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EXPERIMENTAL

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Lung recruitment assessed by total respiratory system input reactance

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Abstract *Purpose:* ALI and ARDS are associated with lung volume derecruitment, usually counteracted by PEEP and recruitment maneuvers (RM), which should be accurately tailored to the patient's needs. The aim of this study was to investigate the possibility of monitoring the amount of derecruited lung by the forced oscillation technique (FOT). *Methods:* We studied six piglets (26 ± 2.5 kg) ventilated by a mechanical ventilator connected to a FOT device that produced sinusoidal pressure forcing at 5 Hz. The percentage of non-aerated lung tissue (V_{tiss}NA%) was measured by whole-body CT scans at end-expiration with zero end-expiratory pressure. Respiratory system oscillatory input reactance (X_{rs}) was measured simultaneously to CT and used to derive oscillatory compliance (C_{X5}), which we used as an index of recruited lung. Measurements were performed at baseline and after several interventions in the following sequence: mono-lateral reabsorption atelectasis, RM, bi-lateral derecruitment induced by broncho-alveolar lavage and a second RM. *Results:* By pooling data from all experimental conditions and all pigs, C_{X5} was linearly correlated to V_{tiss}NA% ($r^2 = 0.89$) regardless of the procedure used to de-recruit the lung (reabsorption atelectasis or pulmonary lavage). Separate correlation analysis on single pigs showed similar regression equations, with an even higher coefficient of determination ($r^2 = 0.91 \pm 0.07$). *Conclusion:* These results suggest that FOT and the measurement of C_{X5} could be a useful tool for the non-invasive measurement of lung volume recruitment/derecruitment.

Keywords Forced oscillation technique · ALI/ARDS · Mechanical ventilation · PEEP · Respiratory mechanics

Introduction

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are associated with atelectasis, disturbed ventilation–perfusion relationship and hypoxemia. Various strategies utilizing positive end expiratory pressure (PEEP) and lung recruitment maneuvers (RM) have been shown to improve lung function, and reduce morbidity and possibly mortality in ARDS [19, 20, 32]. However, there is increasing evidence that excessive mechanical stress leading to overdistention of lung parenchyma induces ventilator-associated lung injury [11, 29, 31]. How lung volume recruitment strategies should be optimized is still not well understood, even if it has been the focus of recent studies [3, 5, 6, 27].

Computed tomography (CT) is currently the gold standard for the quantification of derecruitment and overdistention, but it is expensive and impractical for monitoring the patient in clinical practice.

A possible alternative approach for non-invasive bedside monitoring of recruitment and derecruitment is the assessment of dynamic respiratory mechanics [1, 26, 28]. Dynamic compliance (C_{dyn}) has been shown to be of potential value for the optimization of PEEP in porcine models [5, 6, 27]. However, the estimation of C_{dyn} is strongly affected by both non-linearities and within-breath changes in lung mechanics, and the hidden assumption of a linear relationship between pressure and volume may not be satisfied in diseased lungs [10].

A possible improvement in assessing dynamic respiratory mechanics is provided by the forced oscillation technique (FOT, see ESM for details), which can be easily applied to measure respiratory system impedance (Z_{rs}) during both invasive and non-invasive ventilation [8, 22, 25]. However, up to now the focus of the studies using FOT in ventilated patients has been the measurement of respiratory system resistance (R_{rs}) and how it changes with the forcing frequency [3] or the interpretation of impedance data through mathematical models [22]. These approaches either require that the patient is passively ventilated by the ventilator or have been shown to be poorly sensitive and specific to changes in the mechanics of the periphery of the lung.

In contrast, it has recently been shown that respiratory system reactance (X_{rs}) measured at the oscillatory frequency of 5 Hz is sensitive and specific to changes in peripheral lung mechanics [8, 9, 13].

The aim of the present study was to assess whether X_{rs} measured at 5 Hz could be used to quantify lung volume derecruitment and to evaluate the efficacy of recruitment maneuvers in two different porcine models of lung volume derecruitment, i.e., reabsorption atelectasis and pulmonary lavage.

Part of this work has previously been presented at international meetings and published as abstracts [2, 7].

Methods

We studied six healthy piglets (weight 26 ± 2.5 kg) in a CT-scan room of a university hospital. The study was approved by the local ethics committee.

Animal preparation

Anesthesia was induced by the administration of tiletamine 6 mg kg^{-1}, zolazepam, 6 mg kg^{-1} and xylazine 2.2 mg kg^{-1} i.m., maintained with an infusion of phenobarbital 1 mg/ml, pancuronium 0.032 mg/ml and morphine 0.06 mg ml^{-1} at a rate of 8 ml kg^{-1} h^{-1}. After a bolus injection of fentanyl 10 µg kg^{-1}, the animals were tracheotomized and ventilated through a shortened 8-mm inner diameter endotracheal tube (ETT) (Mallinckrodt, Athlone, Ireland). The animals were initially ventilated using a pressure control mode with peak inspiratory pressure (PIP) and respiratory rate titrated to obtain normocapnea with a tidal volume of 8–10 ml kg^{-1}. PEEP was set to 5 cm H_2O and FiO_2 was 0.5.

Experimental setup and measurements

After preparation each animal was positioned on the bed of a CT scanner. Low amplitude sinusoidal pressure oscillations ($\sim$1.5 cmH_2O peak-to-peak) at 5 Hz were generated by a loudspeaker connected to the inspiratory line of a conventional mechanical ventilator and applied at the inlet of the endotracheal tube. Airflow was measured at the airway opening ($\dot{V}_{\mathrm{ao}}$) and pressure at the tip of the endotracheal tube (P_{tr}) (Fig. 1). All the signals were sampled at 200 Hz, and the frequency response of the system was evaluated [4] and was found to be flat up to at least 20 Hz. The experimental setup for FOT is described in details in the ESM.

Arterial blood gases were sampled at baseline, after single lung ventilation and after lavage to measure PaO_2, $PaCO_2$, pH and SpO_2 (ABL 500, Radiometer, Copenhagen, Denmark).

Systemic and pulmonary arterial pressures, heart rate, SpO_2, end-tidal CO_2 and body temperature were continuously monitored.

Assessment of lung tissues and gas volumes was performed by analyzing whole-body CT scans (Somatom Sensation 16, Siemens, Forchheim, Germany). CT rotation time was 0.5 s at effective 100 mA, 120 kV, collimation 16 × 0.75 and pitch 1.05.

Study protocol

The animals were studied during three different conditions: (1) at baseline, (2) after 10 min of single lung ventilation obtained by advancing the ETT into the mainstem bronchus to induce unilateral left lung atelectasis and (3) after the induction of bilateral ALI by broncho-alveolar lavage performed by repeated instillations of approximately 25 ml kg^{-1} of warm saline solution via the endotracheal tube as previously described [15, 23]. The resulting damage to the lung was confirmed by the rise in pulmonary artery pressure and drop in oxygen saturation. End point for lavage was an increase in mean pulmonary artery pressure to more than 50 mmHg.

For each condition the following measurements/interventions were performed in the following sequence: (1) the animal was initially ventilated in pressure control mode

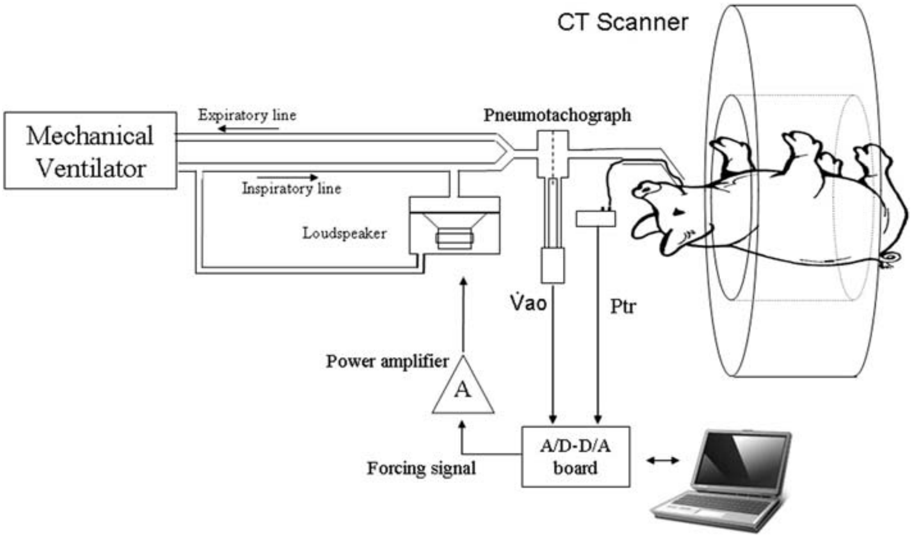


Fig. 1 Experimental setup. Ptr pressure measured at the tip of the tracheal tube; $\dot{V}_{ao}$ airflow measured at the airway opening. The equipment in the figure is not drawn with the same scale

(PIP 18 cmH_2O, PEEP 6 cmH_2O, T_i 1 s, RR 20 bpm and FiO_2 1.0) for at least 15 min to get stable conditions, then the FiO_2 was lowered to 0.21 for 2 min, and the first CT scan was recorded; (2) a recruitment maneuver (RM) was performed by increasing PIP to 40 cmH_2O and PEEP to 20 cmH_2O for 2 min with a RR of 10 bpm, a T_i/T_{tot} of 0.6 and a Fi$O_2 = 1.0$; (3) the original ventilator settings were restored with a FiO_2 of 0.21 for 3 min, and a third CT scan was recorded to assess the efficacy of the RM.

Flow and pressure signals were recorded for the full duration of the experiment, which lasted approximately 100 min, and forced oscillations were continuously applied to the respiratory system.

CT scans were performed during end-expiratory pauses at PEEP = 0 allowing at least 4–5 s of deflation before starting the scan.

Data analysis

Lung mechanics

The estimation of Z_{rs} was obtained from the flow and pressure signals by a least-squares algorithm described elsewhere [9, 14].

To quantify lung volume recruitment/derecruitment, we neglected the contribution of I_{rs} and defined C_{X5} as the oscillatory compliance computed from X_{rs} measured at 5 Hz by FOT (see ESM for details):

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

Impedance data were computed for the full duration of the experiment, producing a continuous tracing of R_{rs}, X_{rs} and C_{X5}. These values were averaged over the periods of expiratory hold needed to perform the CT scans providing a single impedance data point for each CT.

C_{dyn} was calculated by fitting the equation of motion of the respiratory system to P_{tr} and $\dot{V}_{ao}$ data by the least-squares method [16] on approximately 5–10 breaths immediately preceding the CT scan. Lung volume (V) was obtained by numerical integration of $\dot{V}_{ao}$.

Computed tomography analysis

Images were reconstructed with 8-mm slice thickness using a standard body reconstruction filter (B41f, Siemens notation). The images were analyzed using dedicated software (Maluna, Mannheim Lung Analyzing Tool, version 2.02, Mannheim, Germany). The lung contours were manually traced in all the slices to define the regions of interest. The total lung volume was subdivided into overaerated (OA −1,000 to −900 Hounsfield units, HU), normally aerated (−900 to −500 HU), poorly aerated (PA −500 to −100 HU) and non-aerated (NA −100 to +100 HU) volumes as suggested previously [12, 31]. Lung gas (V_{gas}) and tissue (V_{tiss}) volumes were calculated using standard equations [12] for both the whole lung and for each aeration compartment. In this study the amount of derecruited lung was quantified as the volume of tissue in the nonaerated region and expressed as a percentage of total tissue volume as follows:

$$V_{tiss}\mathrm{NA\%} = \frac{V_{tiss}\mathrm{NA}}{V_{tiss}} \times 100 \qquad (2)$$

We chose to express the changes in the recruited lung as changes in non-aerated tissue and not in the total gas volume or in the aerated volume as the latter could also change as a consequence of an increase in alveolar size without changes in the number of recruited alveolar units.

Statistical analysis

Data are expressed as mean ± SD. The relationship between V_{tiss}NA% and C_{X5} and between V_{tiss}NA% and C_{dyn} was evaluated by linear regression analysis, and the determination coefficient (r^2) was calculated. As there were only five different experimental conditions for each animal, we performed the linear regression analysis both intra-individually and, in order to improve statistical reliability, also by pooling all data together.

Results

Lung collapse of different severity and distribution was induced by single lung ventilation and saline lavage. During single lung ventilation V_{tiss} did not change, while V_{tot} reduced mainly due to the development of oxygen reabsorption atelectasis. The subsequent recruitment maneuver was able to restore V_{tot} to values similar to baseline. During saline lavage V_{tot} did not change, but V_{gas} was reduced by alveolar flooding, as indicated by the increase of V_{tiss}. Even if the amount of lung collapse was different after the two interventions, blood gas data showed similar changes compared to baseline (Table 1).

Figure 2 shows how the two interventions affected the total amount of the differently aerated regions (left panel) and how the percentage changes in aeration compartments were distributed in the two lungs (right panel). All CT scans were performed at ZEEP, leading to no significant amounts of over-aerated lung observed in any experimental condition.

Figure 3 shows a CT slice for each experimental condition together with V_{tiss}NA% and C_{X5} from one representative animal. After the single-lung ventilation trial, we observed derecruitment in the dependent region of the non-ventilated lung (left lung atelectasis), an increase in the V_{tiss}NA% and a decrease in C_{X5}. A subsequent recruitment maneuver opened up the lung efficiently and CT data; V_{tiss}NA% and C_{X5} returned to baseline values. The saline lavage induced bilateral lung volume derecruitment, illustrated by the increase of V_{tiss}NA% and the reduction in C_{X5}. This time, the recruitment maneuver was less successful, and CT data and C_{X5} did not return to baseline values.

In Table 1 the average values for V_{tiss}NA%, R_{rs}, X_{rs} and C_{X5} are also reported for each experimental condition. Left lung atelectasis caused an increase in R_{rs} and a decrease in X_{rs} and, consequently, also in C_{X5}. With lung recruitment, changes in R_{rs} were minimal, while C_{X5} increased to near their baseline values. Saline lavage caused more marked changes in C_{X5} than single lung ventilation with left lung atelectasis. C_{X5} fell in proportion to the increase in V_{tiss}NA%.

In Fig. 4 R_{rs} and X_{rs} are plotted versus V_{tiss}NA% by pooling data points from all piglets and conditions to evaluate how they change during lung volume derecruitment. R_{rs} tends to increase with V_{tiss}NA%, but the relationship is very scattered. On the contrary, the X_{rs}–V_{tiss}NA% plot shows a very clear hyperbolic relationship ($y = 1/x$), suggesting a linear relationship between V_{tiss}NA% and C_{X5} (as C_{X5} is inversely proportional to X_{rs}, see Eq. 1). This is clearly shown by Fig. 5 in which C_{X5} is plotted versus V_{tiss}NA%, again pooling data points from all piglets and conditions. The relationship between C_{dyn} and V_{tiss}NA% is also shown for comparison. As the compliance of the respiratory system is frequency dependent, numerical values of C_{X5} (which is measured at 5 Hz) are very different from the ones of C_{dyn} (measured at breathing frequency, 0.5–0.7 Hz). C_{X5} and V_{tiss}NA% show a strong linear correlation ($r^2 = 0.87$), while the

Table 1 CT volumes, blood gases and respiratory mechanics at different protocol steps (baseline, left lung atelectasis, after recruitment maneuver, after lavage and after recruitment maneuver, after lavage)

	Baseline	Left lung atelectasis	After RM	After lavage	After RM, after lavage
CT volumes					
V_{gas} (ml)	302.6 ± 65.2	221.5 ± 51.8	287.2 ± 59.9	130.2 ± 33.7	147.4 ± 40.4
V_{tiss} (ml)	542.7 ± 70.3	567.4 ± 98.5	577.5 ± 71.6	718.1 ± 86.5	732.4 ± 108.6
V_{tot} (ml)	845.3 ± 92.3	788.9 ± 109.6	864.7 ± 77.3	848.3 ± 101.3	879.9 ± 138.7
V_{tiss}NA%	28.90 ± 9.17	50.86 ± 12.19	31.93 ± 11.20	66.91 ± 7.06	62.52 ± 7.02
Blood gas					
PaO_2 (mmHg)	357.28 ± 77.20	80.77 ± 13.69		82.67 ± 49.68	
$PaCO_2$ (mmHg)	40.72 ± 9.32	90.55 ± 20.76		81.97 ± 18.41	
pH	7.76 ± 0.06	7.15 ± 0.10		7.17 ± 0.10	
Mechanics					
R_{rs} (cmH$_2$O*s/l)	3.78 ± 0.83	4.82 ± 1.77	4.92 ± 1.47	6.96 ± 1.83	7.16 ± 1.28
X_{rs} (cmH$_2$O*s/l)	−4.32 ± 0.70	−8.36 ± 2.56	−4.43 ± 0.84	−11.88 ± 4.20	−11.13 ± 4.01
C_{X5} (ml/cmH$_2$O)	7.54 ± 1.25	4.05 ± 0.98	7.38 ± 1.18	2.97 ± 1.02	3.16 ± 1.03

V_{tot} total volume, V_{gas} gas volume, V_{tiss} tissue volumes, V_{tiss}NA% tissue volume of the non-aerated region as a percentage of total tissue volume, R_{rs} respiratory system resistance, X_{rs} respiratory system reactance, C_{X5} compliance calculated from X_{rs}

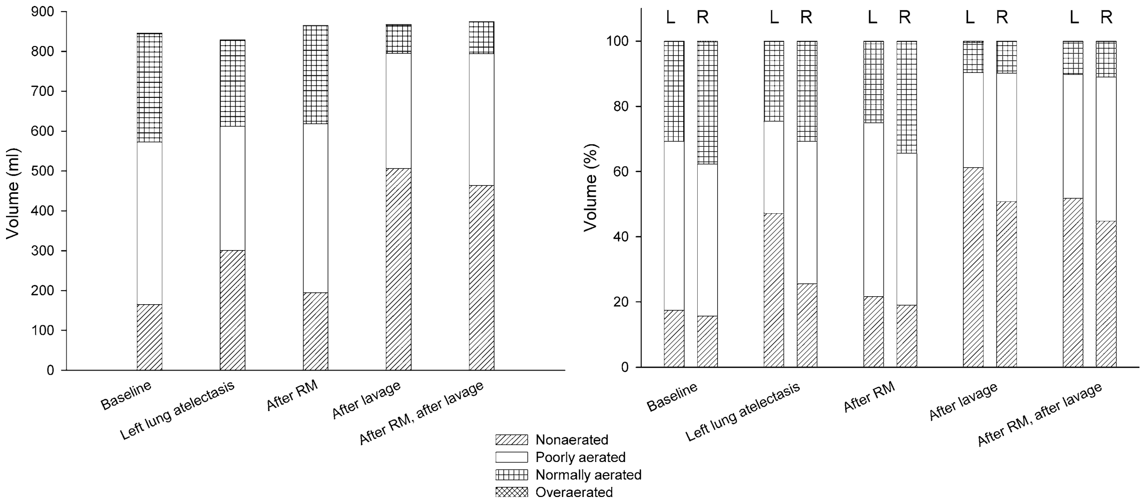
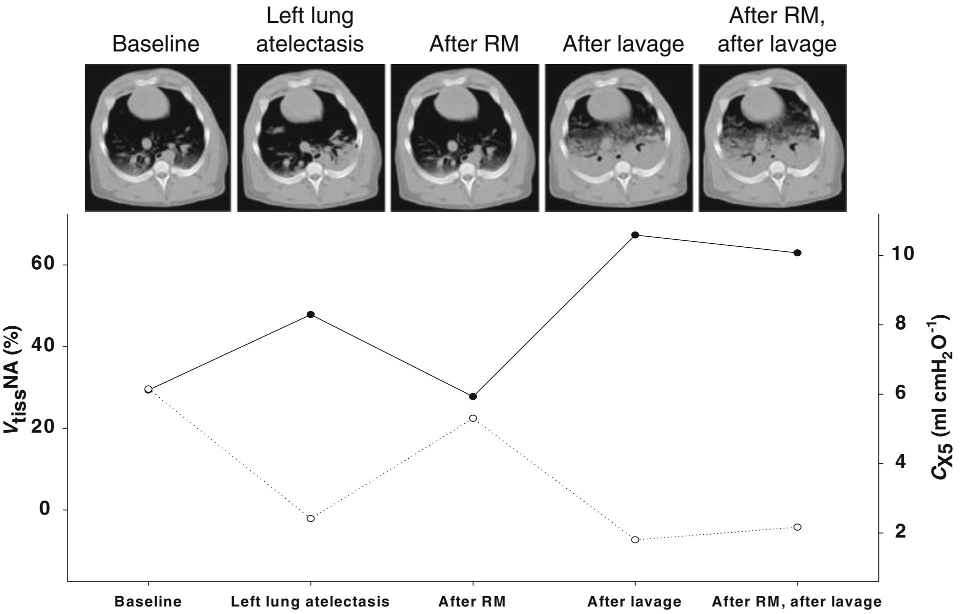


Fig. 2 Subdivision of the whole lung volume into predefined regions at each condition, i.e., at baseline, after the single lung ventilation trial ('left lung atelectasis'), after the first RM ('after RM'), post alveolar lavage ('after lavage') and following the last RM ('after RM, after lavage'). The different regions are non-aerated, poorly aerated, normally aerated and over-aerated, and they are expressed as absolute volume (*left panel*) and as percentage of total lung volume (*right panel*). Data are reported for the whole lung (*left panel*) and subdivided into right and left lungs (*right panel*)

Fig. 3 *Upper panel* CT scans of a representative animal: at baseline, during left lung atelectasis induced by 10 min of single-lung ventilation at 100% oxygen, alter a RM, post broncho-alveolar lavage and after RM after broncho-alveolar lavage. *Lower panel* corresponding non-aerated tissue volume (V_{tiss}NA%, closed symbols, solid line) and C_{X5} (*open symbols*, *dotted line*)



C_{dyn}–V_{tiss}NA% plot also shows a linear relationship, but with a poorer correlation ($r^2 = 0.62$), suggesting that changes in C_{X5} are more sensitive and specific for detecting recruitment or derecruitment of lung volume compared to changes in C_{dyn}.

The same behavior is identified also by the intra-individual regression analysis reported in Table 2. C_{X5} provided not only greater determination coefficients than C_{dyn}, but also higher statistical significance. Moreover, the slopes of the regression lines provided by C_{X5} were more reproducible between animals, with a coefficient of variation of 0.16 compared to 0.29 provided by C_{dyn}.

Discussion

We have evaluated FOT for assessing the development of lung recruitment/derecruitment in two experimental

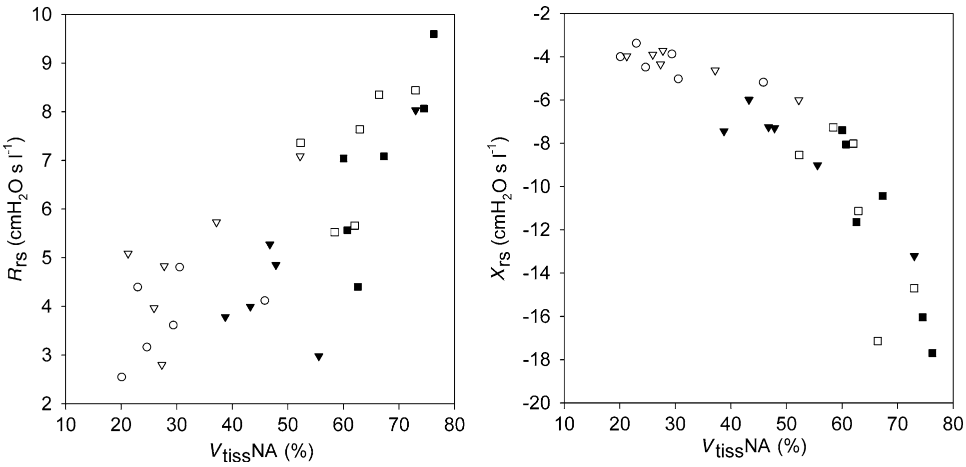


Fig. 4 Respiratory system resistance (R_{rs}) and reactance (X_{rs}) versus non-aerated tissue volume (V_{tiss}NA%) obtained by pooling data points from all pigs and conditions: baseline (*open circles*), left lung atelectasis (*closed triangles*), after RM (*open triangles*), after broncho-alveolar lavage (*closed squares*) and after RM after broncho-alveolar lavage (*open squares*)

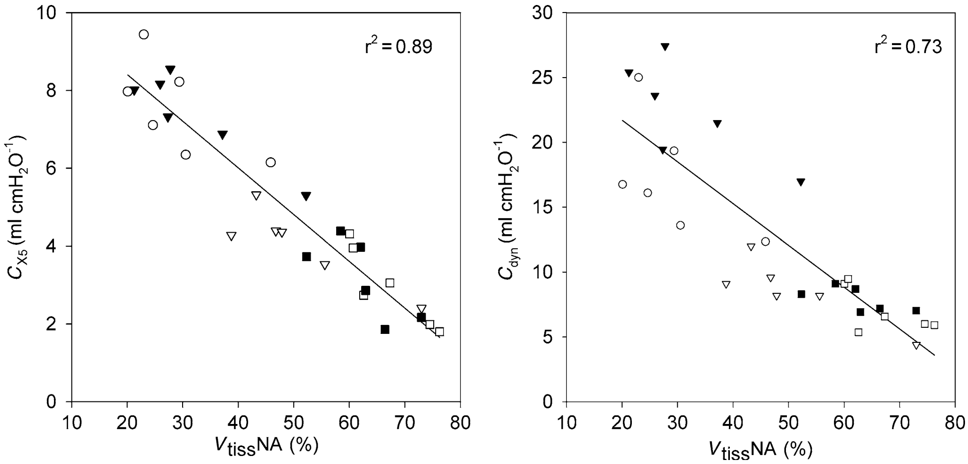


Fig. 5 C_{X5} and dynamic compliance (C_{dyn}) versus non-aerated volume (V_{tiss}NA%) obtained by pooling data points from all pigs and conditions: baseline (*open circles*), left lung atelectasis (*closed triangles*), after RM (*open triangles*), after broncho-alveolar lavage (*closed squares*) and after RM after broncho-alveolar lavage (*open squares*) and linear correlations

Table 2 Linear regression analysis between compliance calculated from X_{rs} (C_{X5}) and percentage volume of non-aerated tissue (V_{tiss}NA%) and between dynamic compliance (C_{dyn}) and V_{tiss}NA% for each animal

Pig no.	C_{X5} versus V_{tiss}NA%			C_{dyn} versus V_{tiss}NA%		
	r^2	*m*	*P*	r^2	*m*	*P*
1	0.87	−1.37	0.02	0.93	−4.88	0.01
2	0.93	−1.22	0.01	0.66	−2.78	NS
3	0.93	−1.15	0.01	0.81	−3.42	0.04
4	0.95	−1.48	0.00	0.82	−4.61	0.03
5	1.00	−1.43	<0.001	0.75	−3.23	0.06
6	0.80	−0.94	0.04	0.67	−2.23	NS
Mean	0.91	−1.27		0.77	−3.53	
SD	0.07	0.20		0.10	1.03	

m Slope, r^2 coefficient of determination

models of collapse—single lung reabsorption atelectasis and bi-lateral surfactant depletion by saline lavage.

The main result of the study was a good (negative) correlation between C_{X5} and V_{tiss}NA%. The linearity of the relationship suggests that C_{X5} is very specific in detecting loss of ventilated lung. Our interpretation of this finding is the following: C_{X5} measures the response of the lung to a pressure stimulus applied at the airway opening. In the simplifying hypothesis that the alveolar units are connected to each other in parallel, the total C_{X5} measures the sum of the compliance of the single alveolar units that are reached by the oscillations and therefore ventilated. Thus, if the distending pressure of the lung is kept constant, changes in C_{X5} should be proportional to the number of alveolar units that are recruited or derecruited.

Advantages, hidden assumptions and limits of C_{X5}

In this study we introduced the definition of a parameter, C_{X5}, derived from X_{rs} to detect and monitor lung volume recruitment and de-recruitment. We chose the forcing frequency of 5 Hz as it is high enough to exclude the low-frequency components typical of the quiet breathing signal, but still low enough to be sensitive changes in lung periphery [9].

Z_{rs} is an overall descriptor of the respiratory system mechanical properties, and therefore its value is affected by several factors other than lung volume recruitment/derecruitment.

First, in our definition of C_{X5} we completely neglected the inertial properties of the respiratory system. This is justified by the fact that, whatever its value is, I_{rs} is mainly related to the geometrical characteristics of proximal airways [24], which are not significantly affected by lung volume recruitment/derecruitment.

Secondly, X_{rs} summarizes the elastic properties of all the components of the respiratory system, including lung tissue and chest wall compliance, and, if these change, also the absolute value of C_{X5} will change.

In this study we found that if we measure C_{X5} before and after an intervention that is mainly affecting lung volume recruitment with a negligible effect on I_{rs} and chest wall compliance, its changes are an accurate and specific quantification of recruitment and de-recruitment. We obtained these experimental conditions by performing all measurements at the same distending pressure (ZEEP) and by studying a homogeneous group of animals. Under these conditions we expect the elastic properties of the alveolar units to be similar at the different protocol steps and the total compliance of the respiratory system to be mainly dependent on the number of alveolar units that are ventilated.

This hypothesis is confirmed not only by the linear relationship found between C_{X5} and V_{tiss}NA% pooling together data from all pigs and conditions, but also by the even greater determination coefficients obtained by considering each single pig separately (Table 2), even if the limited number of experimental conditions undoubtedly makes individual analysis less statistically powerful in comparison to the pooled data.

All these results suggest that even if a single measurement of C_{X5} in a given patient is not highly specific to lung volume recruitment, its changes between before and after an intervention could carry important information on the amount of recruited or derecruited lung volume.

Comparison with C_{dyn}

Several studies evaluated the use of C_{dyn} for PEEP titration. Suarez-Sipman and co-workers [27] studied C_{dyn} during recruitment manuevers followed by stepwise reduction of PEEP in a lavage model of ALI. In a similar design, Carvalho and co-workers [5, 6] compared respiratory system elastance ($E_{rs} = 1/C_{dyn}$) with variations in lung aeration according to CT.

C_{X5} offers three main advantages over C_{dyn} in monitoring lung volume recruitment and derecruitment: first, during the measurement of C_{X5} by FOT, the stimulus applied to the respiratory system induces very small lung volume changes (few ml) with a very short time period (only 0.2 s for a forcing frequency of 5 Hz). In this way the assessment of lung recruitment may be performed at a specific lung volume, minimizing the artifacts due to non-linearities of the respiratory system. On the contrary C_{dyn} is calculated during a whole breath, and this large volume change invalidates the hypothesis of linearity on which the calculation of C_{dyn} is based, especially in diseased lungs.

Second, since C_{X5} may be assessed without altering the patient's breathing pattern and it is not affected by possible spontaneous respiratory muscle activity, it does not require either sedation or the use of an esophageal balloon as for C_{dyn}. In fact, FOT has been successfully applied even during CPAP and non-invasive mechanical ventilation in COPD patients [8].

Third, since C_{X5} may be measured with a high time resolution, it allows the assessment of within-breath changes of lung mechanics. In this way it could be possible to monitor the occurrence of intra-tidal recruitment and intra-tidal over-distension, both of which have a role in ventilator-associated lung injury [21, 29, 30].

Experimental models of lung de-recruitment

Several modeling studies showed that Z_{rs} is affected not only by the reduction of airway caliber, but also by the pattern of distribution of these changes throughout the lung [17, 18]. To be useful in clinical practice, an index of lung volume recruitment/derecruitment should provide information on the amount of lung that has been recruited or derecruited regardless of how the recruitment is distributed. Therefore, the experimental models were chosen to mimic different conditions that regularly occur in anesthesia and intensive care, but still possible to perform in a sequence, with the advantage of sparing animals. The single lung ventilation produced mainly dorsal left-sided atelectasis, which was easily recruitable. The saline lavage induced widespread bilateral collapse, as usually observed in ALI. This model recruits relatively easily with PEEP, but derecruitment will develop again when PEEP is diminished.

Conclusion

In conclusion, C_{X5} is an index of the amount of open and ventilated lung, and thus FOT could be used as a non-invasive tool to monitor the occurrence of recruitment and derecruitment.

In order to be a useful tool for bedside tailoring of mechanical ventilation in ALI/ARDS, C_{X5} should be able to provide a continuous estimation of the amount of lung that is recruited/derecruited by changing PEEP. Thus, future studies are needed in order to validate the use of C_{X5} for long-term monitoring and PEEP titration.

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