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EXPERIMENTAL

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Optimisation of positive end-expiratory pressure by forced oscillation technique in a lavage model of acute lung injury

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Abstract *Purpose:* We evaluated whether oscillatory compliance (C_{X5}) measured by forced oscillation technique (FOT) at 5 Hz may be useful for positive end-expiratory pressure (PEEP) optimisation. *Methods:* We studied seven pigs in which lung injury was induced by broncho-alveolar lavage. The animals were ventilated in volume control mode with a tidal volume of 6 ml/kg. Forced oscillations were superimposed on the ventilation waveform for the assessment of respiratory mechanics. PEEP was increased from 0 to 24 cmH_2O in steps of 4 cmH_2O and subsequently decreased from 24 to 0 in steps of 2 cmH_2O. At each 8-min step, a CT scan was acquired during an end-expiratory hold, and blood gas analysis was performed. C_{X5} was monitored continuously, and data relative to the expiratory hold were selected and averaged for comparison with CT and oxygenation. *Results:* Open lung PEEP ($PEEP_{ol}$) was defined as the level of PEEP corresponding to the maximum value of C_{X5} on the decremental limb of the PEEP trial. $PEEP_{ol}$ was on average 13.4 (±1.0) cmH_2O. For higher levels of PEEP, there were no significant changes in the amount of non-aerated tissue (V_{tissNA}%). In contrast, when PEEP was reduced below $PEEP_{ol}$, V_{tissNA}% dramatically increased. $PEEP_{ol}$ was able to prevent a 5% drop in V_{tissNA}% with 100% sensitivity and 92% specificity. At $PEEP_{ol}$ V_{tissNA}% was significantly lower than at the corresponding PEEP level on the incremental limb. *Conclusions:* The assessment of C_{X5} allowed the definition of $PEEP_{ol}$ to be in agreement with CT data. Thus, FOT measurements of C_{X5} may provide a non-invasive bedside tool for PEEP titration.

Keywords Forced oscillation technique · Lung mechanics · Mechanical ventilation · Positive end-expiratory pressure · Lung volume recruitment · Computed tomography · ARDS

Introduction

Mechanical ventilation is essential in the treatment of patients affected by acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). However, if the ventilatory parameters are not titrated adequately, it may cause volutrauma and atelectrauma as well as worsening of inflammatory processes [15, 31, 38]. Positive end-expiratory pressure (PEEP) improves lung function and may reduce the duration of mechanical ventilation [30]. One goal of a protective ventilatory strategy is to choose a value of PEEP that maximises recruitment while avoiding over-distension. However, the best way to choose the optimal PEEP level is still under investigation.

Computed tomography (CT) provides an objective tool for assessing lung aeration and consequently for establishing optimal ventilation settings [17, 18, 27, 37, 45]. However, CT is not available at the bedside, it is not adequate for a continuous monitoring and it is associated with high doses of ionising radiation.

In clinical practice PEEP is usually adjusted according to oxygenation [43], but this may overlook PEEP-induced over-distension and intra-tidal recruitment/derecruitment. An alternative approach is to set PEEP in order to maximise dynamic compliance (C_{dyn}) [41] or similarly to minimise the elastance (E_{rs}) of the respiratory system ($E_{rs} = 1/C_{dyn}$) [2, 4, 5], during a decremental PEEP trial. Even though C_{dyn} has the advantage of being continuously provided by the ventilator, its estimation is strongly affected by non-linearities, which may be relevant in diseased lungs, and by respiratory muscle activity, requiring either deep sedation or the use of an esophageal balloon in the presence of spontaneous breathing.

We have recently shown that reactance or the oscillatory compliance (C_{X5}) derived from reactance measured by the forced oscillation technique (FOT) at 5 Hz may be used to monitor recruitment/derecruitment during mechanical ventilation, overcoming the limitations mentioned above [9]. Reactance and C_{X5} are measured by analysing the response of the respiratory system to very small oscillatory pressures ($\sim$2 cmH_2O amplitude) with a frequency of 5 Hz.

The aim of the present study was to evaluate the ability of C_{X5} to identify the minimum level of PEEP which should be applied in order to prevent volume derecruitment and to compare it to the gold standard provided by CT.

Materials and methods

The study was carried out at the Departments of Clinical Physiology and Radiology of the University Hospital of Uppsala, Sweden, and it was approved by the local animal ethics committee.

Study population

Seven pigs (weight 29.8 ± 2.1 kg) were studied. A detailed description of animal preparation can be found in the electronic supplementary material.

Experimental protocol

Lung injury was induced by broncho-alveolar lavage. PEEP was increased from 0 to 24 cmH_2O in steps of 4 cmH_2O and subsequently decreased from 24 to 0 in steps of 2 cmH_2O. At each PEEP level, a CT scan was performed during a 10 s expiratory hold, and arterial blood was sampled for gas analysis. The duration of each step was 8 min, the total duration of the experiment was $\sim$150 min.

Experimental set-up and measurements

FOT was applied using a set-up which has been described elsewhere [9]. Briefly, low amplitude ($\sim$2 cmH_2O peak-to-peak) sinusoidal pressure oscillations at 5 Hz were generated by a loudspeaker connected to the inspiratory line of the mechanical ventilator. Flow at the airway opening ($\dot{V}_{ao}$) was measured by a differential pressure transducer and a mesh-type heated pneumotachograph connected at the inlet of the tracheal tube. Pressure (P_{tr}) was measured at the tip of the endotracheal tube by a differential pressure transducer. A detailed description of the set-up and measurements can be found in the electronic supplementary material.

Data analysis

Lung mechanics

The estimation of the respiratory system input impedance (Z_{rs}) was obtained from the flow and pressure signals by a least-squares algorithm [14, 25]. Z_{rs} is composed of a real part, called resistance (R_{rs}), and an imaginary part, called reactance (X_{rs}). X_{rs} was used to compute oscillatory compliance (C_{X5}) using the following equation [9]:

$$C_{X5} = \frac{-1}{2 \cdot \pi \cdot 5 \cdot X_{rs}} \quad (1)$$

C_{X5} data were averaged over the periods of expiratory hold needed to perform CT scans, providing a single data point for each CT scan.

Open lung PEEP ($PEEP_{ol}$) was defined as the PEEP level corresponding to a maximum in X_{rs} and C_{X5} during the decremental trial.

C_{dyn} was calculated by fitting the equation of motion of the respiratory system to P_{tr} and $\dot{V}_{ao}$ by the least-squares method on approximately 5–10 breaths immediately preceding the CT scan. An extension of the equation of motion, including a volume-independent (C1) and a volume-dependent (C2) component of compliance, was also considered [26, 34].

Computed tomography analysis

Changes in lung aeration were studied by whole-body CT scans. Images were reconstructed with 8-mm slice

thickness and analysed using dedicated software (Maluna 2.02). The total lung volume was subdivided into over-aerated (OA, −1,000 to −900 HU), normally aerated (A, −900 to −500 HU), poorly aerated (PA, −500 to −100 HU) and non-aerated (NA, −100 to +100 HU) volumes as previously suggested [17, 45]. Lung gas (V_{gas}) and tissue (V_{tiss}) volumes were calculated using standard equations [17] for the whole lung and for each aeration compartment. The amount of derecruited lung was quantified as the volume of tissue in the non-aerated region and expressed as a percentage of total tissue volume (V_{tissNA}%). Similarly, the percentage amounts of aerated (V_{tissA}%) and poorly aerated (V_{tissPA}%) tissue were calculated.

Statistical analysis

Data are expressed as mean ± SD. Significance of differences between different PEEP levels was tested by one-way ANOVA for repeated measurements. Multiple comparison after ANOVA was performed using Holm-Sidak test. Differences between $PEEP_{ol}$ and the corresponding PEEP on the inflation limb of the curve were tested by paired *t* test. Differences were considered statistically significant for $p < 0.05$. The sensitivity and specificity of C_{X5} for the detection of lung collapse was calculated using CT as a reference.

A detailed description of the methods used for data analysis can be found in the electronic supplementary material.

Results

Figure 1 shows the average behaviour of X_{rs}, C_{X5}, C_{dyn}, V_{tissNA}% and blood gases.

During inflation X_{rs}, C_{X5} and C_{dyn} significantly increased until a PEEP of 16 cmH_2O, after which they tended to decrease. The decremental limbs of these curves were shifted upwards and to the left compared to the inflation limbs and reached maximum values at PEEP 14 cmH_2O for X_{rs} and C_{X5} and at 12 cmH_2O for C_{dyn}. C1 versus PEEP presented a similar shape compared to C_{dyn}, with a maximum at PEEP 12 cmH_2O on the decremental limb. During inflation V_{tissNA}% significantly decreased from PEEP of 0 to 20 cmH_2O, while during deflation it did not change significantly until $PEEP_{ol}$, after which it significantly increased. During deflation $PaCO_2$ was always lower than during inflation and presented a minimum at 12 cmH_2O. PaO_2 increased with PEEP in a sigmoidal way, deflation values being higher than inflation values at each PEEP level.

Figure 2 shows C_{X5}, blood gases and CT data and a representative CT slice (~1 cm above the diaphragmatic dome) during deflation from one representative animal. The CT images show the regional distribution of differently aerated regions.

Comparing individual animals, the shapes of the curves were similar. In particular, X_{rs} and C_{X5} always showed a dome-shaped behaviour reaching maximum values at, on average, a PEEP of 13.4 ± 1.0 cmH_2O. C_{dyn} and C1 also displayed similar shape, but reached their maximum values at a lower PEEP compared to FOT data (12.0 ± 1.6 and 12.6 ± 1.5 cmH_2O respectively).

To characterise the behaviour of various parameters around $PEEP_{ol}$, we averaged the data considering for each animal the differences between the values measured at $PEEP_{ol}$ and those measured two steps immediately before and after $PEEP_{ol}$ (Fig. 3). As expected, C_{X5} presented negative differences with respect to $PEEP_{ol}$ for all protocol steps. C_{dyn} displayed a similar shape but with the maximum on average one step (2 cmH_2O) lower than C_{X5}. PaO_2 increased slightly for PEEP levels higher than $PEEP_{ol}$, while it sharply decreased for PEEP levels lower than $PEEP_{ol}$. $PaCO_2$ presented positive differences with respect to $PEEP_{ol}$. Finally, V_{tissNA}% abruptly increased for PEEP levels lower than $PEEP_{ol}$, indicating the beginning of derecruitment.

Haemodynamic variables, CT volumes and respiratory mechanics parameters are reported in Table 1.

FOT was able to detect lung collapse with 100% sensitivity and 92% specificity compared to CT.

Figure 4 shows the differences in C_{X5}, PaO_2 and V_{tissNA}% between $PEEP_{ol}$ and the corresponding value on the incremental limb of the curve. C_{X5} at $PEEP_{ol}$ was significantly higher than at the corresponding PEEP on the incremental limb of the curve; PaO_2 was significantly higher and V_{tissNA}% was significantly lower.

Discussion

In the present study we evaluated the use of FOT for bedside identification of the lowest PEEP able to prevent lung derecruitment after a recruitment manoeuvre in a surfactant-depletion model of ALI. We compared FOT data with the distribution of lung aeration as measured by whole-lung CT scan.

The main finding of this study was that FOT could identify $PEEP_{ol}$ in good agreement with CT. In particular, C_{X5} identified the minimum PEEP level required to maintain lung recruitment with high sensitivity and specificity.

Comparison with other studies

The use of lung mechanics in dynamic conditions to optimise PEEP, originally suggested more than 30 years

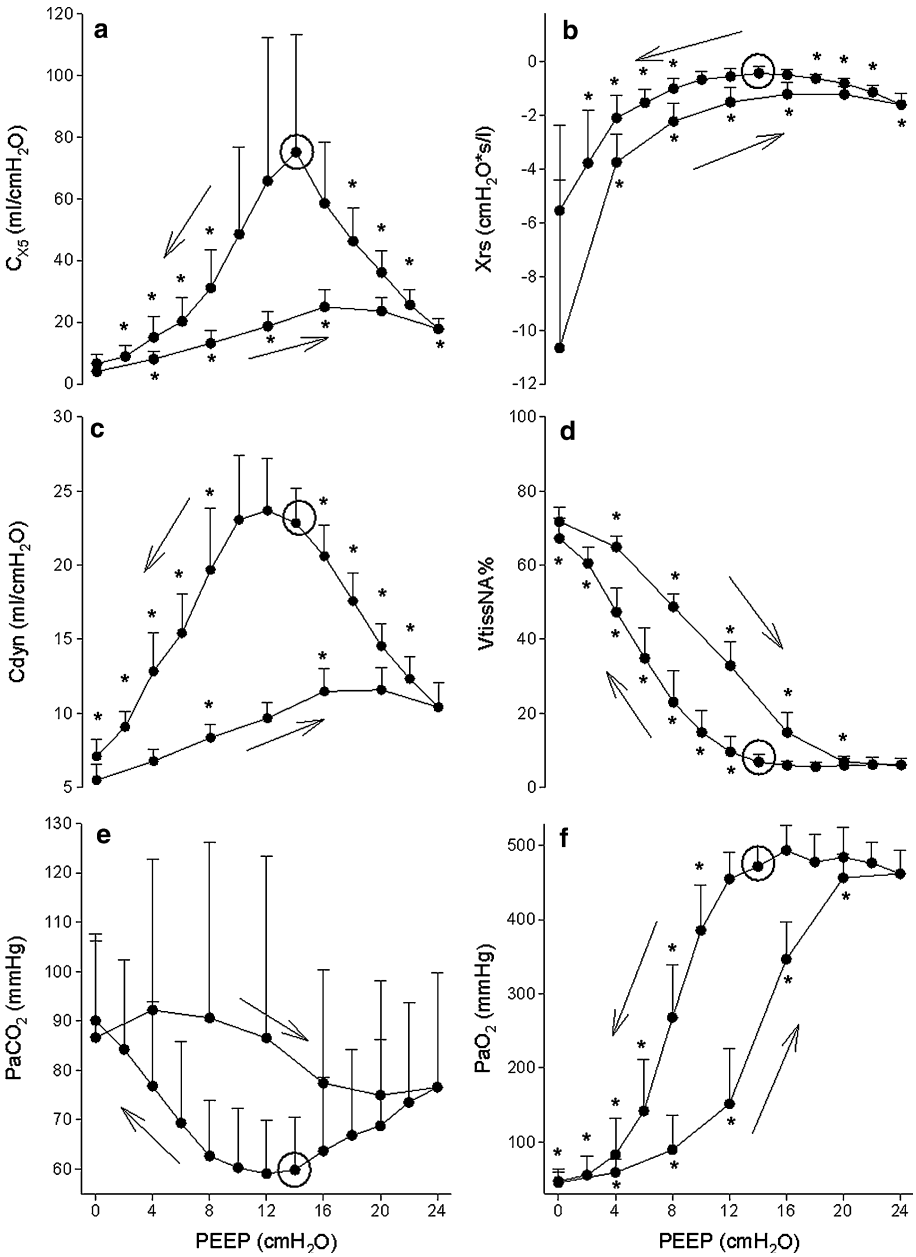

Fig. 1 Relationship between PEEP for all pigs during the inflation-deflation PEEP trial and **a** oscillatory compliance (C_{X5}), **b** respiratory system reactance (X_{rs}), **c** dynamic compliance (C_{dyn}), **d** percentage amount of non-aerated tissue (V_{tissNA}%), **e** partial pressure of carbon dioxide ($PaCO_2$) and **f** partial pressure of oxygen (PaO_2). Values are mean and SD. The *arrows* identify the inflation and deflation limbs of the curve. The *circles* identify the optimum PEEP defined as the maximum C_{X5} value reached during the deflation limb. *$p < 0.05$ compared to the previous step

ago by Suter et al. [42], has recently been re-evaluated [2, 4, 5, 41], providing promising results for the bedside optimisation of mechanical ventilation.

We have recently shown that C_{X5} derived from X_{rs}, measured by single frequency FOT at 5 Hz, is very sensitive to lung volume recruitment and derecruitment [9]. This approach offers three main advantages over dynamic respiratory mechanics estimated by multi-linear regression analysis. First, the stimulus applied during FOT induces very small lung volume changes, minimising the artefacts due to non-linearities of the respiratory system. In contrast, to calculate dynamic compliance multi-linear regression analysis is performed over a whole breath. In this large volume range, the lung does not behave linearly and compliance is not constant. To compensate for this, it is possible to assess compliance at different volume increments by the SLICE method [22] or to add a volume-dependent term in the equation of motion [26, 34], but in this way the convergence properties of the fitting are reduced. Second, since C_{X5} is not affected by the spontaneous respiratory activity of the patients, it does not require either sedation or the use of an esophageal balloon. The current need for deep sedation or muscle paralysis to perform accurate PEEP titration guided by static or dynamic compliance is the major impediment for a more widespread use of lung mechanics to select PEEP.

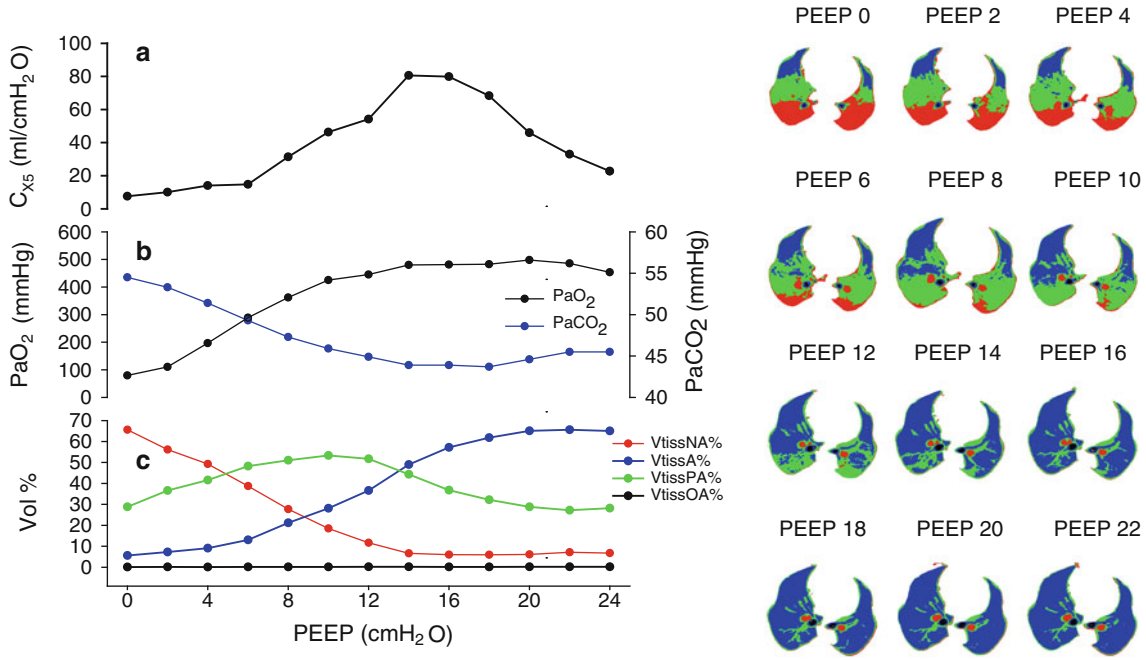

Fig. 2 **a** Oscillatory compliance (C_{X5}), **b** blood gases (PaO_2 in *black* and $PaCO_2$ in *blue*) and **c** percentage of the tissue volume of differently aerated regions (*black* over-aerated, *blue* normally, *green* poorly and *red* non-aerated regions) obtained during the deflation limb of the PEEP trial from a representative animal. *Right* A representative CT slice (selected approximately 1 cm above the diaphragmatic dome) of the same animal at the different PEEP levels. *Color code* for regions as above

Third, since C_{X5} may be measured with a high time resolution (0.2 s at 5 Hz), it allows the assessment of within-breath changes in lung mechanics. In this way it could be possible to monitor intra-tidal recruitment and over-distension, both of which have a role in ventilator-associated lung injury [21, 29, 30]. It is possible to account for intra-tidal recruitment or over-distension also by introducing a volume-dependent component of compliance in the equation of motion [26, 34] or by analysing the shape of the dynamic pressure-time curve [20, 34] during constant-flow ventilation. The disadvantage of all these approaches is that they require sedation.

We found a systematic difference between PEEP corresponding to the maximum C_{dyn} and PEEP corresponding to the maximum C_{X5}, the latter being on average 2 cmH_2O greater than the former (Fig. 3). Interestingly, this result is in good agreement with a mathematical modelling study [24] reporting that open lung PEEP is greater than the PEEP providing maximum tidal PV slope and therefore maximum C_{dyn}. In fact, PEEP is currently set one step higher than the PEEP at which C_{dyn} achieves a maximum. However, this is an empirical rule which is not based on a clearly defined physiological reason. The use of a volume-dependent component of compliance, even if it provided slightly greater values for optimum PEEP compared to C_{dyn}, was not able to provide the same optimum PEEP as that identified by C_{X5}.

Another result of this work is that it gives further support for the significance of titrating PEEP during decremental PEEP trials. This is clearly shown by the higher values of X_{rs} found on the deflation limb compared to the ones measured during deflation at $PEEP_{ol}$. In a mathematical model of ARDS, Hickling [24] showed that, with incremental PEEP, the PEEP level associated with the maximum mean tidal PV slope did not coincide with open lung PEEP. The interpretation supported by our data is that during incremental PEEP the lung is recruited by the peak pressure, while during deflation, PEEP prevents the collapse of the lung that has already been fully recruited.

Limitations of the study

The total Z_{rs} measures the mechanical properties of the whole respiratory system, which comprises both lung and chest wall. During a PEEP trial, changes in end-expiratory lung volumes are shared between the lung and the chest wall. Since chest wall compliance (C_{cw}) changes with volume, it will affect X_{rs} and C_{X5}, potentially impairing the accuracy of X_{rs} regarding the evaluation of lung volume recruitment. However, from a mathematical simulation (see Appendix 1), we estimated that the contribution of C_{cw} changes to X_{rs} changes was negligible compared to the effect of recruitment/derecruitment.

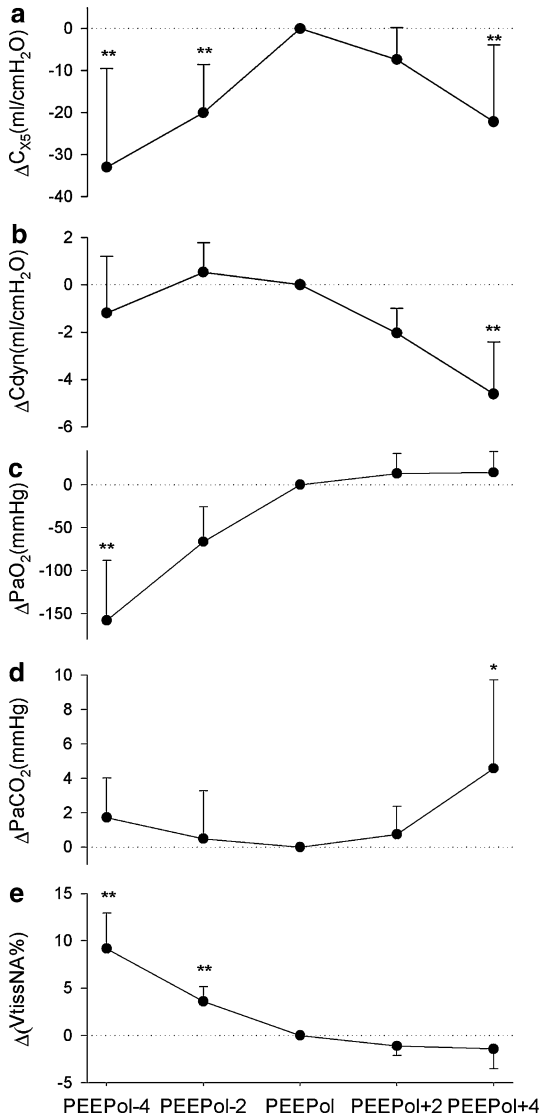

Fig. 3 Differences in **a** oscillatory compliance (C_{X5}), **b** dynamic compliance (C_{dyn}), **c** partial pressure of oxygen (PaO_2), **d** partial pressure of carbon dioxide ($PaCO_2$) and **e** percentage amount of non-aerated tissue (V_{tissNA}%) with respect to open lung PEEP ($PEEP_{ol}$) at the two steps preceding and following $PEEP_{ol}$. *$p < 0.05$, **$p < 0.01$ with respect to $PEEP_{ol}$

The thresholds separating different aeration regions used in this study are those internationally recommended [16, 17, 32, 33, 36]. However, these thresholds are arbitrary, and they may influence the estimation of the amount of recruited and hyperinflated volume. We used a cut-off density between the aerated and the over-aerated region of −900 HU, similar to Vieira et al. [45] while other groups used cut-off levels of −800 HU [7]. The absolute cut-off may differ due to differences in CT calibration [1] and CT resolution [44].

Compared to other studies using similar animal models [6, 19], we found analogous results regarding CT data but not for the amount of over-aerated tissue, which was negligible in our study. The disparity may be explained by the higher slice thickness used in the present study. It has been demonstrated that low spatial resolution CT provides adequate data for most of the aeration partitions, but it may significantly underestimate lung over-inflation in patients with acute lung injury [44]. Since the aim of the present study was to correlate the amount of lung volume derecruitment with FOT data, the CT analysis had to be extended to the whole lung with the lung perimeter segmented manually to avoid errors in the separation of collapsed lung with chest wall tissues. We accomplished this task by analysing more than 3,300 8-mm slices; the choice of thinner slices would have required manual processing of almost 20,000 images without significantly contributing to the main message of the study.

Moreover, over-aerated regions identified by CT represent lung tissue overfilled with gas. Conversely, overdistension is defined as the condition of excessive mechanical stress applied to lung tissue, and it is related to alveolar wall tension. In severe ARDS, in which the whole lung has an increased mass, high levels of PEEP may result in local over-distension even if the average density of the region is greater than −900 HU [17]. Therefore, the occurrence of mechanical distension that is detected by FOT at end-expiration may not be directly related to the amount of over-aerated volume measured by CT.

In this study we used a model of ALI where natural surfactant is removed from the alveolar space by repetitive sequences of bronchial lavage/drainage [3]. This model is characterised by atelectasis resulting from distal airway collapse with much less contribution of inflammation and oedema [23, 39, 40]. The lung is easily recruitable, and the model may thus more closely mimic the clinical conditions of surfactant deficiency in premature neonates rather than the typical ARDS seen in adult intensive care units. In human ARDS, PEEP-induced lung re-aeration probably results from the displacement of the gas-liquid interface distally in the alveolar space, and it is unlikely that PEEP acts by exceeding hypothetical 'threshold opening pressures' [28, 29]. Even if these mechanisms of lung volume recruitment are quite different, the mechanical consequences on input impendance (Z_{in}) measurements are likely similar.

Nevertheless, an important advantage of FOT at 5 Hz is that it is not affected by the spontaneous breathing of the patient, as confirmed by the results of several studies [11, 12, 14]. Moreover, FOT at 5 Hz has been successfully applied during continuous positive airway pressure (CPAP) [13] and non-invasive mechanical ventilation in COPD patients. Future investigations should address PEEP titration by FOT in patients on pressure support.

Another attractive feature of this technique is that it allows measurements of within-breath changes of respiratory mechanics [13, 14]. This is potentially useful during mechanical ventilation to assess intra-tidal recruitment

Table 1 Haemodynamic variables, CT volumes and respiratory mechanics parameters at open lung PEEP ($PEEP_{ol}$), and two steps before and two steps after $PEEP_{ol}$

	$PEEP_{ol}$ + 4	$PEEP_{ol}$ + 2	$PEEP_{ol}$	$PEEP_{ol}$ − 2	$PEEP_{ol}$ − 4
Haemodynamics					
HR (bpm)	139.7 ± 37.2*	132.4 ± 36.7	127.4 ± 29.5	122.3 ± 28.5**	120.6 ± 24.8*
M_{AP} (mmHg)	88 ± 13.1	85.7 ± 15.1	87.4 ± 14.2	86.6 ± 12.0	86.9 ± 10.5
M_{PAP} (mmHg)	31.3 ± 6.4**	30.1 ± 5.7*	29.3 ± 6.0	27.7 ± 5.5	28.6 ± 4.7
CT volumes					
V_{tiss} (ml)	831.35 ± 77.78	824.23 ± 78.29	817.78 ± 87.74	800.03 ± 89.22*	769.71 ± 96.20**
V_{gas} (ml)	1,180.58 ± 62.70**	1,055.08 ± 61.98**	926.23 ± 65.51	755.64 ± 83.08**	603.64 ± 53.93**
V_{NA} (ml)	2.42 ± 0.56*	2.73 ± 0.73*	3.47 ± 1.16	5.73 ± 1.80**	9.43 ± 2.79**
V_{tissNA}%	5.59 ± 1.24%	5.90 ± 1.47*	7.01 ± 2.22	10.60 ± 3.07**	16.20 ± 4.39**
V_{PA} (ml)	400.95 ± 130.83**	464.23 ± 132.34**	541.17 ± 132.42	614.66 ± 99.90**	616.45 ± 74.56*
V_{tissPA}%	29.66 ± 7.97**	34.67 ± 8.29**	41.10 ± 7.84	48.88 ± 6.91**	52.42 ± 4.43**
V_A (ml)	1,558.64 ± 108.16**	1,360.58 ± 108.41**	1,139.37 ± 97.29	848.37 ± 115.85**	622.66 ± 58.39**
V_{tissA}%	63.15 ± 6.04**	57.80 ± 6.95**	50.26 ± 6.86	38.93 ± 6.36**	30.12 ± 4.27**
V_{oA} (ml)	3.86 ± 1.68*	3.19 ± 0.99*	2.75 ± 0.78	2.90 ± 1.38	2.33 ± 0.84
V_{tissOA}%	0.02 ± 0.01*	0.01 ± 0.01*	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.00*
Mechanics					
R_{rs} (cmH_2O·s/l)	1.87 ± 0.31	1.88 ± 0.36*	1.92 ± 0.38	2.10 ± 0.39**	2.29 ± 0.47**
X_{rs} (cmH_2O·s/l)	−0.68 ± 0.20**	−0.55 ± 0.23*	−0.50 ± 0.22	−0.68 ± 0.25**	−0.84 ± 0.22**

HR Heart rate, M_{AP} mean arterial pressure, M_{PAP} mean pulmonary arterial pressure, V_{tiss} tissue volume, V_{gas} gas volume, V_{NA} non-aerated volume, V_{tissNA}% percentage of non-aerated tissue, V_{PA} - poorly aerated volume, V_{tissPA}% percentage of poorly aerated tissue, V_A aerated volume, V_{tissA}% percentage of aerated tissue, V_{OA} over-aerated volume, V_{tissOA}% percentage of over-aerated tissue, R_{rs} respiratory system resistance, X_{rs} respiratory system reactance

* $p < 0.05$, ** $p < 0.01$ with respect to $PEEP_{ol}$

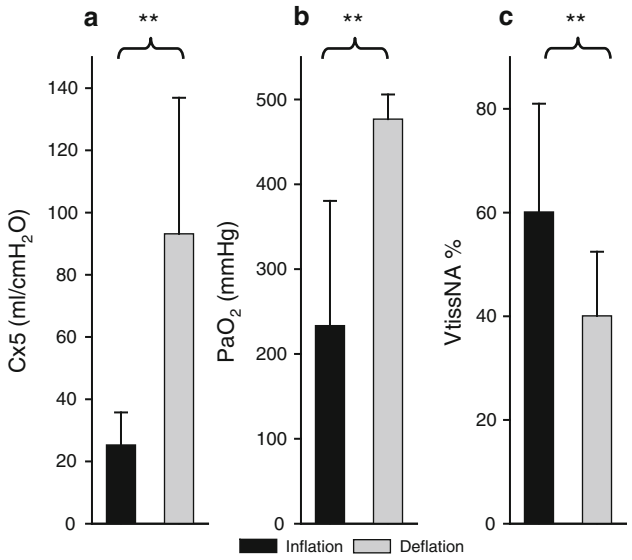

Fig. 4 Oscillatory compliance (C_{X5}), oxygenation (PaO_2) and percentage amount of non-aerated tissue (V_{tissNA}%) at open lung PEEP ($PEEP_{ol}$) (*grey bars*) and at the same PEEP value on the inflation limb of the curve (*black bars*). **$p < 0.01$

and over-distension. In the present study we reported only values of X_{rs} measured at end-expiration because they are more appropriate to the aim of detecting the minimum level of PEEP able to prevent lung volume derecruitment. Future studies are required in order to validate FOT measurements at end-inspiration and to investigate whether intra-tidal changes in FOT parameters can be used to identify cyclic recruitment and over-distension to guide the clinician in the choice of ventilatory settings.

Finally, even if there is clear evidence that an appropriate ventilation optimisation strategy based on measurement of lung mechanics reduced inflammatory markers in ARDS patients compared to oxygenation-based ventilation tailoring [35], future studies are needed to evaluate if an X_{rs}-based optimisation strategy performs better than the other approaches in terms of inflammatory response.

Conclusion

This study demonstrates that the measurement of X_{rs} by FOT during a decreasing PEEP trial identifies the lowest PEEP able to maintain the lung recruited as confirmed by whole-lung CT scans in a surfactant-depletion model of ALI.

Considering that FOT is non-invasive, that it can be easily integrated in commercial mechanical ventilators and that the computation of X_{rs} can be automated, this technology is potentially useful for optimising PEEP during mechanical ventilation of ALI/ARDS patients.

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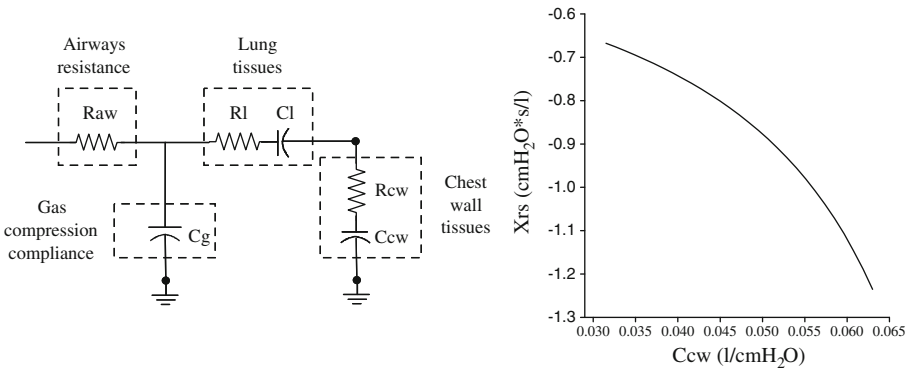

Fig. 5 *Left* Lumped parameter model of the respiratory system. *Raw* Airways resistance, *Cg* gas compression compliance, *Rl* lung tissue resistance, *Cl* lung tissue compliance, *Rcw* chest wall tissue resistance, *Ccw* chest wall tissue compliance. *Right* Reactance changes as a function of chest wall compliance when C_{cw} is reduced by one-half

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Appendix 1

Effect of chest wall compliance

To quantify the effect of chest wall compliance changes on X_{rs} changes we used a simple lumped parameter model of the respiratory system as in [10] (see Fig. 5, left). Briefly, an airway resistance compartment (R_{aw}) leads to a gas compression compliance (C_g) in parallel with the tissue compartment. The tissue compartment has separate properties for the lung and chest wall tissues. Specifically, R_{aw} was set to 5.0 cmH_2O s/l [9], lung tissue resistance (R_l) to 0 (no Newtonian component to parenchymal tissues), and chest wall resistance (R_{cw}) to 1.0 cm H_2O s/l [21]. Assuming an FRC of approximately 800 ml, C_g was set to 0.0008 l/cmH_2O. The compliances of lung tissue and chest wall were set equal to $C_l = 0.05$ and $C_{cw} = 0.063$ l/cmH_2O, respectively [8]. With these values, the model provided an X_{rs} of -0.67 cmH_2O s/l. Considering that an increase in PEEP of 40 cmH_2O could result in a C_{cw} reduction up to 50% of its value at FRC (as shown in [8]), we estimated the value of X_{rs} when C_{cw} was reduced by one-half. In this condition, X_{rs} was -1.23 cmH_2O s/l (see Fig. 5, right). In summary, the expected impact of C_{cw} on X_{rs} is 0.56 cmH_2O s/l over a range of 40 cmH_2O, which means, on average, 0.014 cmH_2O s/l per cmH_2O PEEP change. Considering that when PEEP was reduced by 2 cmH_2O from $PEEP_{ol}$, X_{rs} was reduced by 0.18 cmH_2O (Fig. 3), we can conclude that the contribution of C_{cw} changes to X_{rs} changes during the PEEP trial was negligible compared to the contribution of recruitment/derecruitment.

References

1. Bakker ME, Stolk J, Putter H, Shaker SB, Parr DG, Piitulainen E, Russi EW, Dirksen A, Stockley RA, Reiber JH, Stoel BC (2005) Variability in densitometric assessment of pulmonary emphysema with computed tomography. Invest Radiol 40:777–783
2. Bellardine Black CL, Hoffman AM, Tsai LW, Ingenito EP, Suki B, Kaczka DW, Simon BA, Lutchen KR (2007) Relationship between dynamic respiratory mechanics and disease heterogeneity in sheep lavage injury. Crit Care Med 35:870–878
3. Berggren P, Lachmann B, Curstedt T, Grossmann G, Robertson B (1986) Gas exchange and lung morphology after surfactant replacement in experimental adult respiratory distress syndrome induced by repeated lung lavage. Acta Anaesthesiol Scand 30:321–328
4. Carvalho AR, Jandre FC, Pino AV, Bozza FA, Salluh J, Rodrigues R, Ascoli FO, Giannella-Neto A (2007) Positive end-expiratory pressure at minimal respiratory elastance represents the best compromise between mechanical stress and lung aeration in oleic acid induced lung injury. Crit Care 11:R86
5. Carvalho AR, Jandre FC, Pino AV, Bozza FA, Salluh JI, Rodrigues R, Soares JH, Giannella-Neto A (2006) Effects of descending positive end-expiratory pressure on lung mechanics and aeration in healthy anaesthetized piglets. Crit Care 10:R122
6. Carvalho AR, Spieth PM, Pelosi P, Vidal Melo MF, Koch T, Jandre FC, Giannella-Neto A, de Abreu MG (2008) Ability of dynamic airway pressure curve profile and elastance for positive end-expiratory pressure titration. Intensive Care Med 34:2291–2299
7. Dambrosio M, Roupie E, Mollet JJ, Anglade MC, Vasile N, Lemaire F, Brochard L (1997) Effects of positive end-expiratory pressure and different tidal volumes on alveolar recruitment and hyperinflation. Anesthesiology 87:495–503
8. De RE, Liu JM, Blomquist S, Dahm PL, Thorne J, Jonson B (2001) Elastic properties of the lung and the chest wall in young and adult healthy pigs. Eur Respir J 17:703–711

9. Dellaca RL, Andersson OM, Zannin E, Kostic P, Pompilio PP, Hedenstierna G, Pedotti A, Frykholm P (2009) Lung recruitment assessed by total respiratory system input reactance. Intensive Care Med 35(12):2164–2172
10. Dellaca RL, Black LD, Atileh H, Pedotti A, Lutchen KR (2004) Effects of posture and bronchoconstriction on low-frequency input and transfer impedances in humans. J Appl Physiol 97:109–118
11. Dellaca RL, Duffy N, Pompilio PP, Aliverti A, Koulouris NG, Pedotti A, Calverley PM (2007) Expiratory flow limitation detected by forced oscillation and negative expiratory pressure. Eur Respir J 29:363–374
12. Dellaca RL, Pompilio PP, Walker PP, Duffy N, Pedotti A, Calverley PM (2009) Effect of bronchodilation on expiratory flow limitation and resting lung mechanics in COPD. Eur Respir J 33:1329–1337
13. Dellaca RL, Rotger M, Aliverti A, Navajas D, Pedotti A, Farre R (2006) Noninvasive detection of expiratory flow limitation in COPD patients during nasal CPAP. Eur Respir J 27:983–991
14. Dellaca RL, Santus P, Aliverti A, Stevenson N, Centanni S, Macklem PT, Pedotti A, Calverley PM (2004) Detection of expiratory flow limitation in COPD using the forced oscillation technique. Eur Respir J 23:232–240
15. Dreyfuss D, Saumon G (1998) Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 157:294–323
16. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G (2006) Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 354:1775–1786
17. Gattinoni L, Caironi P, Pelosi P, Goodman LR (2001) What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med 164:1701–1711
18. Gattinoni L, Pelosi P, Crotti S, Valenza F (1995) Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 151:1807–1814
19. Grasso S, Stripoli T, Sacchi M, Trerotoli P, Staffieri F, Franchini D, De M, Valentini V, Pugliese P, Crovace A, Driessen B, Fiore T (2009) Inhomogeneity of lung parenchyma during the open lung strategy: a computed tomography scan study. Am J Respir Crit Care Med 180:415–423
20. Grasso S, Terragni P, Mascia L, Fanelli V, Quintel M, Herrmann P, Hedenstierna G, Slutsky AS, Ranieri VM (2004) Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. Crit Care Med 32:1018–1027
21. Guérin C, Levrat A, Pontier S, Annat G (2008) A study of experimental acute lung injury in pigs on zero end-expiratory pressure. Vet Anaesth Analg 35:122–131
22. Guttmann J, Eberhard L, Fabry B, Zappe D, Bernhard H, Lichtwarck-Aschoff M, Adolph M, Wolff G (1994) Determination of volume-dependent respiratory system mechanics in mechanically ventilated patients using the new SLICE method. Technol Health Care 2:191
23. Hafner D, Germann PG, Hauschke D (1998) Effects of rSP-C surfactant on oxygenation and histology in a rat-lung-lavage model of acute lung injury. Am J Respir Crit Care Med 158:270–278
24. Hickling KG (2001) Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. Am J Respir Crit Care Med 163:69–78
25. Kaczka DW, Ingenito EP, Lutchen KR (1999) Technique to determine inspiratory impedance during mechanical ventilation: implications for flow limited patients. Ann Biomed Eng 27:340–355
26. Kano S, Lanteri CJ, Duncan AW, Sly PD (1994) Influence of nonlinearities on estimates of respiratory mechanics using multilinear regression analysis. J Appl Physiol 77:1185–1197
27. Malbouisson LM, Muller JC, Constantin JM, Lu Q, Puybasset L, Rouby JJ (2001) Computed tomography assessment of positive end-expiratory pressure-induced alveolar recruitment in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 163:1444–1450
28. Martynowicz MA, Minor TA, Walters BJ, Hubmayr RD (1999) Regional expansion of oleic acid-injured lungs. Am J Respir Crit Care Med 160:250–258
29. Martynowicz MA, Walters BJ, Hubmayr RD (2001) Mechanisms of recruitment in oleic acid-injured lungs. J Appl Physiol 90:1744–1753
30. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L (2008) Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 299:646–655
31. Parker JC, Hernandez LA, Peevy KJ (1993) Mechanisms of ventilator-induced lung injury. Crit Care Med 21:131–143
32. Puybasset L, Cluzel P, Gusman P, Grenier P, Preteux F, Rouby JJ (2000) Regional distribution of gas and tissue in acute respiratory distress syndrome. I. Consequences for lung morphology. CT Scan ARDS Study Group. Intensive Care Med 26:857–869
33. Puybasset L, Gusman P, Muller JC, Cluzel P, Coriat P, Rouby JJ (2000) Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. CT Scan ARDS Study Group, Adult Respiratory Distress Syndrome. Intensive Care Med 26:1215–1227
34. Ranieri VM, Giuliani R, Fiore T, Dambrosio M, Milic-Emili J (1994) Volume-pressure curve of the respiratory system predicts effects of PEEP in ARDS: “occlusion” versus “constant flow” technique. Am J Respir Crit Care Med 149:19–27
35. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54–61
36. Rouby JJ, Puybasset L, Cluzel P, Richecoeur J, Lu Q, Grenier P (2000) Regional distribution of gas and tissue in acute respiratory distress syndrome. II. Physiological correlations and definition of an ARDS Severity Score. CT Scan ARDS Study Group. Intensive Care Med 26:1046–1056
37. Rouby JJ, Puybasset L, Nieszkowska A, Lu Q (2003) Acute respiratory distress syndrome: lessons from computed tomography of the whole lung. Crit Care Med 31:S285–S295
38. Slutsky AS, Ranieri VM (2000) Mechanical ventilation: lessons from the ARDSNet trial. Respir Res 1:73–77
39. Spragg RG, Smith RM, Harris K, Lewis J, Hafner D, Germann P (2000) Effect of recombinant SP-C surfactant in a porcine lavage model of acute lung injury. J Appl Physiol 88:674–681

40. Steinberg J, Schiller HJ, Halter JM, Gatto LA, Dasilva M, Amato M, McCann UG, Nieman GF (2002) Tidal volume increases do not affect alveolar mechanics in normal lung but cause alveolar overdistension and exacerbate alveolar instability after surfactant deactivation. Crit Care Med 30:2675–2683
41. Suarez-Sipmann F, Bohm SH, Tusman G, Pesch T, Thamm O, Reissmann H, Reske A, Magnusson A, Hedenstierna G (2007) Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study. Crit Care Med 35:214–221
42. Suter PM, Fairley B, Isenberg MD (1975) Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292:284–289
43. Takeuchi M, Goddon S, Dolhnikoff M, Shimaoka M, Hess D, Amato MB, Kacmarek RM (2002) Set positive end-expiratory pressure during protective ventilation affects lung injury. Anesthesiology 97:682–692
44. Vieira SR, Nieszkowska A, Lu Q, Elman M, Sartorius A, Rouby JJ (2005) Low spatial resolution computed tomography underestimates lung overinflation resulting from positive pressure ventilation. Crit Care Med 33:741–749
45. Vieira SR, Puybasset L, Richecoeur J, Lu Q, Cluzel P, Gusman PB, Coriat P, Rouby JJ (1998) A lung computed tomographic assessment of positive end-expiratory pressure-induced lung overdistension. Am J Respir Crit Care Med 158:1571–1577