Title: Use of Dead Space Fraction for PEEP titration: identification of open lung

Weishuai Bian, Wei Chen, Yangong Chao, Lan Wang, Liming Li, Jian Guan,
Xuefeng Zang, Jie Zhen, Bo Sheng, Xi Zhu.

The work presented here was carried out in collaboration between all authors.
WB, WC and YC defined the research theme. WB, WC, YC, LW, LL, JG and XZ
designed methods and experiments, carried out the laboratory experiments, analyzed
the data, interpreted the results and wrote the paper. JZ and BS carried out the
laboratory experiments, and co-worked on associated data collection and their
interpretation. XZ co-designed experiments, discussed analyses, interpretation, and
presentation. All authors have contributed to, seen and approved the manuscript.

BACKGROUND: High levels of positive end-expiratory pressure (PEEP) in
combination with low tidal volumes have been used to manage patients with severe
acute respiratory distress syndrome (ARDS). Elevated dead space fraction (the ratio
of dead space to tidal volume [VD/VT]) is a feature of ARDS. However, the
application of lowest VD/VT method to titrate optimal PEEP(Po) in patients with
severe ARDS remains under recognized. Therefore, we performed the study to
evaluate the effect of VD/VT in PEEP titration via analyzing the relationship between
VD/VT and oxygen delivery(DO$_2$), alveolar tidal volume(Valv).

METHODS: With seven mixed breed adult male swine with ARDS induced by
oleic acid ventilated in volume-controlled mode we conducted a recruitment
maneuver, then set PEEP at 20 cm H$_2$O, and then we reduced PEEP stepwise, by
2cmH$_2$O every 10 min, until 0 cm H$_2$O. After each PEEP decrement step we measured arterial oxygen partial pressure plus arterial carbon dioxide partial pressure(PaO$_2$+PaCO$_2$). We defined the “optimal” PEEP as the PEEP step above which PaO$_2$ + PaCO$_2$ started to less than 400 mmHg. VD/VT, pulmonary mechanics parameters, gas exchange parameters, and hemodynamic parameters were recorded during the pre-lesion, lesion, Po+4cmH$_2$O, Po+2cmH$_2$O, Po, Po-2cmH$_2$O, Po-4cmH$_2$O period.

**RESULTS:** After RM, during Po+2cm H$_2$O period, VD/VT decreased to the lower value (mean ± standard deviation (SD): 61.43±10.33%) than during the lesion period (mean ± SD: 72.29±8.58%) ($P$ < 0.05), while DO$_2$ and Valv reach to the highest values(562.96±302.81ml/min, 111.79±42.63ml respectively) from 424.10±162.25 ml/min and 92.06±35.22ml. Dynamic tidal respiratory compliance (Cdyn) value was significantly higher during the Po period(20.6±5.6 ml/cmH$_2$O) than during the lesion period(14.4±5.5 ml/cmH$_2$O) ($P$ < 0.05). Multiple regression analysis was done to determine the correlations between VD/VT and Cdyn, DO$_2$, Valv. The VD/VT was found to be significantly affected by DO$_2$ and Valv. The $r^2$ values for DO$_2$ and Valv were recorded as 0.866 and 0.823.

**CONCLUSIONS:** A significant change of VD/VT, DO$_2$, Valv, Cdyn and arterial oxygenation could be induced by PEEP titration in swine with ARDS. The lowest VD/VT after RM and PEEP ventilation is strongly associated with the highest DO$_2$ and Valv. The minimal VD/VT indicate a maximum amount of effectively expanded alveoli and can be used to assess PEEP Titration in ARDS.
**Key words:** acute respiratory distress syndrome; dead space fraction; PEEP; recruitment maneuver; oxygen delivery; alveolar tidal volume.

**Introduction**

Acute respiratory distress syndrome (ARDS) is common in critically ill patients admitted to intensive care units (ICU). ARDS could induce pathophysiologic mechanisms of alveolar collapse, hyoxemia, vascular dysfunction and elevated dead space fraction (the ratio of dead space volume to tidal volume [VD/VT])[1, 2]. And the mortality rate is as high as 40%[3, 4].

The lung-protection strategy combines the use of high levels of positive end-expiratory pressure (PEEP) and low tidal volumes to prevent the end expiratory alveolar collapse, increase functional residual capacity and effective alveolar ventilation volume, reduce VD/VT and improve the hypoxemia[5, 6]. However, the application of higher levels of PEEP may be harmful[7, 8], since it will increase inflation of lung regions that are already open, the ventilator induced lung injury and risk of hemodynamic abnormalities.

Many experimental studies have been designed to define the optimal PEEP(Po) level based on a lot of methods during a recruitment maneuver (RM) with decremental PEEP, including lung maximum dynamic tidal respiratory compliance(Cdyn), maximum PaO₂, maximum PaO₂+PaCO₂, or inflation lower Pflex, deflation upper Pflex on the P–V curve[9]. But which method is best, there is still great uncertainty.
In recent years there are many studies about the application of VD/VT method to assess the effects of lung recruitment and PEEP titration in patients with severe ARDS[10-13]. Measuring VD/VT is a more specific value compared to oxygen, because it is based upon carbon dioxide’s relatively high diffusability across tissue membranes[14], and CO$_2$ exchange depends strictly upon alveolar ventilation volume(Valv)[15]. Measuring VD/VT may be superior to oxygenation indices(PaO$_2$/FiO$_2$, OI) in assessing lung recruitment[12]. So VD/VT may be useful for pulmonary endothelial injury as a more perfusion-sensitive variable and as an indicator of lung recruitment versus overdistention in patients with ARDS[16-19].

However, some studies[17, 20] failed to find similar effect on VD/VT during PEEP titration. Beydon et al[17] investigated how physiological, airway and alveolar VD varied with PEEP from zero to 15 cm H$_2$O and analyzed possible links to respiratory mechanics in ten consecutive ALI patients. Alveolar VD did not vary systematically with PEEP. However, in individual patients a decrease of alveolar VD paralleled a positive response to PEEP with respect to oxygenation.

In severe ARDS patients intrapulmonary shunt and ventilation-perfusion abnormalities cause serious hypoxemia, which can compromise oxygen delivery(DO$_2$) and result in tissue hypoxia and progress to multi-organ failure or death[21]. Some scholars believe that the maintenance of adequate DO$_2$ to the peripheral tissues in ARDS patients is essential and associated with survival[22].

The ventilatory at relatively high level PEEP ensures adequate alveolar ventilation[15], which yields improved oxygenation, oxygen content in arterial blood
and DO\textsubscript{2}. But James and associates published a study in which higher airway pressure might yield a significant decrease in DO\textsubscript{2} in ARDS. Because of the higher airway pressure leads to diminished venous return and cardiac output (CO)[23]. So how to find the PEEP, which can effectively increase effective Valv, but does not affect the cardiac function and DO\textsubscript{2}, is the key of mechanical ventilation strategy in ARDS.

A previously reported study, which applied incremental PEEP, found a relationship between maximum DO\textsubscript{2} and the lowest VD/VT, which both resulted in the greatest total static compliance[24]. But in the study multiple regression analysis was not done to determine the correlations between VD/VT and Cdyn or DO\textsubscript{2} with different PEEP change. The purpose of this study is to realize VD/VT Change Induced by Different PEEP Levels in ARDS, influential factors of VD/VT and the feasibility of VD/VT in guiding the optimal PEEP titration.

Methods

Animals and anesthesia

This was a prospective, sham controlled, in vivo animal study. The study was approved by the animal ethics committee of Beijing Shijitan Hospital, Affiliated to Capital Medical University, Beijing, China.

Eleven healthy male swine with average weight of 40.19 ± 5.86 kg were provided by the animal center of Pinggu Hospital of Capital Medical University (License: SYXK(B) 2010-0016), in which four experimental swine were eliminated due to death or failure to establish the ARDS model. Swine were fasted for
24 hours then studied in the supine position and orotracheally intubated (Hi-Lo Evac Tracheal Tube, Tyco Healthcare, Pleasanton, California, USA) during deep intramuscularly anesthesia with ketamine (35 mg/kg), 3% pentobarbital sodium (30 mg/kg) and diazepam (1.5 mg/kg). A Swan-Ganz catheter (Edwards Lifesciences LLC, Irvine, California, USA) was inserted into the right internal jugular vein using the Seldinger technique and connected to the monitoring system. After line placement, the anesthetic was switched to total intravenous anesthesia with continuous infusion of Pentobarbital (2 mg/kg/h), Ketamine (3 mg/kg/h) and Pipecurium bromide (0.03 mg/kg/h). In all swine, a 4-French gauge arterial thermodilution catheter (PICCO, Pulsion Medical Systems, Munich, Germany) was inserted via the left femoral artery for clinical monitoring of arterial pressure, continuous CO measurements. The arterial catheter was connected to a computer for pulse contour analysis (Pulsion Medical Systems, Munich, Germany). All of the punctures were under the guidance of B-sonography.

**Monitoring**

**Blood Gas Analysis**

We conducted arterial blood gas analysis (GEM PREMIER 3000, Lexington MA, USA) 30 minutes after beginning mechanical ventilation (pre-lesion stage), 90 minutes after injection of oleic acid (lesion stage), after recruitment maneuvers and 10 minutes after each PEEP adjusted (different PEEP stage).

**Hemodynamic measurements**

Cardiac output index (CI), Mean systemic arterial pressure, Global
End-diastolic Volume index (GEDI), Intra-thoracic Blood Volume index (ITBI), Extravascular Lung Water index (ELWI), Systemic Vascular Resistance index (SVRI) were measured by the thermodilution method using the PICCO system. Central Venous Pressure (CVP) was monitored with the Swan-Ganz catheter in the right internal jugular vein.

**VD/VT measurements**

We measured VD/VT using noninvasive partial carbon dioxide rebreathing technique method (NICO Cardiopulmonary Management System, Wallingford, Connecticut, USA), which calculated the partial pressure of mixed-expired CO$_2$, then acquired by the Enghoff modification of the Bohr equation as follows:

$$\frac{V_D}{V_T} = \frac{(P_{aCO_2} - P_{eCO_2})}{P_{aCO_2}}$$

where $P_{eCO_2}$ is mean expired CO$_2$[25]. An arterial blood gas sample was obtained when the $P_{eCO_2}$ variability on the NICO monitor was $\leq 1$ mm Hg within 5 min. The NICO sensor fits between the Y-piece and the endotracheal tube.

**Oxygen metabolism monitoring**

The DO$_2$ was defined as the product of CO and arterial O$_2$ content (CaO$_2$). The CaO$_2$ was calculated from the PaO$_2$, Hgb concentration, and O$_2$ saturation (SaO$_2$):

$$CaO_2 = Hgb \times 1.34 \times SaO_2 + 0.003 \times PaO_2$$

The oxygen consumption (VO$_2$) was calculated as the product of CO and arterial-venous oxygen difference content. The venous O$_2$ content (CvO$_2$) was calculated as:

$$CvO_2 = Hgb \times 1.34 \times SvO_2 + 0.003 \times PvO_2$$
Oxygen extraction ratio (ERO\(_2\)) was calculated as:

\[
ERO_2 = \frac{V_O}{D_O^2}
\]

**Protocol**

After intubation, ventilation was initiated using a Servo-i ventilator (Siemens Maquet Critical Care AB, Slona, Sweden) in volume control ventilation mode with the following initial parameters: tidal volume (VT) 8 ml/kg, FIO\(_2\):1.0 and PEEP 5 cmH\(_2\)O, respiratory rate 40 breaths/min, and inspiratory to expiratory time (I:E) ratio 1:2. These settings were maintained for 30 min to achieve stabilization.

The study consisted of the following seven experimental periods: i) Pre-lesion period. Introduction of catheters and mechanical ventilation using the initial parameters; ii) Lesion period. ARDS was induced by the intravenous administration of oleic acid; iii) PEEP period 1 (Po+4). During 4 cmH\(_2\)O above the optimal PEEP period; iv) PEEP period 2 (Po+2). 2 cmH\(_2\)O above the optimal PEEP; v) PEEP period 3 (Po). The optimal PEEP; vi) PEEP period 4 (Po-2). 2 cmH\(_2\)O below the optimal PEEP; vii) PEEP period 5 (Po-4). 4 cmH\(_2\)O below the optimal PEEP. The optimal PEEP identified by Best PaO\(_2\)+PaCO\(_2\) method in this study.

**ARDS Induction**

After recording pre-lesion hemodynamic, gas exchange, respiratory mechanics measurements and oxygen metabolism in the supine position at the ventilatory settings described previously, oleic acid (Sigma-Aldrich inc. St. Louis, MO, USA) was slowly injected in the right atrium (0.2 ml·kg\(^{-1}\) in 40 ml of saline) within 15 min via the Swan-Ganz catheter. This was followed by a 90-min injury stabilization period.
before initiating the experimental protocol. A successful model of ARDS was defined by PaO$_2$/FiO$_2$ ratio <200 mm Hg (1 mmHg=0.133 kPa) for 90 min after oleic acid injection[26]. All swine received a continuous intravenous saline infusion at a rate of 100 ml/h.

**Recruitment maneuvers**

Ventilator parameters were adjusted on the following settings and data gathered at every step: PCV peak pressure 35 cmH$_2$O, PEEP 20 cmH$_2$O, inspiratory time 0.6 s, rate 40/min, FiO$_2$ 1.0. Then the PEEP setting remained unchanged and pressure control was increased by a 5cmH$_2$O interval and step to obtain a peak airway pressures from 40 to 50 cmH$_2$O until PaO$_2$+PaCO$_2$>400 mmHg. Every step was maintained for 2 min, followed by a 15-min stabilization period with peak pressure 35 cmH$_2$O. If PaO$_2$+PaCO$_2$>400 mmHg, the maneuver recruitment was considered complete[27].

**PEEP titration**

After PaO$_2$+PaCO$_2$>400 mmHg, all swine underwent a decremental PEEP titration in volume control mode. PEEP was decreased in 2 cmH$_2$O steps (from 20 to 0 cmH$_2$O) and maintained at each level for 10 minutes. After each step physiologic data, including Cdyn, VD/VT, DO$_2$PaO$_2$/FiO$_2$ etc. were gathered. The optimal "open-lung PEEP" were identified by the following four different methods:

1. Best PaO$_2$+PaCO$_2$: As PEEP gradually was reduced, PaO$_2$ + PaCO$_2$ started to decrease to less than 400 mmHg. The optimal PEEP was set 2 cmH$_2$O above this pressure[9].
2. Best Cdyn[28]: which was achieved as determined by a rise in compliance and then a fall with each PEEP step.

3. Lowest VD/VT: which was achieved as determined by a decrease in VD/VT and then a rise with each PEEP step.

4. Optimal oxygenation: another method to titrate the optimal PEEP below which PaO$_2$/FIO$_2$ fell by at least 10%[29].

**Statistical Analysis**

All data were analyzed using statistics software (IBM-SPSS 19, Armonk, NY, USA). Measurements and other recorded values were expressed as mean±standard deviation (SD). Analysis of variance (ANOVA) was used for comparison of all variables collected during seven assessment periods. Paired T-test was applied comparing the means of the values of the optimal PEEP from different methods. Logistic regression analysis was used to investigate the correlations between VD/VT and Cdyn, DO$_2$, Valv or OI. A $P<0.05$ was considered statistically significant.

**Results**

1. The optimal PEEP identified by four different methods(Best PaO$_2$+PaCO$_2$, Lowest VD/VT, Optimal oxygenation and Best Cdyn) respectively were: 13.14±1.35 cmH$_2$O, 15.71±1.80 cmH$_2$O, 13.43±1.51 cmH$_2$O and 14.14±2.91cmH$_2$O. The optimal PEEP was higher by Lowest VD/VT than another method, but there were no statistically significant differences between the monitored values($P>0.05$).

2. VD/VT Change Induced by Different PEEP Levels

There was a significant increase in VD/VT to 72.29±8.58ml during the lesion
period from 56±11.06ml during the pre-lesion period (P<0.05). After RM, at optimal
PEEP +2cm H₂O, VD/VT decreased to the lowest value 61.43±10.33ml (vs lesion
P<0.05). When PEEP decreased to P-4cm H₂O, VD/VT significantly increased to
70.8±8.61ml. But at the optimal PEEP+4 cm H₂O VD/VT was higher (65.86±8.86ml)
(Fig. 1 and Table 1).

3 Change of PaO₂/FİO₂ During PEEP Decrement

There was a statistically significant decrease in PaO₂/FİO₂ from 564±159 mmHg
during the pre-lesion period to 79±23 mmHg during the lesion period (P<0.05). After
RM, PaO₂/FİO₂ values significantly increased from 179±122 mmHg to 372±136
mmHg, when PEEP increased from Optimal P-4cm H₂O to Optimal P+2cmH₂O. But
PaO₂/FİO₂ decreased again at Optimal P+4cmH₂O. (Fig. 2 and Table 1).

4 Cdyn, DO₂ and Valv change During PEEP Decrement

Compared to the pre-lesion and another PEEP station after RM, Cdyn value was
significantly higher on the pressure level of optimal PEEP. But DO₂ and Valv values
were significantly higher on the pressure level of optimal PEEP+2 cmH₂O. (Fig. 2, 3
and Table 1).

5 Hemodynamic Change Induced by Different PEEP Levels

CI, ITBI, GEDI, SVRI did not change significantly during the pre-lesion, lesion
and variable PEEP period (P>0.05). A increment in CVP were observed during the
variable PEEP period relative to the pre-lesion, lesion period (P<0.05), and CVP
increased obviously with PEEP increasing. Compared to the pre-lesion period,
EVLWI values were notably higher during the lesion and variable PEEP period (P
<0.05), but there were no significantly alterations on all PEEP steps (Table 2).

6 Relationship Between VD/VT and PaO$_2$/FiO$_2$, Cdyn, Valv, DO$_2$

Multiple regression analysis was done to determine the correlations between VD/VT and Cdyn, DO$_2$, Valv, PaO$_2$/FiO$_2$. The regression equation is:

$$y=92.073-0.193x_1-0.01x_2-0.008x_3+0.107x_4$$

where, $y$, $x_1$, $x_2$, $x_3$, $x_4$ represent VD/VT, Valv, DO$_2$, PaO$_2$/FiO$_2$, Cdyn respectively.

And the $r^2$ value is 0.872($P<0.01$). The VD/VT was found to be significantly affected by DO$_2$ and Valv. The $r^2$ values for DO$_2$ and Valv were recorded as 0.866 and 0.823, respectively. But PaO$_2$/FiO$_2$ and Cdyn had not statistically significant effects on VD/VT($P>0.05$).

Discussion

In this trial, a decremental PEEP procedure was performed after an RM in swine with ARDS. We observed that PEEP caused a significant change of VD/VT, DO$_2$, Valv, Cdyn, and PaO$_2$/FiO$_2$. Our results suggest that VD/VT, might become a clinically useful bedside tool for assessing collapsed alveolar opening and titrating the optimal PEEP in ARDS.

A markedly elevated VD/VT can develop early in the course of ARDS, which could be due to obstruction of pulmonary blood flow in the extra-alveolar pulmonary circulation[30, 31], injury of pulmonary capillaries by thrombotic and inflammatory mechanisms[32, 33] and increasing areas with a low ventilation, which may impair carbon dioxide clearance[34]. As shown in Figure 1, VD/VT during the lesion period increased significantly than during the pre-lesion period.
With the increase of PEEP, alveolar ventilation is improved obviously, VD/VT also showed a trend of decline. But the higher PEEP may cause effective alveolar ventilation volume decreased and VD/VT increased because of over-distention of well ventilated alveoli, that were mentioned in a controlled study by Fengmei et al[13], They also figured that the PEEP level corresponding to the minimal VD/VT after the recruitment maneuver was found to be 12 cm H₂O.

In our study, the optimal PEEP identified by Lowest VD/VT was 15.71±1.80cmH₂O, which was Close to the optimal PEEP corresponding to the maximum compliance and Optimal oxygenation. Our data are in agreement with the study by Maisch et al[18], which showed that different PEEP levels after RM caused significant changes in VD/VT as well as in PaO₂/FIO₂, and compliance in ARDS patients.

As can be seen from the calculating formula of VD/VT, VD/VT is inversely related to the CO₂ elimination. The CO₂ elimination by the lung is influenced by effective alveolar surface area, alveolar ventilation, and cardiac output[15, 35, 36].

After the recruitment and optimal PEEP, the lung’s capacity for CO₂ elimination is increased, because alveolar ventilation significantly increased.Our study also shows that in the PEEP levels ranging from Optimal P-4 to Optimal P+2 cm H₂O, there was a decreasing trend in VD/VT and an increasing trend in Valv. But in the PEEP of Optimal P+4cmH₂O VD/VT increased along with the decrease of Valv. And there is obvious correlation between VD/VT and Valv(P<0.01). Previous studies[37] have also demonstrated that VD was significantly increased in the higher PEEP
20cmH₂O group, which was induced by hyperinflated lung region.

Furthermore, higher PEEP could increase VD/VT by reduction in cardiac output[38, 39]. Because the PEEP range in our study is less than 20cmH₂O, CI, GEDI, ITBI, SVRI has no obvious statistical difference in ARDS and each PEEP state.

Also found in our study: during the lesion period DO₂ is lower significantly than during the pre-lesion period. From the formula of DO₂, DO₂ may be reduced in several pathologic states: 1. reduced CO, 2. a reduction in the oxygen-carrying capacity of blood due to hemorrhage or anemia, 3. decreased oxygen uptake by the lung (which decreases oxygen saturation), 4. impaired diffusion from blood to tissue[40]. A prospective randomized trial demonstrated that the pattern of DO₂<550 ml/min·m² was associated with Lower survival[41].

Maintaining adequate DO₂ to the peripheral tissues in patients with ARDS is essential in preventing shock-related multisystem organ failure (MSOF). According to the observations of James et al[22], Survivors of ARDS have greater DO₂ than do nonsurvivors. Survival may be explained by the strong inverse relation between DO₂ and development of MSOF, which developed in no survivors and in 63% of nonsurvivors.

Application of lung recruitment and the optimal PEEP ventilation is one of the main measures to improve DO₂[21]. We found that after lung recruitment DO₂ increased from 424.10±162.25 ml/min during the lesion period to 562.96±302.81 ml/min during the optimal PEEP+2cmH₂O, OER decline to 40.14±11.14 from 44.86±7.6.
However, with the further increase of PEEP, DO\textsubscript{2} has showed a downward trend. Because CO had no obvious change in our study, higher PEEP led to a drop in DO\textsubscript{2} by regional overdistention of well ventilated alveoli\cite{42}, decreased alveolar ventilation volume (as can be seen in figure 4), or more ventilator-induced lung injury from overdistention\cite{43}. So Mohamed Abdelsalam thought that a lung-protective strategy aims to provide a patient with ARDS a Optimal DO\textsubscript{2} that is adequate to avoid tissue hypoxia while minimizing the detrimental effects of the toxic ventilatory support required to maintain normal arterial oxygenation\cite{21}.

In addition, in ARDS secondary to severe sepsis syndrome, VO\textsubscript{2} and OER were significantly lower when DO\textsubscript{2} was increased. Such an abnormality was associated with defective cellular oxygen utilization, predicting a very poor prognosis\cite{34}. But in this ARDS model induced by oleic acid, in order to ensure the organ and tissue oxygen utilization, VO\textsubscript{2} did not change significantly, and OER increased, that illustrate no obvious defective peripheral oxygen utilization.

In this study we found VD/VT decreased gradually with the increase of PEEP and reached minimum during Po+2cmH\textsubscript{2}O period. At the same time, DO\textsubscript{2} and Valv increased gradually to a maximum value at Po+2cmH\textsubscript{2}O. And further more, there is obvious inverse correlation between VD/VT and DO\textsubscript{2}, \(r^2=0.866, P<0.01\) and between VD/VT and alveolar tidal volume\(r^2=0.823, P<0.01\) from multiple regression analysis. But no obvious linear relationship between VD/VT and OI, Cdyn. Because OI is nonspecific for judging recruitment effect, and insensitive to the overdistention of alveoli\cite{13}. For Cdyn it were not in parallel found by Rothen et al.
that the changes of compliance and the amount of atelectasis estimated by computed
tomography[44].

We thought that in the optimal PEEP (15.71 ± 1.80cmH₂O in our study) identified by lowest VD/VT, DO₂ get maximum value along with the largest alveolar ventilation volume. There was no significant statistical difference compared with the optimal PEEP identified by the other 3 methods. Therefore, titration of optimal PEEP based on the minimum VD/VT method has certain feasibility and VD/VT can reflect the degree of DO₂ and alveoli distention.

Limitations

There are limitations to our study. In the context of recruitment and PEEP, alveolar ventilation volume could not be assessed by direct computed tomography methods. In addition, we did not evaluate PEEP more than 20cmH₂O after RM in the ARDS model, so we cannot comment on the effect of higher PEEP on VD/VT, DO₂, Valv etc. under those circumstances. Finally, our sample size of Seven swine is relatively small, and arguably underpowered to detect an important effect.

Conclusions

Measurement of VD/VT also is valuable in assessing the effects of lung recruitment. The minimal VD/VT can be used as one of many choices to Assess PEEP Titration in ARDS. In the context of recruitment and a PEEP titration procedure, a reduction of the VD/VT and increase in DO₂, Valv, indicated a maximum amount of effectively expanded alveoli. The VD/VT might be used prospectively in future clinical trials, particularly when the goal is to evaluate the benefit of an open-lung
Acknowledgments

This work was supported by a grant from National Natural Science Foundation of China (No. 81372043).

Declaration of Interest

The authors declare that they have no conflict of interest.

References


42. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld


### Table 1
Respiration and oxygen metabolism parameters of the ARDS animal model in different condition (mean ± SD)

<table>
<thead>
<tr>
<th>PEEP(cmH₂O)</th>
<th>pre-lesion</th>
<th>Optimal P+4</th>
<th>Optimal P+2</th>
<th>Optimal P</th>
<th>Optimal P-2</th>
<th>Optimal P-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD/VT(%)</td>
<td>56±11.06</td>
<td>72.29±8.06</td>
<td>65.86±8.06</td>
<td>61.43±10</td>
<td>64.71±9.6</td>
<td>70±10.30</td>
</tr>
<tr>
<td>Valv(ml)</td>
<td>146.11</td>
<td>92.06±3.45</td>
<td>98.23±37</td>
<td>111.79±4</td>
<td>109.86±4</td>
<td>99.3±38.8</td>
</tr>
<tr>
<td>DO₂</td>
<td>817.4±327.8</td>
<td>424.10±162.25*</td>
<td>554.67±2</td>
<td>562.96±3</td>
<td>551.86±3</td>
<td>460.64±2</td>
</tr>
<tr>
<td>VO₂</td>
<td>213.08</td>
<td>211.06±85.33</td>
<td>220.83±6</td>
<td>218.17±8</td>
<td>206.01±9</td>
<td>173.66±6</td>
</tr>
<tr>
<td>ERO₂(%)</td>
<td>29.29±11.07</td>
<td>44.86±7.5</td>
<td>44±14.17</td>
<td>42.14±11</td>
<td>40.14±11</td>
<td>40.83±11</td>
</tr>
<tr>
<td>OI (mmHg)</td>
<td>564±15</td>
<td>79.23±7.96</td>
<td>311±171</td>
<td>372±136</td>
<td>338±141</td>
<td>291±66</td>
</tr>
<tr>
<td>Cdyn(ml/cmH2O)</td>
<td>38.1±6.35</td>
<td>14.4±5.7</td>
<td>17.4±3.5</td>
<td>19.4±5.4</td>
<td>20.6±5.6</td>
<td>18.5±2.0</td>
</tr>
</tbody>
</table>

* P < .05 was considered significant, comparing the pre-lesion, +P < .05 was considered significant, comparing the lesion.

### Table 2
Hemodynamics parameters of the ARDS animal model in different condition(mean ± SD)

<table>
<thead>
<tr>
<th>PEEP(cmH₂O)</th>
<th>pre-lesion</th>
<th>Optimal P+4</th>
<th>Optimal P+2</th>
<th>Optimal P</th>
<th>Optimal P-2</th>
<th>Optimal P-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP(mmHg)</td>
<td>6.2±2.0</td>
<td>8.4±2.8</td>
<td>11.9±1.8*</td>
<td>11.6±2.2</td>
<td>11.1±3*</td>
<td>10.8±2.8*</td>
</tr>
<tr>
<td>CI</td>
<td>4.99±2.1</td>
<td>3.67±1.8</td>
<td>3.64±1.8*</td>
<td>3.56±2.0</td>
<td>3.56±2.0</td>
<td>2.93±1.53</td>
</tr>
<tr>
<td>ITBI</td>
<td>709.3±23</td>
<td>678.3±20</td>
<td>585.7±13</td>
<td>593.13±2</td>
<td>611±224.</td>
<td>689.88±2</td>
</tr>
<tr>
<td>GEDI</td>
<td>567.4±18</td>
<td>543.09±1</td>
<td>468.86±1</td>
<td>475.01±1</td>
<td>488.3±18</td>
<td>552.27±1</td>
</tr>
<tr>
<td>(L/min/m²)</td>
<td>2.67</td>
<td>5.13</td>
<td>3.27</td>
<td>10.19</td>
<td>82</td>
<td>40.3</td>
</tr>
<tr>
<td>(ml/m²)</td>
<td>5.91</td>
<td>64.25</td>
<td>06.79</td>
<td>67.94</td>
<td>0.74</td>
<td>92.10</td>
</tr>
<tr>
<td></td>
<td>EVLWI (ml/kg)</td>
<td>10.76±4.</td>
<td>17.61±6.</td>
<td>17.33±4.8</td>
<td>17±4.86*</td>
<td>16.93±5.8</td>
</tr>
<tr>
<td>-----</td>
<td>--------------</td>
<td>-----------</td>
<td>----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>42</td>
<td>3</td>
<td>2</td>
<td>8</td>
<td>.17</td>
</tr>
<tr>
<td>SVRI (dyn.sec.cm⁻¹⁻m⁻²)</td>
<td>1372.43±</td>
<td>1986.8±1</td>
<td>1982.06±</td>
<td>2179.6±1</td>
<td>2213.23±</td>
<td>2541.27±</td>
</tr>
</tbody>
</table>

*P < .05 was considered significant, comparing the pre-lesion, +P < .05 was considered significant, comparing the lesion.
Fig. 1. Changes of dead space fraction (VD/VT) during the pre-lesion, lesion and decremental PEEP after recruitment maneuver period. *P < .05 was considered significant, comparing the pre-lesion; + P < .05 was considered significant, comparing the lesion.
Fig. 2. Changes of oxygenation indices (OI) and maximum dynamic tidal respiratory compliance (Cdyn) during the pre-lesion, lesion and decremental PEEP after recruitment maneuver period. *$P < .05$ was considered significant, comparing the pre-lesion, +$P < .05$ was considered significant, comparing the lesion.
Fig. 3. Changes of oxygen delivery (DO$_2$) and alveolar tidal volume (Valv) during the pre-lesion, lesion and decremental PEEP after recruitment maneuver period. *P < .05 was considered significant, comparing the pre-lesion.