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Laboratory Investigation

LABORATORY INVESTIGATION

Measurement of relative lung perfusion with electrical impedance and positron emission tomography: an experimental comparative study

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Abstract

Background: Electrical impedance tomography (EIT) with indicator dilution may be clinically useful to measure relative lung perfusion, but there is limited information on the performance of this technique.
Methods: Thirteen pigs (50–66 kg) were anaesthetised and mechanically ventilated. Sequential changes in ventilation were made: (i) right-lung ventilation with left-lung collapse, (ii) two-lung ventilation with optimised PEEP, (iii) two-lung ventilation with zero PEEP after saline lung lavage, (iv) two-lung ventilation with maximum PEEP (20/25 cm H_2O to achieve peak airway pressure 45 cm H_2O), and (v) two-lung ventilation under unilateral pulmonary artery occlusion. Relative lung perfusion was assessed with EIT and central venous injection of saline 3%, 5%, and 10% (10 ml) during breath holds. Relative perfusion was determined by positron emission tomography (PET) using ^{68}Gallium-labelled microspheres. EIT and PET were compared in eight regions of equal ventro-dorsal height (right, left, ventral, mid-ventral, mid-dorsal, and dorsal), and directional changes in regional perfusion were determined.
Results: Differences between methods were relatively small (95% of values differed by less than 8.7%, 8.9%, and 9.5% for saline 10%, 5%, and 3%, respectively). Compared with PET, EIT underestimated relative perfusion in dependent, and overestimated it in non-dependent, regions. EIT and PET detected the same direction of change in relative lung perfusion in 68.9–95.9% of measurements.
Conclusions: The agreement between EIT and PET for measuring and tracking changes of relative lung perfusion was satisfactory for clinical purposes. Indicator-based EIT may prove useful for measuring pulmonary perfusion at bedside.

Keywords: electrical impedance tomography; indicator dilution; positron emission tomography; regional pulmonary perfusion

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Editor's key points

- Electrical impedance tomography with indicator dilution may provide clinically useful information on relative lung perfusion.
- There is limited information on the performance of this technique.
- In anaesthetised, mechanically ventilated pigs, the performance of electrical impedance tomography with indicator dilution in detecting pathological changes in perfusion was compared with gold-standard positron emission tomography.
- Acute changes in relative lung perfusion detected by electrical impedance tomography and positron emission tomography were similar.
- Indicator-based electrical impedance tomography can assess regional pulmonary function at the bedside.

The efficiency of pulmonary gas exchange depends on ventilation/perfusion matching, which is associated with an average ratio close to 1.0 in healthy subjects.[1] In acute lung injury, however, low ventilation/perfusion ratios can develop in collapsed regions, resulting in hypoxaemia.[2] Whilst mechanical ventilation can help to improve ventilation of those regions, dead space may increase.[3]

Bedside measurements of regional ventilation and perfusion may help refine the clinical management of patients with impaired gas exchange. The multiple inert gas elimination technique can assess global ventilation and perfusion compartments, but it is cumbersome to perform in clinical practice.[4] Radiotracer-based imaging techniques, such as single photon emission CT and positron emission tomography (PET), are able to measure ventilation and capillary blood flow.[5] However, they require ionising radiation, precluding their widespread use.[6]

Electrical impedance tomography (EIT) is a radiation-free technique that measures relative ventilation and potentially also perfusion based on thoracic electrical conductivity. Ventilation causes proportionally large changes of electrical conductivity, and thus, can be reliably measured by EIT.[7,8] In contrast, perfusion and intra-thoracic blood volume shifts result in EIT signals of modest amplitudes.[9] However, i.v. boluses of saline solutions change blood conductivity substantially over several cardiac cycles, and, upon modelling of tracer kinetics, can be used for measurements of relative lung perfusion with EIT.[10,11]

In the present study, we determined the relative lung perfusion using EIT with saline indicator technique and PET with ^{68}Gallium (^{68}Ga)-labelled microspheres during different conditions of ventilation and perfusion in pigs. We hypothesised that indicator-based EIT is able to measure and track changes of relative lung perfusion.

Methods

The Institutional Animal Care and Welfare Committee and the Government of the State of Saxony, Germany approved all animal procedures (DD24-5131/354/64).

Animal preparation

After premedication (midazolam 1 mg kg^{-1} and ketamine 10 mg kg^{-1}, intramuscularly), 13 pigs were intravenously anaesthetised (ketamine 10–15 mg kg^{-1} h^{-1}; midazolam 0.7–1.2 mg kg^{-1} h^{-1}), paralysed (atracurium 3 mg kg^{-1} h^{-1}), oro-tracheally intubated, mechanically ventilated (Evita® XL; Drägerwerk AG & Co. KGaA, Lübeck, Germany) in the supine position, and continuously monitored (Infinity® Delta Monitor; Drägerwerk AG & Co. KGaA). Adequate anaesthesia depth was ensured by adjusting anaesthesia infusions in response to increases in mean arterial blood pressure and heart rate. At the end of each experiment, pigs were killed by administering thiopental 2g i.v., followed by 50 mL KCl 1M i.v.

Lungs were ventilated in volume-controlled mode with fraction of inspired oxygen of 1.0, tidal volume of 8 ml kg^{-1}, PEEP of 5 cm H_2O, inspiratory:expiratory ratio of 1:1, constant airway flow of 35 L min^{-1}, and ventilatory frequency to pHa between 7.35 and 7.45. An 8.5 French sheath was inserted in the right internal carotid artery and a pulmonary artery catheter advanced through another sheath placed in the right external jugular vein. A mini-laparotomy was performed for direct insertion of a urinary catheter (14 Ch) into the bladder. An elastic EIT belt with 16 electrodes (Drägerwerk AG & Co. KGaA) was placed and kept in mid-chest position throughout experiments. Then, lungs were recruited with continuous positive airway pressure (CPAP) of 40 cm H_2O for 40 s.

Lung imaging

Computed tomography (CT)-based attenuation correction (acCT) scans were reconstructed with 2.0 mm slice thickness, yielding matrices with 512×512 pixels (1.37×1.37 mm^2). PET images were reconstructed with 2.0 mm slice thickness, yielding matrices with 168×168 pixels (2.03×2.03 mm^2). Image reconstruction was carried out iteratively (ordered subset expectation maximisation, six iterations, four subsets, Gaussian post-filtering with a 5 mm kernel) with attenuation correction using acCT scans. Co-registration of acCT to the corresponding PET scans was conducted. ^{68}Ga–PET net activity was calculated subtracting the background ^{68}Ga activity. To account for differing amounts of ^{68}Ga, values were normalised to the total activity within lungs, yielding relative regional perfusion ($Q_{rel,PET}$). The PET volume was projected on a 2D cross section to allow for comparison with EIT (Supplementary material S1).

Electrical impedance tomography

EIT measurements were conducted with an operating frequency of 130 kHz and 50 frames s^{-1}. Apart from a deviating thorax contour derived from porcine CT images, the applied reconstruction algorithm was consistent with the commercially available software of PulmoVista® 500 (Drägerwerk AG & Co. KGaA). Each EIT image of the resulting reconstructed temporal image series consisted of 32×32 pixels. EIT image reconstruction is described in detail in Supplementary material S1. Briefly, the cardiac region was removed from the images and the EIT signal normalised to the overall detected signal, yielding relative regional perfusion ($Q_{rel,EIT}$).

The images were subdivided into eight regions of interest (ROI) (4 on each side of the thorax), which were determined from acCT scans within the EIT sensitivity region during optimal PEEP. A vertical and a horizontal delimiter through the centroid and the most ventral and most dorsal boundary of the segmented lung region were determined, yielding regions of ventral *vs* dorsal and left *vs* right lung. Ventral and dorsal areas were further divided into two subregions (ventral, mid-ventral, mid-dorsal, and dorsal). The ventral and dorsal ROI

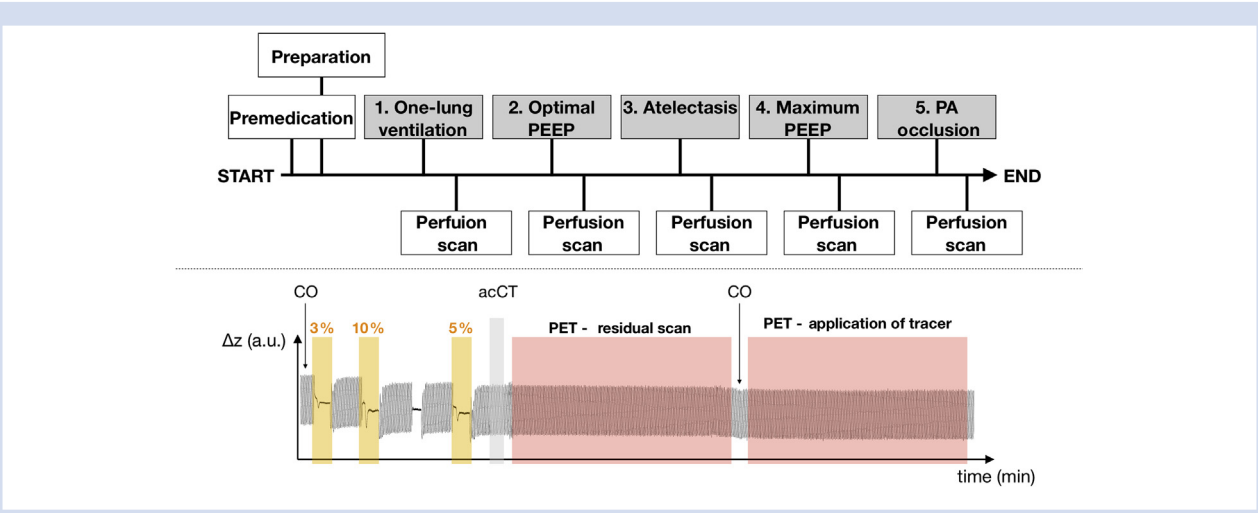

Fig. 1. Time course of interventions. At each ventilation/perfusion condition (1–5), EIT scanning was performed continuously. Perfusion scans were performed with EIT and boluses of saline with different concentrations (3%, 10%, and 5%; orange bars), followed by PET imaging (red bars). The signal (Δz) shown in the lower subplot represents the global impedance measured with EIT during one-lung ventilation; swings with higher amplitude represent tidal ventilation, whilst the flatter parts of the signal correspond to the impedance variation during injection of saline boluses during breath holds. acCT, CT-based attenuation correction; CO, cardiac output; EIT, electrical impedance tomography; PET, positron emission tomography; a.u., arbitrary unit.

were not limited at respective lung boundaries to account for an increase in lung volume during different perfusion conditions (see Supplementary material S1 for further explanation). For each ROI, $Q_{rel,PET}$ and $Q_{rel,EIT}$ were calculated.

Experimental protocol

Five different ventilator strategies were used sequentially to change ventilation/perfusion matching (Fig. 1). The following fixed sequences achieved optimal haemodynamic and respiratory stability during the entire experiment: (i) right lung ventilation (*one-lung ventilation*) using a bifurcated endobronchial blocker (EZ-Blocker™; Teleflex Medical Europe Ltd., Athlone, Ireland) placed to occlude the left main bronchus, (ii) two-lung ventilation with PEEP optimised to minimal lung collapse as assessed with EIT[12 13] (*optimal PEEP*), (iii) two-lung ventilation with zero PEEP after saline lung lavage (*atelectasis*), (iv) two-lung ventilation with a maximum PEEP of 20 or 25 cm H_2O in injured lungs (*maximum PEEP*) to achieve a peak airway pressure of approximately 45 cm H_2O, and (v) two-lung ventilation in injured lungs with unilateral pulmonary artery occlusion (*PA occlusion*) by permanent insufflation of the distal balloon of a pulmonary artery catheter. Details on the induction of the ventilation/perfusion matching conditions are provided in Supplementary material S1. Tidal volume was 5 ml kg^{-1} during one-lung ventilation, and increased to 8 ml kg^{-1} during two-lung ventilation. Other mechanical ventilator settings to maintain adequate gas exchange are shown in Supplementary material S1.

Experimental measurements

Measurements were followed a predefined sequence (Fig. 1). Initially, mixed venous and arterial blood gas analyses (blood gas analyser ABL80™ FLEX BASIC; Radiometer, Copenhagen, Denmark) were performed, and cardiac output was determined by thermodilution (Vigilance II Monitor; Edwards Lifesciences, Irvine, CA, USA). Thereafter, relative perfusion measurements by EIT (PulmoVista 500, Drägerwerk AG & Co. KGaA) were conducted during breath holds at mean airway pressure. Five seconds after the start of each breath hold, saline 3%, 10%, and 5% (10 ml) was injected manually as boluses via the central venous lumen of the pulmonary artery catheter, resulting in a total load of approximately 9 g sodium chloride (NaCl) per animal. Between consecutive injections, tidal ventilation was resumed for 90 s. After measurements with EIT, low-dose helical CT scans of the thorax were obtained for attenuation correction of the PET images (acCT) (Biograph™ 16 Hi-Rez PET/CT; Siemens, Knoxville, TN, USA). After a single-frame PET scan to measure the residual background activity, the relative perfusion was determined at each condition using ^{68}Ga-labelled tracer and PET scanning, as described elsewhere.[14] Briefly, ^{68}Ga-labelled albumin microspheres with diameter in the range of 10–30 μm were injected central intravenously and PET scans were acquired in three bed positions to include the whole lung. For each PET scan, the amount of injected radiotracer was chosen in order to increase the activity level by five-fold.

Statistical analysis

An explorative analysis was conducted to assess the degree of agreement between EIT and PET for measurement of relative lung perfusion. The primary endpoint was the mean difference of relative lung perfusion between EIT and PET. An agreement between EIT using a specific saline concentration and PET was defined as 95% of differences within 10% (limit of agreement [LoA]).

Data are given as mean (standard deviation [SD]). The strength of correlation between the EIT- and PET-derived relative lung perfusion was calculated by Pearson's correlation coefficient. The root mean square error (RMSE) was

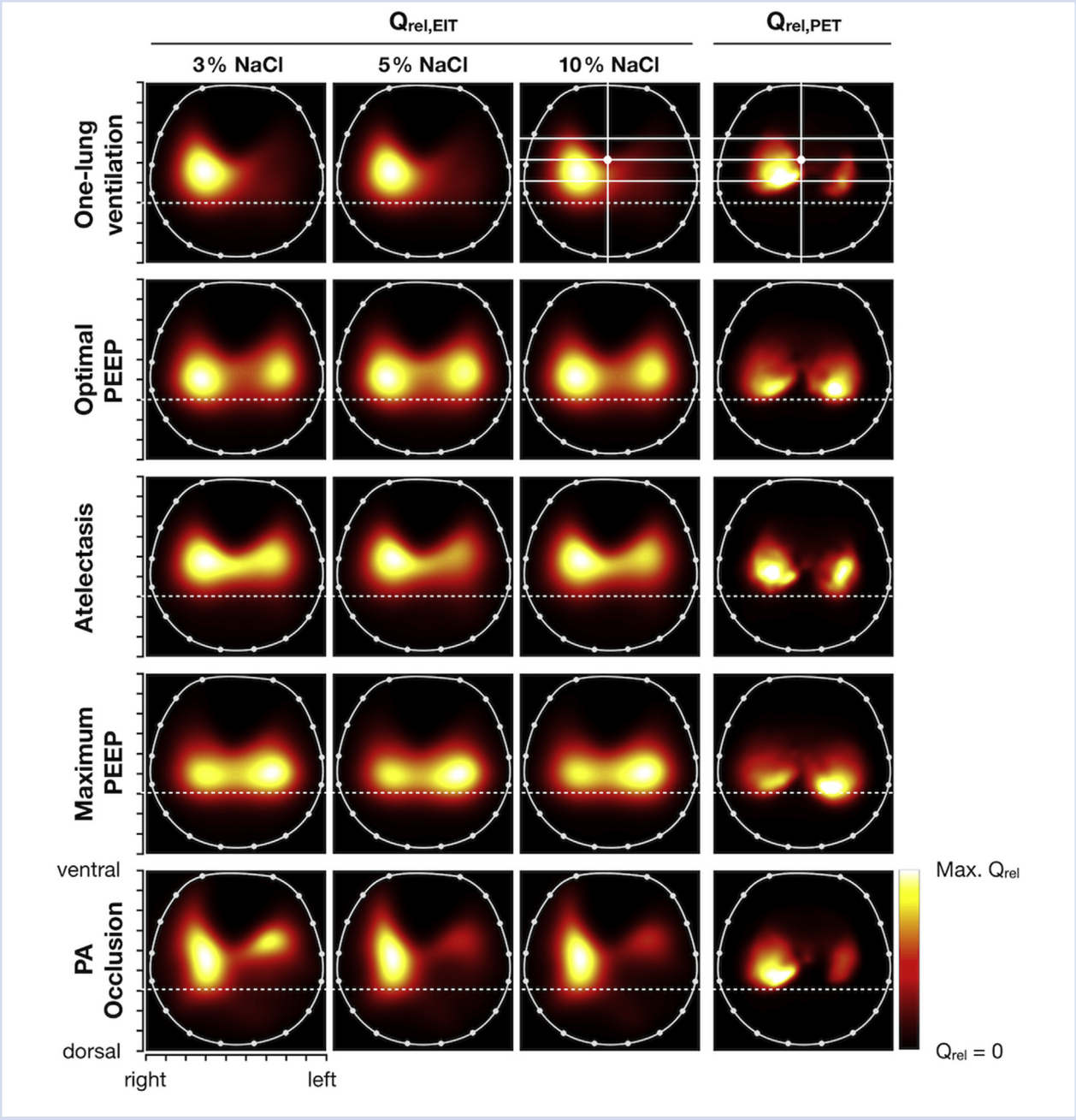

Fig. 2. Images of lung perfusion of one representative animal under different conditions recorded with EIT ($Q_{rel,EIT}$) and PET ($Q_{rel,PET}$) during i.v. saline boluses at breath hold. Left three rows represent different saline concentrations used for bolus injection. The corresponding PET projection based on ^{68}Gallium is shown in the right row. The colour scale was consistent for all figures. White solid lines in the right upper perfusion images represent the distribution of lung regions of equal ventro-dorsal height created from corresponding CT scans, whereas white dashed lines represent dorsal lung borders based on CT-based attenuation correction. EIT, electrical impedance tomography; NaCl, sodium chloride; PA occlusion, block of a main pulmonary artery; PET, positron emission tomography.

calculated to describe the average magnitude of differences between methods. The agreement between imaging methods was assessed with bias (mean difference between methods) and precision (SD of the difference between methods), as proposed by Bland and Altman.[15,16]

The ability of EIT to track the direction of change in relative lung perfusion measured by PET was assessed by concordance analysis between the following conditions: (i) from optimal PEEP to one-lung ventilation, (ii) from optimal PEEP to PA occlusion, (iii) from maximum PEEP to atelectasis, and (iv) from maximum PEEP to optimal PEEP. Changes in relative perfusion <2% in PET were deemed as not clinically relevant, and thus, excluded from the analysis.

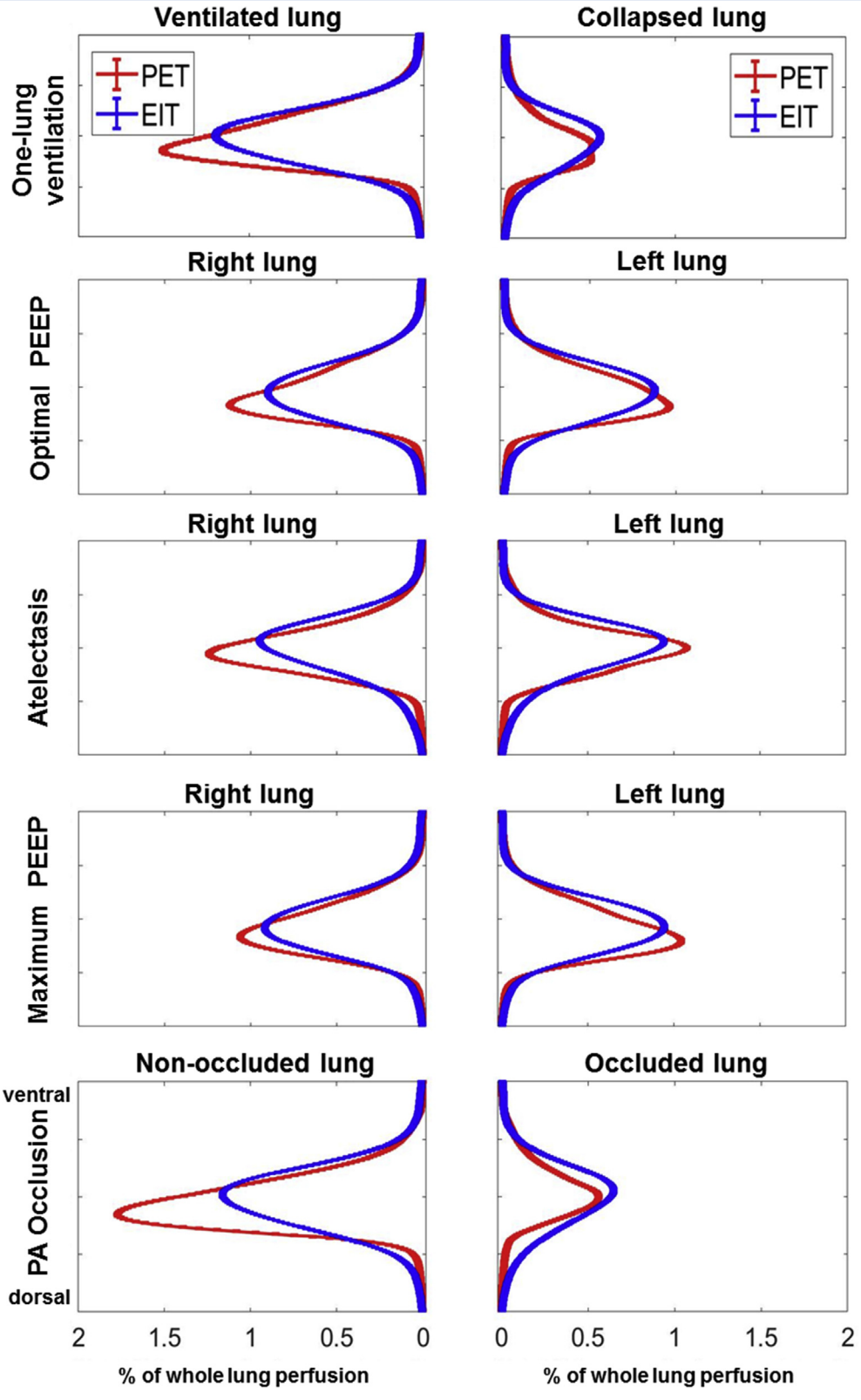

Fig. 3. Mean regional distribution of lung perfusion of all animals along the ventro-dorsal gradient recorded with PET (red lines) and EIT using saline 10% (blue lines). Standard deviation is represented by line thickness. EIT, electrical impedance tomography; PA occlusion, block of a main pulmonary artery; PET, positron emission tomography.

Statistical analysis was performed with MATLAB R2017a (MATLAB and Statistics Toolbox Release 2017a; MathWorks, Natick, MA, USA).

Results

One animal died before PA occlusion, and sufficient occlusion of the pulmonary artery was not achieved in another animal, yielding a total of 504 EIT and PET paired measurements. Gas exchange and haemodynamics, and respiratory variables, are depicted in Supplementary Tables S1 and S2, respectively.

Relative perfusion

Representative maps of relative perfusion are displayed in Figure 2. Also, representative videos showing the passage of the indicator (saline 10%) through the field of view of EIT at each ventilation/perfusion matching condition are shown in Supplementary videos 1–5.

Figure 3 shows the mean distributions of lung perfusion along the ventral–dorsal gradient. In PET and in EIT measurements with saline 3%, 5%, and 10%, one-lung ventilation and PA occlusion led to a perfusion defect in the ipsilateral lung, whilst atelectasis reduced the relative perfusion in dorsal compared with ventral zones. Optimal PEEP and maximum PEEP resulted in similar distributions of relative perfusion.

Concordance between EIT and PET

For 95% of all measurements with saline concentrations of 10% and 5%, respectively, relative perfusion differences between EIT and PET were less than 9% (Fig. 4; Supplementary Table S3). With saline 3%, 95% of differences between methods were less than 10%. The RMSE for differences in relative perfusion between PET and EIT using saline 10%, 5%, and 3% was 4.4%, 4.5%, and 5.7%, respectively. Compared with PET, EIT overestimated the perfusion in non-dependent regions, and underestimated it in dependent regions (Fig. 4), irrespective of the saline concentration (Supplementary Table S3).

The closest agreement between PET and EIT using saline 10%, 5%, and 3%, respectively, was observed at optimal PEEP (LoA: 5.6%, 5.4%, and 6.2%) and maximum PEEP (LoA: 4.5%, 4.3%, and 4.5%), whereas the largest difference was observed during PA occlusion (LoA: 13.4%, 14.0%, and 15.5%), followed by atelectasis (LoA: 9.7% for all concentrations).

Ability to track changes in perfusion

EIT was able to predict the direction of change in relative perfusion within each ROI, as measured by PET, in 84.1%, 83.0%, and 82.5% of all measurements using saline 10%, 5%, and 3%, respectively. For all saline concentrations, the lowest and highest agreement rates were observed between maximum PEEP and optimal PEEP, and optimal PEEP and one-lung ventilation, respectively (Supplementary Table S4), as illustrated for saline 10% in Figure 5 (lowest: 68.9%; highest: 95.9%).

The capability of EIT to track changes in relative perfusion was highest with saline 10%, and slightly lower with saline 5% and 3% (Supplementary Table S4).

Discussion

The main findings of this study were that, compared with PET, the relative perfusion measured by indicator-based EIT (i)

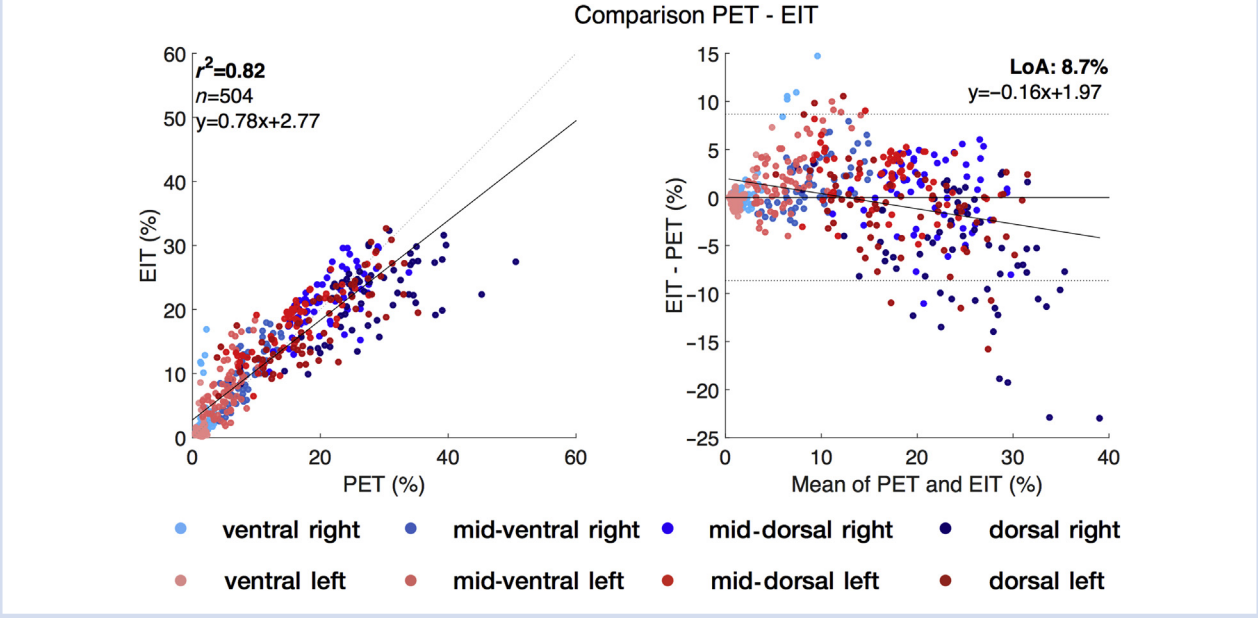

Fig. 4. Correlation and Bland–Altman plot for EIT-based perfusion estimation using saline 3% and PET, with lung images divided into eight lung regions of equal ventro-dorsal height. Five conditions of different lung perfusion are included. Dashed lines represent limits of agreement (95% confidence interval). Lighter dots represent non-dependent ROI; darker dots represent dependent ROI. Compared with PET, EIT reveals proportionally higher perfusion signals in non-dependent ROI, but lower signals in dependent ROI (compare solid regression line with slope and intercept). EIT, electrical impedance tomography; LoA, limit of agreement; PET, positron emission tomography; ROI, region of interest; SD, standard deviation.

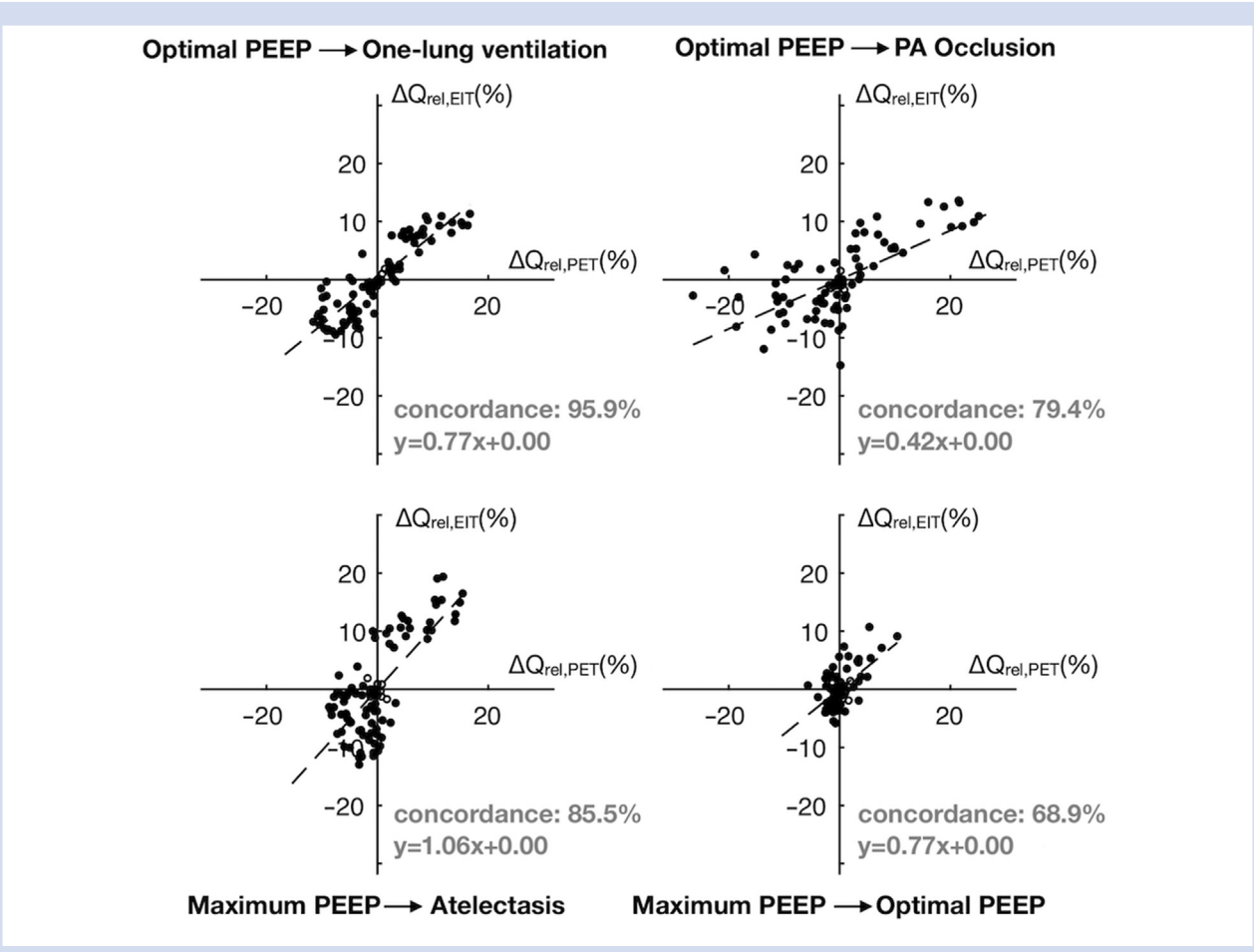

Fig. 5. Scatterplots of changes in relative perfusion for selected conditions of ventilation/perfusion matching. Values were obtained with EIT using saline 3% ($\Delta Q_{rel,EIT}$) and PET ($\Delta Q_{rel,PET}$). The predictive ability (concordance) was determined for $\Delta Q_{rel,PET}$ and $\Delta Q_{rel,EIT}$ <2% only (closed dots). Dashed lines represent linear regression, and respective regression equations are given. EIT, electrical impedance tomography; OLV, one-lung ventilation; PA occlusion, block of a main pulmonary artery; PET, positron emission tomography.

showed LoA below a threshold of 10% across different lung regions with all tested saline concentrations (3%, 5%, and 10%), (ii) was slightly underestimated in dependent and overestimated in non-dependent lung regions, and (iii) tracked the same direction of change in relative perfusion in 68.9–95.9% of measurements.

Previous studies showed that relative pulmonary perfusion can be measured by EIT using an injection of saline 20%.[10 11] More recently, lower saline concentrations were successfully used to detect perfusion defects.[17] In the present study, we modified the indicator-based approach and used saline concentrations that are even more suitable for clinical use. Also, we evaluated the performance of EIT during different conditions of ventilation/perfusion matching, covering important extremes of gas exchange impairment. PET was chosen as a reference because it allows imaging of the entire lung with relatively high spatial resolution. This is of particular interest, as EIT measurements represent rather volumetric than planar information.[17] Also, after i.v. injection into the pulmonary artery, almost all ^{68}Ga-labelled microspheres were trapped in the pulmonary capillaries and arterioles during the first pass, whilst other organs remained unaffected.[18] Therefore, PET measurements more closely reflect pulmonary microcirculation than previously applied alternative modalities for pulmonary perfusion imaging, such as CT perfusion imaging based on first-pass kinetics of iodine.[10]

A major strength of this study was its stringent and *a priori* defined criteria of precision. We deemed an LoA between methods of 10% difference in relative perfusion in single ROI as necessary. This applies not only in extreme conditions of pulmonary perfusion defects (e.g. thromboembolism),[17] but also during routine therapeutic interventions (e.g. adjustments of PEEP). We opted for dividing EIT images into four gravitationally dependent regions per lung in order to account for possible heterogeneities in relative perfusion that are still relevant for optimisation of regional ventilation/perfusion matching.

Our observation that, compared with PET, the relative perfusion measured by EIT was overestimated in non-dependent and underestimated in dependent regions is, at least in part, in agreement with a previous investigation.[11] Despite adapting the EIT reconstruction algorithm to the body shape of the analysed species, the regional amplitude response in EIT might have still been influenced by the amount of tissue surrounding the lung and its composition.[19] Whilst ventral lung regions are closer to the electrodes in pigs

compared with humans, the distance between dorsal lung regions and electrodes is larger because of a more pronounced spine, and bigger muscle and fat tissue content. Although attenuation correction of the PET measurements allows for correction for inhomogeneous tissue distribution within the lung (e.g. air, blood, and tissue) and thorax, no such correction is feasible for EIT measurements. Such effects may be less pronounced in humans, potentially resulting in a better agreement between imaging methods, compared with the porcine model. Additionally, an incomplete removal of the cardiac EIT region might have contributed to an underestimation of dorsal zones.

Amongst the different conditions of ventilation/perfusion matching, EIT performed better during one-lung ventilation, optimal PEEP, and maximum PEEP compared with atelectasis and PA occlusion. A possible explanation is that the impedance decreased in dorsal lung regions after lung lavage. In atelectatic tissue that was still present during the subsequent PA occlusion, the background impedance is lower in dependent than non-dependent lung regions. This may have affected the accuracy of EIT.

We also observed that, in atelectasis and PA occlusion, central haemodynamic parameters, especially cardiac output, showed deviations between EIT and PET imaging. This might have resulted in alterations of lung perfusion during PET and EIT measurement, although a constant cardiac output (and consequently lung perfusion) was the basis of the comparison of the methods. However, changes of the initial steady state may have caused an overestimation of the differences in lung perfusion. The agreement of the two methods might therefore be even better than observed in this study.

Despite the systematic differences, EIT detected the direction of change in relative perfusion that resulted from variations in ventilation/perfusion matching. However, EIT underestimated the magnitude of change compared with PET, as suggested by the concordance analysis. The best concordance was achieved for changes in regional perfusion between one-lung ventilation and optimal PEEP, whilst a lower concordance was achieved for changes between maximum PEEP and optimal PEEP. For the latter, changes in relative perfusion were marginal, potentially increasing the sensitivity of the concordance analysis.

Limitations

Measurements were conducted in pigs and EIT algorithms for image reconstruction were adapted to this species regarding the underlying thorax contour. Changes in haemodynamic state induced by the administration of inotropic/vasoactive drugs or impairment of vascular integrity as observed during sepsis were not covered by the study protocol.

Potential clinical implications of the findings

Previous studies addressing the measurement of relative perfusion distributions by EIT used relatively high loading of NaCl in order to improve the signal-to-noise ratio in indicator dilution.[10,11] It is well known that excessive saline infusion can cause osmotic demyelination syndrome and electrolyte imbalances (hyperchloraemia, hypernatraemia, and hypokalaemia) associated with metabolic acidosis, and impair the functioning of the renal cortex.[19–21] Our data show that reduced volumes (e.g. 10 ml) of saline concentrations as low as 10%, 5%, and even 3% for indicator dilution are still adequate for assessing the relative perfusion with EIT whilst limiting NaCl loading. Thereby, multiple measurements of relative perfusion at the bedside, for example, during titration of mechanical ventilation, can be conducted at lower risk of side-effects.

Conclusion

Under different conditions of ventilation/perfusion matching in pigs, the agreement between PET and indicator-based EIT, using saline concentrations as low as 3%, for measurement of lung perfusion was satisfactory. Indicator-based EIT may prove useful for the assessment of regional pulmonary function at the bedside.

Authors' contributions

Study conception/design: all authors.
Data acquisition: TB, TK, MK, AB, CB, MS, MH, JR, PH, LV, MM, MA, BS.
Data processing: TB, TK, MK, AB, RH, BS.
Data analysis/interpretation: all authors.
Drafting manuscript: TB, TK, MK, AB, RH, BS, MGA.
All authors critically revised the manuscript for important intellectual content, and approved the final version to be submitted.

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Declarations of interest

CB and BS are employees at and draw salary from Drägerwerk AG & Co. KGaA. MK received research funding from Drägerwerk AG & Co. KGaA. The remaining authors have disclosed that they do not have any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2019.04.056.

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