EXPERIMENTAL

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Monitoring dead space during recruitment and PEEP titration in an experimental model

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Abstract *Objective:* To test the usefulness of dead space for determining open-lung PEEP, the lowest PEEP that prevents lung collapse after a lung recruitment maneuver. *Design:* Prospective animal study. *Setting:* Department of Clinical Physiology, University of Uppsala, Sweden. *Subjects:* Eight lung-lavaged pigs. *Interventions:* Animals were ventilated using constant flow mode with VT of 6 ml/kg, respiratory rate of 30 bpm, inspiratory-to-expiratory ratio of 1 : 2, and FiO_2 of 1. Baseline measurements were performed at 6 cmH_2O of PEEP. PEEP was increased in steps of 6 cmH_2O from 6 to 24 cmH_2O. Recruitment maneuver was achieved within 2 min at pressure levels of 60/30 cmH_2O for Peak/PEEP. PEEP was decreased from 24 to 6 cmH_2O in steps of 2 cmH_2O and then to 0 cmH_2O. Each PEEP step was maintained for 10 min. *Measurements and results:* Alveolar dead space (VD_{alv}), the ratio of alveolar dead space to alveolar tidal volume (VD_{alv}/VT_{alv}), and the arterial to end-tidal PCO_2 difference (Pa-$_{ET}CO_2$) showed a good correlation with PaO_2, normally aerated areas, and non-aerated CT areas in all animals (minimum–maximum $r^2 = 0.83$–0.99; $p < 0.01$). Lung collapse (non-aerated tissue > 5%) started at 12 cmH_2O PEEP; hence, open-lung PEEP was established at 14 cmH_2O. The receiver operating characteristics curve demonstrated a high specificity and sensitivity of VD_{alv} (0.89 and 0.90), VD_{alv}/VT_{alv} (0.82 and 1.00), and Pa – $_{ET}CO_2$ (0.93 and 0.95) for detecting lung collapse. *Conclusions:* Monitoring of dead space was useful for detecting lung collapse and for establishing open-lung PEEP after a recruitment maneuver.

Keywords Dead space · Lung recruitment · SBT-CO_2 · Atelectasis · Oxygenation · PEEP

Introduction

Acute lung injury (ALI) is characterized by varying degrees of atelectasis and edema [1, 2]. Ventilatory treatment with low airway pressures, low tidal volume, high inspired oxygen fraction, or tracheal suctioning may favor alveolar collapse [3, 4, 5]. Such collapse may also be cyclic with repeated opening and closing of unstable pulmonary units over the respiratory cycle, promoting lung injury and impeding gas exchange [6, 7, 8].

Lung recruitment is a process that refers to the re-aeration of previously collapsed lung areas and can be performed by so-called recruitment maneuvers (RM) [9, 10, 11, 12]. An adequate positive end expiratory pressure (PEEP) remains the cornerstone of any ventilatory approach, since it should prevent end expiratory lung de-recruitment; however, the lowest level of PEEP that avoids de-recruitment and at the same time does not overdistend the lung, thus, "open-lung" PEEP (OL-PEEP), is difficult to determine at bedside [13, 14, 15, 16, 17, 18].

Dead space can be viewed as "wasted ventilation" and its calculation is useful to study the efficiency of ventilation [19, 20, 21]. Dead space variables can reflect changes in lung condition such as collapse and recruitment. Lung overdistension can also be characterized by an increase in VD_{alv} and by a decrease in the exhaled volume of CO_2 per breath [22]. A successful RM decreases the arterial to end-tidal PCO_2 difference (Pa-$_{ET}CO_2$) [21], which in turn reduces the calculated dead space by decreasing the shunt [23, 24]. Some publications support the value of monitoring the relationship between ventilation inefficiency and efficiency during positive pressure ventilation. Suter et al. described how the "best" PEEP closely correlated with the lowest dead space as well as with the highest compliance and oxygen transport in ALI patients [25]. McMahon et al. showed that patients with respiratory failure who responded to PEEP therapy with an increase in oxygenation also showed a decrease in dead space [26]; however, other authors failed to find similar effect on dead space during PEEP titration in this kind of patients [27, 28].

We hypothesized that dead-space variables have a close relationship with collapse-recruitment phenomena within the lungs, and thus, could be useful for monitoring the process of OL-PEEP titration.

The aim of this study was to test this hypothesis in an animal model of surfactant depletion, evaluating dead-space variables on a breath-by-breath basis and comparing these values with continuous arterial oxygenation and computed tomography (CT) images of the lungs.

Methods

The study was approved by the Animal Research Committee of Uppsala University (Sweden). Eight Swedish mixed country breed pigs (weight 29.8 ± 2.1 kg) were premedicated with intramuscular zolazepam-tiletamine (6 mg/kg) and were anesthetized with fentanyl ($2.5\,\mu g\,kg^{-1}\,h$) followed by an infusion of ketamine 25–$50\,mg\,kg^{-1}\,h$, midazolam 90–$180\,\mu g\,kg^{-1}\,h$, fentanyl 3–$6\,\mu g\,kg^{-1}\,h$, and pancuronium 0.25–$0.50\,mg\,kg^{-1}\,h$.

Animals were tracheotomized and mechanically ventilated in supine position through a 7-mm ID endotracheal tube (Mallinckrodt, Atholone, Ireland) using a constant flow volume controlled mode (Servoi, Siemens Elema AB, Solna, Sweden) with a tidal volume (VT) of 6 ml/kg, respiratory rate of 30 breaths/min, PEEP level of 6 cmH$_2$O, an inspiratory: expiratory ratio of 1 : 2, and a FiO$_2$ of 1.

Systemic arterial pressure was monitored invasively via a catheter in the femoral artery. Pulmonary artery pressure and cardiac output were continuously monitored by a 7.5-F pulmonary artery catheter CCOmbo (Edwards Lifesciences LLC, Irvine, Calif.). Arterial blood gases were monitored on-line using the multi-parameter intra-arterial sensor Trendcare (Diametrics Medical Ltd, High Newcombe, UK) inserted into the right carotid artery. In vitro and in vivo calibrations of devices were performed before start of the protocol. Hemodynamic and on-line blood gas parameters were stored in a data acquisition system programmed in LabView (National instruments, Austin, Texas). Independent arterial and mixed venous blood gas samples were analyzed on each PEEP level using an ABL 300 and an OSM 3 (Radiometer, Copenhagen, Denmark). Shunt was calculated using the standard formula for oxygen content in blood [29].

CO$_2$ equipment

Dead space was analyzed by the single breath test of CO_2 (SBT – CO_2), computed by integrating expiratory flow and CO_2 signals [21, 22]. The SBT-CO_2 and standard respiratory mechanics were monitored on a breath-by-breath basis with the CO_2SMO*plus* (Novametrix, Wallinford, Conn.) and recorded using the software A*plus*. The CO_2 measurement was performed by a main-stream sensor using non-dispersive infrared technique (accuracy $\pm\,2$ mmHg and resolution 1 mmHg). Airway flow was measured by a fixed orifice, differential pressure flow sensor (range 2–180 l/min and accuracy > 3%). Instrumental dead space of 10 ml was included in the airway dead-space calculations.

VD_{aw} is the airway dead space determined by Fowler's method [20]. Physiological dead space (VD_{phys}) was calculated using Enghoff's modification of Bohr's formula [19] as:

$$VD_{phys} = (PaCO_2 - P_{AE}CO_2)/PaCO_2 * VT,$$

where $P_{AE}CO_2$ is the mean expired alveolar partial pressure [21, 30]. Then, the ratio of physiological dead space to tidal volume (VD/VT) was calculated as:

$$VD/VT = VD_{phys}/VT$$

VD_{alv} was computed subtracting VD_{aw} from VD_{phys}. The alveolar dead space to alveolar tidal volume ratio (VD_{alv}/VT_{alv}) was then obtained dividing VD_{alv} by alveolar tidal volume (VT_{alv}, i.e., the difference between VT and VD_{aw}). $Pa_{-ET}CO_2$ was defined as the difference between arterial and end-tidal partial pressure of CO_2.

To study lung aeration at the end of each PEEP step, computed tomography (CT) of the chest was used (Somatom Sensation 16, Siemens, Forchheim, Germany). Prior to obtaining a transverse CT slice 2 cm cranial of the right diaphragmatic dome during an end-expiratory hold maneuvers of > 4 s, a scout view was obtained on each PEEP level. Exposure time was 0.75 s at 120 mA and 100 kV. Images were reconstructed with 6-mm slice thickness using a standard body reconstruction filter (Siemens notation: B40s). Attenuations of the pulmonary parenchyma were analyzed using the CT image analysis software Maluna (Mannheim Lung Analyzing Tool, version 2.02, Mannheim, Germany). Regions of interest of lungs were manually delineated taking the inner rib cage and the mediastinal structures as the lung boundaries. We used standard definitions of lung aeration according to the attenuation values in Hounsfield units (HU) [31]. Differ-ently aerated lung regions were classified as non aerated (+100 to –100 HU), poorly aerated (–100 to –500 HU), normally aerated (–500 to –900 HU) and hyperinflated (–900 and –1000 HU), respectively. The percentage of voxels per CT slice showing these predefined four ranges of HU was calculated. To avoid inter-observer variations, the CT analysis was performed by the same investigator who was blinded as to the level of PEEP used.

Protocol

The model was induced by surfactant depletion after lung lavage with 35 ml/kg of warm (37 °C) isotonic saline [32]. Lavages were repeated every 5 min until PaO_2 decreased to values below 100 mmHg (FiO_2 of 1). A final observation period of 1 h was added to assure the stability of the model.

A schematic representation of the protocol is shown in Fig. 1. We studied the following ventilation sequence:

1. Baseline measurement at 6 cmH$_2$O of PEEP. Then, PEEP level was increased in 6 cmH$_2$O steps up to 24 cmH$_2$O.
2. A cycling lung recruitment maneuver, performed in pressure control ventilation reaching maximum pressures of 60/30 cmH$_2$O for PIP/PEEP for 2 min, was performed [32]. Ventilation was then returned to the previous ventilatory setting but with a PEEP of 24 cmH$_2$O. We assumed that this high level of PEEP
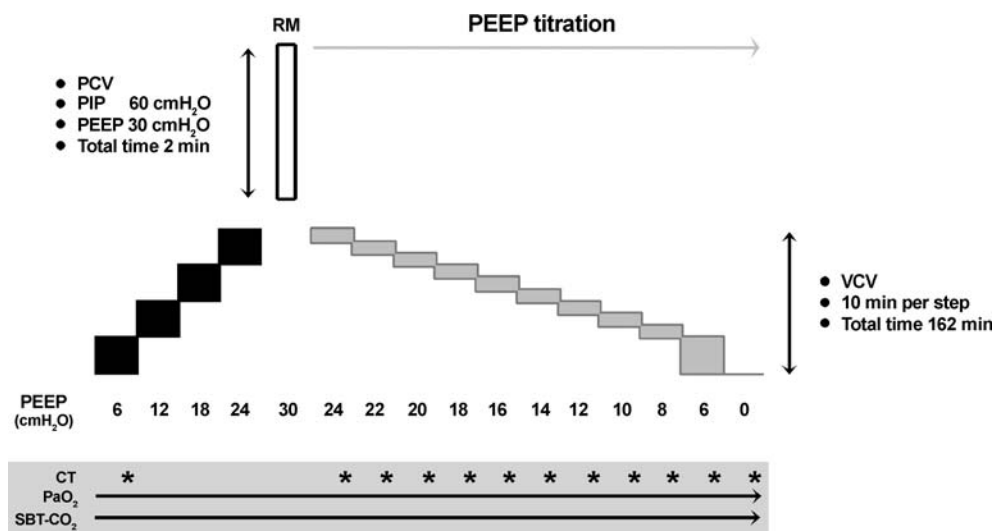

Fig. 1 Protocol design. Baseline measurement was performed at 6 cmH$_2$O of positive end-expiratory pressure (*PEEP*). Then, PEEP was increased in steps of 6 cmH$_2$O of PEEP, from 6 to 24 cmH$_2$O in a volume control mode of ventilation (*VCV*). After PEEP reached 24 cmH$_2$O a recruitment maneuver (*RM*) was performed for 2 min (60 breaths) in a pressure control mode of ventilation (*PCV*) with 60/30 cmH$_2$O of peak inspiratory pressure (*PIP*) and PEEP, respectively. After RM, ventilation was returned to VCV and PEEP was decreased by 2 cmH$_2$O every 10 min starting at 24 cmH$_2$O and going down to 6 cmH$_2$O and finally to ZEEP. Computer tomography images of the chest (CT; *asterisks*) were taken at the eighth minute of each PEEP step. Arterial partial pressure of oxygen (PaO$_2$) and the single-breath test of CO_2(SBT-CO$_2$) were recorded continuously

would surely exceed the OL-PEEP to be determined by the titration method in any of the animals.

3. A descending PEEP titration, where PEEP level was decreased by $2\,cmH_2O$, from 24 to $6\,cmH_2O$ and then to $0\,cmH_2O$. Each PEEP step was maintained for 10 min. In pilot measurements a time lapse of 10 min was enough to reach steady-state conditions in real-time CO_2 and O_2 signals. A complete CO_2 data set was obtained for every breath cycle. Average data from the 30 breaths during the eighth minute of every PEEP step just prior to taking the CT scans and recording the hemodynamic variables represented each PEEP level.

Definition of lung recruitment and collapse

The PaO_2 values $> 400\,mmHg$ [32], an amount of non-aerated zones $< 5\%$, and zones of overly aerated regions $> 85\%$ of the total lung area were considered markers of total lung recruitment and were used to define the "open-lung" condition, i. e., a lung without collapse. During the PEEP trial, we assumed that an increase in non-aerated areas $> 5\%$ defined the start of lung collapse after the RM; therefore, OL-PEEP was defined as the minimum PEEP level that maintained the lungs recruited. Per this definition, OL-PEEP was $2\,cmH_2O$ above the PEEP level at which first signs of collapse occur.

Statistical analysis was performed using MatLab (MatLab, The MathWorks, Inc., Natick, Mass.). Variables were analyzed by ANOVA with Dunnett's post test adjustment taking baseline ($6\,cmH_2O$ of PEEP prior to RM) or $24\,cmH_2O$ of PEEP after RM as reference values. Pearson's correlation coefficient (r^2) between dead-space variables and oxygenation and CT data was calculated. Data are presented as mean and SD or minimum–maximum values. Analysis of the receiver operating characteristics curve (ROC) was used to determine the sensitivity and specificity of each dead space variable in predicting lung derecruitment as pre-defined by a cut-off level $> 5\%$ of non-aerated lung on CT.

Results

Measurements were performed in eight pigs. None of the animals presented barotrauma or died during the protocol. All variables of the protocol are shown in Table 1.

Results revealed a good correlation between PaO_2 and normally aerated (r^2 minimum–maximum: 0.92–0.99; $p < 0.001$) and an inverse correlation between PaO_2 and non-aerated regions (r^2 minimum–maximum: 0.88–0.99; $p < 0.001$), confirming that, in all animals, arterial oxygenation—and thus, the amount of lung tissue available for gas exchange—matched closely with the amount of normally aerated areas. Dead-space variables were closely related to the recruitment-collapse phenomena as observed

Table 1 Dead space variables, PaO_2, normally (NA) and non-aerated areas ($NonA$) during descending PEEP titration. Comparison was done using 6 or $24\,cmH_2O$ of PEEP as reference

PEEP (cmH_2O)	6 before RM	24	22	20	18	16	14	12	10	8	6	0
VD_{aw} (ml)	78±17	101±12	97±12	95±14	92±13†	89±14	88±14	86±14	85±15	85±14	83±15	73±15*
VD_{alv} (ml)	40±11	11±8.4	10±8.2	10±9.9	11±9.9	12±8.6	16±8.0	20±6.8†	23±6.7	27±6.4	30±6.3	52±9.8*
VD_{phys} (ml)	119±12	112±14	107±14	105±15†	103±15	101±14	103±13	106±15	108±13	111±13	113±13	125±10*
VD/VT	0.59±0.1	0.58±.01	0.59±.01	0.58±.01	0.55±.01	0.54±.01	0.54±.02	0.53±.01†	0.52±0.1	0.52±.01	0.53±.01	0.53±.01*
VD_{alv}/VT_{alv}	0.33±0.1	0.08±.01	0.07±.01	0.07±.01	0.07±.01	0.09±.01	0.12±.01	0.16±.01†	0.19±.01	0.23±.01	0.28±.01	0.39±.01
$Pa\text{-}_{ET}CO_2$ (mmHg)	20±6	4.3±3.9	3.9±3.5	3.6±2.8	3.4±2.7	4.0±2.5	5.2±2.6	7.6±3.4†	9.1±3.8	11.5±3.5	14.5±3.6	24.1±5.6
PaO_2 (mmHg)	89±64	556±33	557±26	554±25	544±23	520±47	477±83	408±115†	347±127	273±123	184±91	57±25*
NA (%)	27±4	89±4.4	88±4.8	86±5.2	84±6.9	80±7.5	74±8.1	66±7.0†	59±7.5	48±9.0	36±13	17±5.5*
NonA (%)	38±11	2.3±1.3	2.4±1.6	2.6±1.4	2.4±1.6	2.8±2.1	4.3±3.8	7.1±5.5†	11±7.3	18±8.2	27±10	59±12*

Values are presented as mean and SD

All values were statistically significant when compared with baseline PEEP $6\,cmH_2O$ prior to the recruitment maneuver (RM), except as indicated by asterisk (p = n.s.)

† The first statistical change compared with $24\,cmH_2O$ of PEEP after RM ($p < 0.05$)

Table 2 Data analysis was performed during descending PEEP titration. Value of r^2 in eight pigs is presented as minimum−maximum. p-value of all correlations < 0.05. *NA* normally aerated areas, *NonA* non-aerated areas, *PaO2* partial pressure of O_2 in arterial blood, *VDaw* airway dead space, *VDalv* alveolar dead space, *VDphys* physiological dead space, *VD/VT* physiological dead space to tidal volume ratio, *VDalv/VTalv* alveolar dead space to alveolar tidal volume ratio, ETCO2 end-tidal partial pressure of CO_2, *Pa-ETCO2* arterial to end-tidal PCO_2 difference

|	PaO_2	NA	NonA
VD_{aw} (ml)	0.83/0.99	0.78/0.94	−0.78/0.95
VD_{alv} (ml)	−0.83/0.97	−0.90/0.99	0.84/0.99
VD_{phys} (ml)	−0.72/0.83	−0.66/0.87	0.70/0.95
VD/VT	−0.62/0.80	−0.58/0.74	0.70/0.77
VD_{alv}/VT_{alv}	−0.93/0.98	−0.96/0.98	0.90/0.98
Pa-ETCO2 (mmHg)	−0.90/0.98	−0.92/0.98	0.97/0.99

Table 3 Receiver operator characteristics (ROC) analysis. Sensitivity and specificity of each variable studied during a PEEP reduction trial to diagnose early lung collapse predefined by the cut-off point of $> 5\%$ of non-areated area on CT. *Area* area under the ROC curve

	Sensitivity	Specificity	Area
VD_{aw} (ml)	0.64	0.90	0.87
VD_{alv} (ml)	0.89	0.89	0.96
VD_{phys} (ml)	0.71	0.67	0.73
VD/VT	0.90	0.86	0.95
VD_{alv}/VT_{alv}	1.00	0.82	0.99
Pa-ETCO2 (mmHg)	0.95	0.93	0.99
SHUNT (%)	1.00	0.74	0.94

by CT and PaO_2. During the PEEP titration phase, VD_{alv}, VD_{alv}/VT_{alv}, and Pa-ETCO2 were the dead-space variables that correlated best with the amount of non-aerated tissue (Table 2).

After successful lung recruitment, the "open lung" condition had been reached at 24 cmH2O of PEEP with corresponding mean plateau pressure (P_{plat}) of

41 ± 3.5 cmH2O. Lung collapse during the PEEP trial occurred at a mean PEEP value of 12 cmH2O (P_{plat} of 21 ± 1.6 cmH2O). Dead-space data showed also a significant change at 12 cmH2O of PEEP (Table 1); thus, the "open-lung" condition was maintained during decremental PEEP until a mean PEEP value of 14 cmH2O (P_{plat} of 23 ± 1.2 cmH2O), defining the OL-PEEP in these pigs.

The ROC analysis demonstrated a high specificity and sensitivity of VD_{alv}, VD_{alv}/VT_{alv}, and Pa-ETCO2 for detecting lung collapse, whereas VD_{aw} and VD/VT did not show such good estimations (Fig. 2; Table 3).

Fig. 2 Analysis of the receiver operating characteristic curve (ROC) for dead-space variables and lung collapse as defined by the level of PEEP at which the percentage of non aerated tissue exceeded 5% of the total CT slices. p-value < 0.05 for alveolar dead space (VD_{alv}), alveolar dead space to alveolar tidal volume ratio (VD_{alv}/VT_{alv}), the arterial to end-tidal PCO_2 difference (*Pa-ETCO2*), and physiological dead space (VD_{phys}). *VDaw* airway dead space, *VD/VT* ratio of physiological dead space to tidal volume
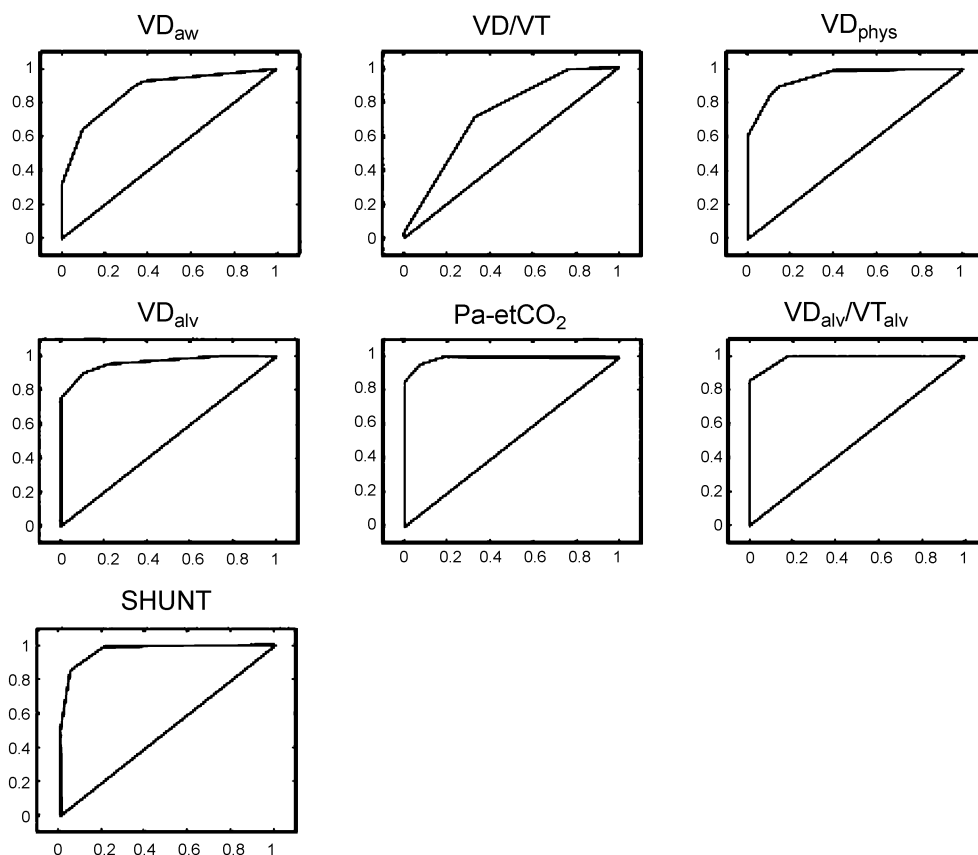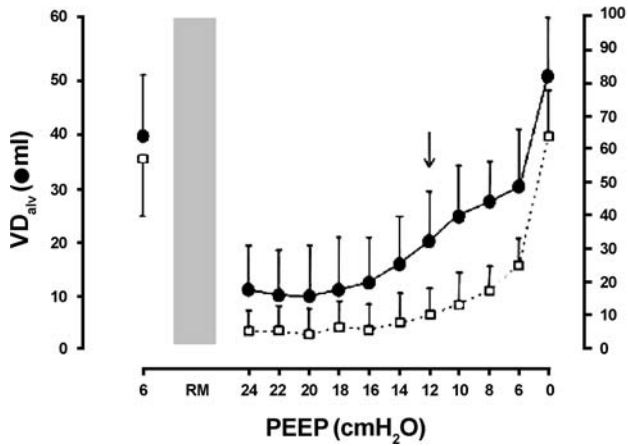
Fig. 3 Behavior of alveolar dead space (VD_{alv}) and shunt during PEEP titration. The *arrow* indicates the lung collapse

Fig. 3 shows the parallel behavior of shunt and VD_{alv}. The changes of VD_{aw} along the protocol are presented as the ratio of VD_{aw}/VT and its relationship with VD/VT and VD_{alv}/VT_{alv} (Fig. 4).

Ventilatory data are shown in Table 4. At levels greater than 20 cmH_2O of PEEP plateau pressures presented values above those recommended [33]; however, according to CT definition less than 0.7% of lung tissue on the CT slices was hyperinflated even at PEEP > 20 cmH_2O. For this reason, hyperinflated areas are not included in the results. In addition, dead-space data did not show a functional alveolar overdistension at 24 cmH_2O of PEEP and corresponding P_{plat} of 41 ± 3.5 cmH_2O, despite known increases in the volume of the conducting airways (Fig. 3; Table 1).
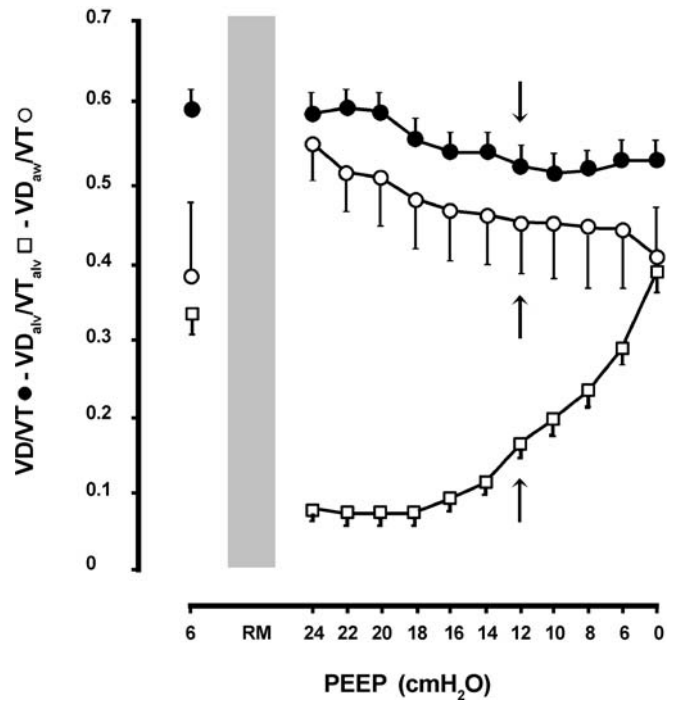

Fig. 4 Ratio of airway dead space to tidal volume (VD_{aw}/VT) during PEEP titration. The effect of airway distension on the ratio of physiological dead space to tidal volume (VD/VT), but not on the ratio of alveolar dead space to alveolar tidal volume (VD_{alv}/VT_{alv}), is clearly visible. *Arrows* indicate the moment of lung collapse

Highest dynamic compliance and lowest dynamic expiratory airway resistance were observed at the OL-PEEP. The opposite findings were observed at lowest and highest PEEP levels.

Table 4 Ventilatory data presented as mean and SD. *PIP* peak inspiratory pressure, P_{plat} plateau pressure, *VT* tidal volume, C_{dyn} dynamic compliance, R_{dyn} expiratory dynamic airway resistance, $PaCO_2$ partial pressure of CO_2 in the arterial blood, $ETCO_2$ end-tidal partial pressure of CO_2

PEEP (cmH_2O)	PIP (cmH_2O)	P_{plat} (cmH_2O)	VT (ml)	C_{dyn} (ml/cmH_2O)	R_{dyn} (ml/cmH_2O/s)	$PaCO_2$ (mmHg)	$ETCO_2$ (mmHg)	pH
6 before RM	29 ± 3.3	28 ± 3.0	181 ± 19	11 ± 1.8	14 ± 9	60 ± 7	39 ± 4	7.24 ± 0.1
24	43 ± 3.9	41 ± 3.5*	183 ± 17*	13 ± 2.0*	11 ± 7	48 ± 5	45 ± 7	7.29 ± 0.2
22	38 ± 3.1†	36 ± 2.8†	186 ± 18*	17 ± 2.8	10 ± 6	47 ± 5	45 ± 4	7.29 ± 0.1
20	34 ± 2.9†	32 ± 1.9†	187 ± 17*	20 ± 2.9†	9 ± 6†	46 ± 5	44 ± 5	7.30 ± 0.1
18	30 ± 2.1*†	28 ± 1.1*†	185 ± 17*	22 ± 2.6†	8 ± 5†	45 ± 4†	43 ± 4†	7.31 ± 0.1
16	27 ± 1.8*†	25 ± 1.0*†	189 ± 16*	25 ± 2.9†	8 ± 5†	45 ± 5†	42 ± 3*†	7.31 ± 0.0
14	25 ± 1.8†	23 ± 1.2†	189 ± 17*	26 ± 3.5†	8 ± 5†	46 ± 5†	41 ± 3*†	7.32 ± 0.1
12	24 ± 1.7†	21 ± 1.6†	188 ± 18*	25 ± 3.9†	8 ± 5†	47 ± 6	39 ± 3*†	7.31 ± 0.1
10	23 ± 1.9†	20 ± 1.8†	189 ± 18*	23 ± 3.9†	9 ± 5†	48 ± 6	39 ± 3*†	7.30 ± 0.1
8	22 ± 2.1†	20 ± 1.9†	188 ± 18*	20 ± 3.3†	9 ± 6	49 ± 5	38 ± 3*†	7.30 ± 0.2
6	23 ± 2.6†	20 ± 2.4†	187 ± 20*	16 ± 29	11 ± 7	51 ± 6†	37 ± 3†	7.28 ± 0.1
0	26 ± 4.2†	23 ± 4.0*†	179 ± 18*	10 ± 1.7*	15 ± 10*†	61 ± 6†	38 ± 4*†	7.22 ± 0.2*†

Values are presented as mean and SD

Comparison was done using 6 or 24 cmH_2O of PEEP as reference. All values were statistically significant when compared with 6 of PEEP prior to the recruitment maneuver (*RM*), except as indicated by asterisk (*p* = n.s.)

† The first statistical change compared with 24 cmH_2O after RM (*p* < 0.05)

At the highest PEEP level, the lowest but still acceptable mean arterial pressures (61 ± 7 mmHg) and cardiac indeces (3.2 ± 0.9 l min^{-1}/m^2) were observed, whereas mean pulmonary arterial pressure remained almost constant along the study. We did not apply any specific hemodynamic treatment during the protocol other than fixed i.v. fluid of 5 ml kg^{-1} and dopamine infusion of 3–4 μ kg^{-1}.

Discussion

In this surfactant-depleted model, a decremental PEEP trial was performed after a cycling recruitment maneuver. Dead-space variables were compared with two well-established methods for monitoring the lung's volumetric state and gas exchange. We found that VD_{alv}, VD_{alv}/VT_{alv}, and Pa–ETCO$_2$ were the parameters most closely correlated with atelectatic lung areas on CT scan as well as with arterial oxygenation. These variables also showed a high sensitivity and specificity for detecting early lung collapse during a PEEP titration trial following lung recruitment.

Our results, if confirmed in patients with ALI, suggest that dead-space variables, in the context of recruitment and a PEEP titration procedure, might become a clinically useful bedside tool for implementing a lung protective ventilation strategy based on OL-PEEP.

As lung collapse induces changes in both, ventilation distribution and gas exchange, VD should be a better tool for assessing overall respiratory function than oxygenation, because the latter one does not allow inferences on "ventilation." Despite the fact that VD suffers from the same limitation as PaO$_2$ (i. e., they both require arterial blood gases), VD may become a practical bedside tool, thus replacing CT images for OL-PEEP determination.

At lowest PEEP levels the pigs showed a similar behavior between VD_{alv} and shunt, supporting the notion that alveolar dead space is "fictitious" in origin, meaning that shunt creates a dead-space effect when VD_{alv} is calculated according to Enghoff's modification of Bohr's formula [19, 21]. This is a known effect of an increased Pa-ETCO$_2$ difference and was called shunt-related dead space (Fig. 3). An increase in "real" VD_{alv}, i. e., the true presence of areas with a high V/Q, did not occur even at 24 cmH$_2$O of PEEP, suggesting that the more homogeneous distribution of ventilation prevented the occurrence of a significant alveolar overdistension even at these high pressures. This phenomenon is clearly shown in Fig. 3 and Table 1, where VD_{alv} remains at low values paralleled by minimal amounts of non-aerated lung and shunt during the open-lung condition.

Pa-ETCO$_2$, a clinical index commonly used to estimate dead space, showed a similar behavior as VD_{alv} during the protocol (Table 1). As soon as PEEP decreased below OL-PEEP, Pa-ETCO$_2$ started to increase again, marking the beginning of lung collapse.

Our data are in agreement with those of Gattinoni et al. [34] in patient with ARDS. In those patients who "responded" to prone positioning, PaCO$_2$ decreased. This decrement in PaCO$_2$ was most likely due to a recruitment of some additional tissue for gas exchange which was finally associated with a better outcome. Our results indicated the same recruitment effect: After the recruitment, the lung's capacity for CO$_2$ elimination is increased. This, in turn, corresponds with a decrement in arterial PCO$_2$ (Tables 1, 4).

VD_{aw} presented a close positive correlation with PaO$_2$ and normally aerated areas. A similar change in airway caliber related to transmural pressures has been reported earlier [35]; therefore, it seems that gas exchanging peripheral units are kept open at the expense of an increase in airway dead space. The increase in airway diameter was also responsible for the differences observed between VD/VT and VD_{alv}/VT_{alv}, as the former more global ratio is "contaminated" by the effect of PEEP on airway dead space, whereas the latter is not (Figs. 3, 4). This fact suggests that the dead space portion of the alveolar gas provides more meaningful information than the classical VD/VT ratio when monitoring of the lung collapse-recruitment phenomena is of the essence.

These changes in dead space agree with those reported by Wenzel et al. in an animal model of ALI [36]. In their study, the administration of exogenous surfactant decreased dead space due to a partial recruitment of atelectatic lung areas. Furthermore, the results of the current study agree well with the findings of our previous studies in anesthetized patients [23, 24].

On the contrary, neither Blanch et al. [27] nor Beydon et al. [28] showed the same positive effect on dead space when using levels of PEEP between 0 and 15 cmH$_2$O in acutely injured lungs. These opposing results are most likely due to the absence of any genuine lung-recruitment effect in their patients. Putting these thoughts together, differences in the results of these studies may in fact be the demonstration of the significant physiological changes in dead space, which are induced by lung-recruitment maneuvers as compared with the isolated use of PEEP without them.

Limitations of the study

The saline lavage model behaves differently from clinical ALI and fails to reproduce the vascular and inflammatory pathology of early acute respiratory failure [37]. This model is generally more "recruitable," i. e., it responds more to increases in airway pressures than other models of lung injury but shows less hemodynamic compromise [37]. Therefore, changes in dead-space variables could have been overestimated in the experimental model used as compared with real patients. Rosenthal et al. demonstrated that there is no such thing as a perfect

animal model that could imitate the complex nature of ALI or ARDS [38]; thus, data from other experimental models of ALI, but more importantly from patients, would be needed to confirm our results.

The use of two-dimensional CT scans for assessing three-dimensional volumes of lung aeration has limitations. The main limitation of our approach was to take only one juxta-diaphragmatic CT slice for analysis, a technique that need not be representative for the entire lung [31]. Also, analysis of hyperinflated areas was difficult due to inherent limitations of CT technology as a tool for assessing hyperinflation, especially when a single-slice technique is used [1, 2, 14, 31, 39].

tal model of surfactant depletion. After lung recuitment, the parameters alveolar dead space, ratio of alveolar dead space to alveolar tidal volume, and $Pa\text{-}ETCO_2$ showed high specificity and sensitivity for establishing OL-PEEP. VD_{alv}/VT_{alv}, as opposed to VD/VT, agreed well with the gold standard defined by CT. VD_{alv}/VT_{alv} should replace the classical ratio whenever alveolar aeration is to be optimized.

Conclusion

Monitoring of dead space during PEEP titration was useful for detecting early signs of lung collapse in an experimen-

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