat (cmH2O) | PaO2* (mmHg) | PaCO2* (mmHg) | pH* | MAP (mmHg) |
|------------|------------|---------|------------------|----------|---------------|---------------|-------------|--------------|----|------------|
| 1          | 31         | 310     | 18               | 0.28     | 0.7           | 11.4          | 100         | 37           | 7.43 | 85         |
| 2          | 30         | 300     | 20               | 0.30     | 0.0           | 16.0          | 85          | 38           | 7.44 | 84         |
| 3          | 24         | 250     | 26               | 0.36     | 0.0           | 15.0          | 80          | 35           | 7.38 | 86         |
| 4          | 30         | 300     | 17               | 0.28     | 0.0           | 14.0          | 122         | 28           | 7.53 | 90         |
| 5          | 26         | 260     | 20               | 0.26     | 0.0           | 8.5           | 124         | 36           | 7.41 | 69         |
| 6          | 30         | 270     | 23               | 0.35     | 0.3           | 14.0          | 101         | 37           | 7.42 | 89         |

Mean 28 282 21 0.31 0.17 13.2 102 35 7.44 84
SD 3 25 3 0.04 0.29 2.7 18 4 0.05 8

* inspiratory oxygen fraction was 21%  
MAP = mean systemic arterial blood pressure; PEEPi = total positive end-expiratory pressure; Pplat = plateau pressure; Rf = respiratory frequency; V' = inflation flow; VT = tidal volume.
chest level and connected to a A/D card (MP 100; Biopac Systems, Santa Barbara, CA, USA). Systemic arterial blood pressure, airway pressure and airflow (Fleish 2, Lausanne, Switzerland) were continuously recorded, sampled at 200 Hz, and analyzed with Acknowledge software (Biopac MP100 Systems, Santa Barbara, CA, USA). The value of VT was obtained from the numerical integration of the airflow signal.

Protocol
Once preparation was completed the animal was installed into the PET camera in a supine position. Two sets of experiments were performed in each animal. First, from its baseline value of 10 ml/kg, VT was randomly changed to 6, 8, and 15 ml/kg on ZEEP. Second, while VT was kept constant at 10 ml/kg, positive end-expiratory pressure (PEEP) was randomly changed from 5 to 15 cmH2O by a 5 cmH2O-step procedure. Each step was applied for five minutes (Figure 1).

In three animals, acute lung injury (ALI) was subsequently created by injecting 3 ml/kg hydrochloric acid 0.1 M via the endotracheal tube, after having increased FiO2 to 100%. The target was to obtain partial pressure of arterial oxygen (PaO2) less than 300 mmHg 10 minutes after inhalation. Additional doses of 1 ml/kg each were allowed to be used to reach this objective. Reinjection of HCl was needed once in only one animal. Once the target was reached, PEEP was set to 3 cmH2O for two hours to obtain stabilization. At the end of the stabilization period, two sets of experiments were performed. First, at PEEP 5 cmH2O, VT was randomly changed to 8 and 12 ml/kg for 10 minutes each from the baseline of 10 ml/kg. Second, PEEP of 10 and 15 cmH2O were applied in a random order for 10 minutes, at VT 10 ml/kg. The respiratory rate was titrated to keep arterial pH above 7.20 and intrinsic PEEP lower than 1 cmH2O.

Arterial blood gas was obtained from 2 ml of arterial blood injected into a cartridge (BG Cartridge, Gamida, Eaubonne, France) for immediate pH, partial pressure of carbon dioxide (PCO2) and partial pressure of oxygen (PO2) analysis using blood gas analyzer (IRMA Trupoint™, ITC, Edison, NJ, USA). At the end of each step, the following measures were assessed in this order: mean systemic arterial blood pressure; total PEEP (PEEPt) and end-inspiratory elastic recoil pressure of the respiratory system (Pplat, rs) by occluding the airways at the end of expiration for three seconds and at the end of the immediately following inspiration for four seconds, respectively; and lung ventilation.

Assessment of regional ventilation with EIT and PET
The EIT signals were recorded continuously from the onset to the end of each experimental condition. PET assessment of ventilation was performed as follows (Figure 1). First, a transmission scan was made within 10 minutes. Then, the 13N-N2 tracer continuously produced by the cyclotron fed the ventilator and was washed-in into the lungs through the endotracheal tube, and administered synchronously with the mechanical insufflations from the activation of an electronic valve [4]. Once the activity of the tracer monitored from the camera screen plateaued, entry function of the tracer, that is, the amount of activity entering the lung, was measured at the end of each experimental condition. PET assessment of ventilation was performed as follows (Figure 1). First, a transmission scan was made within 10 minutes. 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laser projection onto the pig’s thorax. Camera bed was then positioned so that the EIT electrodes were located at PET mid-field of view. The information contained in seven contiguous PET slices located at mid-field of view was then averaged, assuring an acceptable match between regions studied with both imaging techniques.

The investigators in charge of EIT (IF) and PET (JCR) analyses were blinded to the definition of each condition and, moreover, analyzed the data independently.

EIT scans were generated using the weighted backprojection reconstruction procedure along equipotential lines [7]. EIT data was evaluated offline in terms of tidal volume (V_T_EIT) and change in lung volume (V_L) in four ROIs corresponding to the anterior and posterior area of the right and left lungs, respectively. V_L reflected the shift in lung mid-capacity with PEEP relative to ZEEP [8]. ROIs were drawn around both lungs using PET transmission scans, on seven contiguous tomographic slices encompassing 5.1 cm of lung height. Lung volume measured with PET scans, on seven contiguous tomographic slices encompassing 5.1 cm of lung height. Lung volume measured with PET slices located at mid-field of view was then averaged, assuring an acceptable match between regions studied with both imaging techniques.

\[
\text{VA}_{\text{atten}}(\text{ml}) = \sum_{i=1}^{n} \text{VA}_{\text{atten}}(i)
\]

\[
V_{\text{PET}}(\text{ml/min}) = \sum_{i=1}^{n} \frac{V(i)(\text{ml/min}/100 \text{ ml} \ V_i)}{\text{region volume}/100}
\]

where i refers to the i-th voxel of the region and n to the total number of voxels of the corresponding region.

**Statistical analysis**

The values are presented as their mean ± SD. The relationships of V_T_EIT (arbitrary units, a.u.) to V_PET (ml/min), in the first part of the experiment, were performed over the whole lungs from linear regression [9]. Then, in each quadrant, the values of V_T_EIT were computed as ml/min by using the following equation:

\[
V_{\text{T_EIT}} \ Q (\text{ml/min}) = V_{\text{T_EIT}} \ Q (\text{a.u.})/V_{\text{T_EIT}} \ global (\text{a.u.}) \times V_{\text{T_EIT predicted}} (\text{ml/min})
\]

Linear regression was performed by using the least square method. Bias and agreement were assessed from the Bland and Altman representation [10]. The non-uniformity distribution of errors in regional measurements was checked by inspecting plots of residuals vs. predicted values. The statistical analysis was performed using SPSS statistical software (version 15.0 for Windows, SPPS Inc., Chicago, IL, USA). P < 0.05 was taken as the statistically significant threshold.

**Results**

For technical reasons, PET images in the PEEP trial in pig number 2 and of V_F 10 ml/kg on ZEEP in pig number 4 were not available. Therefore, in this pig ΔVA_atten could not be computed. Moreover, pig number 6 did not experience V_F 8 ml/kg in the ALI condition. Therefore, 23 normal conditions and 8 ALI conditions were available for the data analysis.

**Effects of changing V_F at ZEEP on ventilation**

We found a strong correlation between global V_T_EIT and V_PET (Figure 2a) over both conditions. The coefficients of determination were 0.95 and 0.91 (P < 0.001) in normal and ALI conditions, respectively. There were no bias and narrow limits of agreement (-37.42 to +37.42 ml/min) over both conditions (Figure 2b). The bias amounted to 5.77 and limits of agreement -24.49 to +36.03 ml/min for normal condition, and -16.59 and -55.26 to +22.08 ml/min for ALI condition. For regional ventilation, the correlation was slightly weaker but still significant (Figure 3a) over both conditions. The coefficients of determination were 0.63 in normal condition and 0.73 in ALI condition (P < 0.01). There were no fixed bias and narrow limits of agreement (-29.01 to +29.08 ml/min) over both conditions (Figure 3b). The bias was 1.47 and limits of agreement -27.91 to +28.66 ml/min for the normal condition, and 0.91 and -27.94 to +29.76 ml/min for ALI.

**Effects of PEEP on lung volume**

We found a strong correlation between global VA_atten and V_L over both conditions (Figure 4a). The coefficients of determination were 0.96 and 0.94 (P < 0.001) for normal and ALI, respectively. There were no bias and acceptable limits of agreement (-38.16 to +38.16 ml) over both conditions (Figure 4b). The bias (limits of agreement) were 0.28 (-30.17 to +29.61) ml for normal condition and 0.62 (-51.53 to +52.78) ml for ALI. At the regional level, the correlation was lower but still significant over both conditions (Figure 5a). The coefficients of determination were 0.76 (P < 0.01) and 0.54 (P <
0.05) for normal and ALI, respectively. There was no bias and limits of agreement ranged from -31.96 to +31.48 ml over both conditions. The bias (limits of agreement) were 0.21 (-26.17 to +26.58) ml for normal condition and -2.54 (-41.88 to +36.80) ml for ALI. The results pertaining to ΔVAatten instead of VAatten were similar (not shown).

Inspection of plots of residuals vs. predicted values disclosed that errors in measurements were uniformly distributed (Figure 6).

**Discussion**

The present study showed that the measurement of lung ventilation and volume with EIT compared favourably with PET assessment. In contrast to previous validation studies using established lung imaging modalities, it must be stressed that in our present study the comparison between the two techniques was performed at the same time. Therefore, lung ventilation and volume were assessed with the same ventilatory history.

EIT could be an important tool in the future because it might allow the intensivist to monitor the regional lung ventilation and volume at the bedside in ICU patients and to manage ventilatory settings on this basis. Therefore, the validity of the measurements obtained with EIT is crucial. PET is a gold standard to quantify lung ventilation on a regional basis. Hinz and colleagues, in a porcine model of oleic acid-induced lung injury, compared SPECT and EIT [3] to measure lung ventilation. The linear relationship between regional ventilation measured with SPECT and EIT, both expressed in percentage of total ventilation, had a slope of 0.82, an intercept of 0.73, and R² of 0.92. Although the slope of the relationship of regional ventilation with both techniques was identical in the two studies, the val-
ues of $R^2$ were lower in our study. Indeed, the regional points were scattered as shown on Figure 3a. In the study by Hinz and colleagues [3], the Bland Altman plots of the ventilation expressed in percentage clearly indicated a proportional bias with the slopes of the linear relationships drawn over the experimental points of the difference to the mean different from 0. This was not the case in our study, which was unbiased.

Apart from non-spatial coincidence in the ROIs drawn with each technique, which is a potential flaw in any such validation studies, two reasons for lower $R^2$ in our study may be raised. First, the present study was performed on ZEEP, so ventilation heterogeneity across quadrants should be expected in connection with anesthesia-related atelectasis. On the other hand, PEEP 5 cmH$_2$O in the study by Hinz and colleagues [3] may have homogenized lung ventilation in the easily recruitable model of oleic acid-induced ALI. Ventilation heterogeneity is expected to increase errors related to spatial coincidence between techniques and may have jeopardized the results in the present study. Second, unlike the study by Hinz and colleagues [3], we applied a wide range of $V_T$. This may have challenged EIT validity to assess lung ventilation, because lung water and blood redistribution induced by $V_T$ change may affect the EIT signal.

Frerichs and colleagues compared the measurements of aerated lung volume with EIT and electron beam CT [11] and found significant correlations between the two methods. Significant correlations were also obtained between EIT and CT scan by Victorino and colleagues [2] in ARDS patients. More recently, Wrigge and colleagues simultaneously compared CT scan and EIT in pigs whose lungs were injured by acid aspiration or oleic acid plus abdominal hypertension [12] and found that both techniques were highly correlated ($R^2 = 0.63$ to 0.88, $P < 0.0001$, bias <5%) in both injuries. The variability between methods was lower in direct than indirect ALI.
In the present study the values of lung ventilation and volume measured with EIT have been quantified and expressed as ml/min and ml, respectively, and not as arbitrary units. This attempt at quantification is a relevant approach because results can be compared between patients and are more meaningful in the clinical field.

Our study has limitations such as the small number of animals investigated. Moreover, the low spatial resolution of EIT renders a more detailed regional analysis difficult. This is a reason why we did not carry out a pixel-by-pixel analysis over ROIs drawn along a ventral-to-dorsal axis. This latter analysis is, however, being investigated further in our laboratory. Furthermore, ventilation and lung volume measurements with PET have methodological limitations. Briefly, partial-volume averaging and spill-over effects affect radioactivity quantification with PET, mainly in the peripheral parts of the lungs. Furthermore, modelling $^{13}$N kinetics requires several assumptions that are simplification of such a complex physiologic processes such as alveolar ventilation [4]. Nevertheless, PET is an accurate and unbiased tool to quantify alveolar ventilation and lung volume [4]. Finally, the animals were not ventilated in such a way as to prevent VILI (Ventilator-Induced Lung Injury). However, this was not a disadvantage in the present design as it allowed us to compare the EIT and PET findings even with a non-optimized ventilation strategy.
One of the strengths of this study is that EIT was tested during conditions in which its validity was really challenged. As stated above, despite PEEP and VT variation over a wide range of values, EIT measurements remained acceptably correlated with PET at the regional level. This favors the use of EIT in the clinical setting to test the effect of different PEEP levels or recruiting maneuvers. It should be noted that PEEP is not a recruitment maneuver per se, but an appropriate tool to keep the lung open after an adequate and individualized recruitment procedure.

Clinical implications
EIT analysis could be refined and extended further by implementing pixel-by-pixel analysis and by better defining atelectasis, so the functional lung recruitment should be assessed. Indeed, the lung recruitability [13] measured with the CT scan are anatomic features. However, for the lung mass recruited to be a relevant issue it should correspond to an increase in ventilation in those areas which continue to receive blood flow and, hence, should contribute to reduce the functional shunt. It has recently been shown that anatomic shunt and functional shunt do not correlate in ARDS patients [14]. As lung perfusion could be assessed with EIT [15], this tool should be well suited to deal with these key issues. Further studies would be welcome to address these questions.

Conclusions
We found that regional lung ventilation and volume were accurately measured with EIT by using PET as the validation tool, over a wide range of PEEP and VT.

Key messages
- In normal and injured pig lungs EIT accurately measures regional lung ventilation.
- This result is obtained from comparison with PET, which is the gold standard to quantify the regional lung ventilation.

Competing interests
CardinalHealth provided a grant to support the study. These fundings were not used to finance the manuscript. The manuscript was financed by academic funds from the authors’ laboratory. The authors declare no other competing interests.

Authors’ contributions
JCR participated in the design of the study and in all experiments, analyzed the PET data and drafted the paper. CP participated in all experiments and in the PET data analysis. AG participated in all experiments and in the PET data analysis. CT participated in all experiments and provided us with tracers administration. DL participated in all experiments and provided us with tracers administration. FL participated in all experiments and provided us with PET data acquisition. IF participated in the design of the study and initial experiments, analyzed the EIT data and drafted the paper. CG participated in the design of the study and in all experiments, performed the data analysis, and drafted the paper.

Authors’ information
JCR is associate professor of critical care medicine and research director. CP was a research fellow during this experiment. AG was a research fellow during this experiment. CT is a technician in charge of the chemistry in the platform. DL is a pharmacist in charge of the chemistry in the platform. FL is an engineer in charge of the PET camera. IF is a professor of physiology and was a visiting professor at the time of this experiment. CG is a professor of critical care medicine and research director.

Note
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