Application of dead space fraction to titrate optimal positive end-expiratory pressure in an ARDS swine model

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Abstract. This study aimed to apply the dead space fraction [ratio of dead space to tidal volume (VD/VT)] to titrate the optimal positive end-expiratory pressure (PEEP) in a swine model of acute respiratory distress syndrome (ARDS). Twelve swine models of ARDS were constructed. A lung recruitment maneuver was then conducted and the PEEP was set at 20 cm H_2O. The PEEP was reduced by 2 cm H_2O every 10 min until 0 cm H_2O was reached, and VD/VT was measured after each decrement step. VD/VT was measured using single-breath analysis of CO_2, and calculated from arterial CO_2 partial pressure ($PaCO_2$) and mixed expired CO_2 ($PeCO_2$) using the following formula: VD/VT = ($PaCO_2$ - $PeCO_2$)/$PaCO_2$. The optimal PEEP was identified by the lowest VD/VT method. Respiration and hemodynamic parameters were recorded during the periods of pre-injury and injury, and at 4 and 2 cm H_2O below and above the optimal PEEP (Po). The optimal PEEP in this study was found to be 13.25±1.36 cm H_2O. During the Po period, VD/VT decreased to a lower value (0.44±0.08) compared with that during the injury period (0.68±0.10) ($P<0.05$), while the intrapulmonary shunt fraction reached its lowest value. In addition, a significant change of dynamic tidal respiratory compliance and oxygenation index was induced by PEEP titration. These results indicate that minimal VD/VT can be used for PEEP titration in ARDS.

Introduction

Acute respiratory distress syndrome (ARDS) is a severe and life-threatening medical condition that is common in critically ill patients and has a high mortality rate (1). It is a main reason for acute respiratory failure, and is characterized by widespread inflammation in the lungs (1,2). ARDS can induce pathophysiological mechanisms of alveolar collapse, hyoxemia, vascular dysfunction and elevated dead space fraction [the ratio of dead space volume to tidal volume (VD/VT)] (3,4).

Currently, the lung-protection strategy for ventilation involves the use of high positive end-expiratory pressure (PEEP) levels combined with low tidal volumes to prevent end expiratory alveolar collapse, increase functional residual capacity, reduce VD/VT and attenuate hypoxemia (5,6). However, the application of higher levels of PEEP may not be necessarily beneficial, since it increases the inflation of lung regions. Additionally, it will also increase the risk of hemodynamic abnormalities as well as the lung injury induced by ventilation (7,8). Numerous studies have attempted to define the optimal PEEP level on the basis of a variety of methods during a recruitment maneuver (RM) with decreasing PEEP (9-11).

A number of studies have applied the VD/VT method to assess the effects of lung recruitment and PEEP titration in patients with severe ARDS (9-11). VD/VT is a specific value based on the relatively high diffusibility of CO_2 across tissue membranes (12), and the exchange of CO_2 depends strictly on alveolar ventilation volume (13). However, some studies did not find a similar effect on VD/VT during PEEP titration (14,15). Therefore, the application of the lowest VD/VT method to titrate the optimal PEEP in patients with ARDS remains to be investigated.

In the present study, an oleic acid lung-injury model in swine was used to evaluate the effect of varying the PEEP level on dead space fraction. The aim was to realize the changes in VD/VT induced by different PEEP levels in the ARDS swine model and to explore the feasibility of using the VD/VT ratio to guide the optimal PEEP titration.

Materials and methods

Animals and anesthesia. The study was a prospective, sham-controlled and *in vivo* animal study, and was approved by the animal ethics committee of Beijing Shijitan Hospital, affiliated to Capital Medical University (Beijing, China).

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Twelve healthy male swine (age, 11-13 months) with an average weight of 39.13±3.27 kg were provided by the animal center of Pinggu Hospital of Capital Medical University [licence: SYXK (B) 2010-0016]. The animals were housed at 21-27˚C with a humidity of 45-55%, with free access to food and water. Swine were fasted for 24 h and then were orotracheally intubated in the supine position during deep intramuscular anesthesia with ketamine (35 mg/kg; Jiangsu Hengrui Medicine Co. Ltd., Lianyungang, China), 3% pentobarbital sodium (30 mg/kg; Sigma-Aldrich; Merck KGaA, Darmstadt, Germany) and diazepam (1.5 mg/kg; Sigma-Aldrich). A double cavity central venous catheter was inserted into the right internal jugular vein using the Seldinger technique (16) and connected to the monitoring system. Following line placement, the anesthetic was switched to total intravenous anesthesia with continuous infusion of pentobarbital sodium (2 mg/kg/h), ketamine (3 mg/kg/h) and pipecurium bromide (0.03 mg/kg/h; Gedeon Richter Plc., Budapest, Hungary). In all swine, a 4-French gauge arterial thermodilution catheter was inserted via the left femoral artery. The arterial catheter was connected to a computer for pulse contour analysis (Pulsion Medical Systems, Munich, Germany) for the clinical monitoring of hemodynamic measurements.

Monitoring. The respiration parameters of alveolar partial pressure of O_2 (PAO_2)/fraction of inspiration O_2 (FiO_2) ratio (P/F), arterial CO_2 partial pressure ($PaCO_2$) and arterial O_2 saturation (SaO_2) were directly measured through arterial blood gas analysis using the (GEM Premier 3000; Instrumentation Laboratory, Inc., Lexington MA, USA) (17). Lung maximum dynamic tidal respiratory compliance (Cdyn) was monitored using a SERVI-i ventilator (Siemens Maquet Critical Care AB, Slona, Sweden).

The VD/VT ratio was measured via the single-breath analysis of CO_2 (18) (NICO Cardiopulmonary Management System; Novametrix; Philips Respironics, Murrysville, PA, USA). With this method, the partial pressure of mixed-expired CO_2 was calculated followed by the Enghoff modification of the Bohr equation as follows: $VD/VT=(PaCO_2-PeCO_2)/PaCO_2$, where $PeCO_2$ represents mixed expired CO_2 (19). An arterial blood gas sample was obtained when the $PeCO_2$ variability on the NICO monitor was ≤1 mmHg within 5 min. The NICO sensor fitted between the Y-piece and the endotracheal tube.

The intrapulmonary shunt fraction (Qs/Qt) was calculated according to the standard formulae:

$$Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$$
$$CaO_2 = Hb \times SaO_2 \times 1.34 + PAO_2 \times 0.0031$$
$$CvO_2 = Hb \times SvO_2 \times 1.34 + PvO_2 \times 0.0031$$
$$CcO_2 = Hb \times ScO_2 \times 1.34 + PcO_2 \times 0.0031$$
$$ScO_2 \approx 100\%$$
$$PcO_2 \approx PAO_2$$
$$PAO_2 = PiO_2 - PaCO_2/R$$
$$PiO_2 = (PB - PH_2O) \times FiO_2$$

where Qs represents shunted pulmonary blood flow; Qt represents total pulmonary blood flow; CcO_2 represents pulmonary capillary O_2 content; PvO2 represents mixed venous O2 partial pressure; CaO_2 represents arterial O_2 content; CvO_2 represents mixed venous O_2 content; Hb represents hemoglobin; PiO_2 represents partial pressure of inspired O_2; R represents respiratory quotient (0.8); PB represents barometric pressure (~100 kPa on sea level); PH_2O represents saturation vapor pressure (6.3 kPa at 37˚C).

The hemodynamic parameters of cardiac output index (CI), global end-diastolic volume index (GEDI), extravascular lung water index (ELWI), intra-thoracic blood volume index (ITBI) and systemic vascular resistance index (SVRI) were directly measured by the thermodilution method (20) using the PICCO system (Pulsion Medical Systems). The central venous pressure (CVP) was monitored with the central venous catheter in the right internal jugular vein.

Protocol. Following intubation, lungs were ventilated in a volume-controlled ventilation mode, with the following initial parameters: VT of 8 ml/kg, FiO_2 of 1.0, PEEP of 5 cm H_2O, respiratory rate of 40 breaths/min, and inspiratory to expiratory time ratio (I:E) of 1:2. These settings were maintained for 30 min to achieve stabilization.

ARDS induction. After recording pre-injury hemodynamic, gas exchange, respiratory mechanics measurements and oxygen metabolism, 0.2 ml/kg oleic acid (Sigma-Aldrich) in 40 ml saline was slowly (within 15 min) injected in the right atrium via the central venous catheter. After a 90-min injury stabilization period, the experimental protocol was initiated. A successful model of ARDS was defined by P/F <200 mmHg for 90 min following oleic acid infusion (21). Each swine was infused continuously with intravenous saline at a rate of 100 ml/h.

Lung recruitment maneuver. The swine were stabilized for 15 min on the following ventilator settings and followed by data gathering: Pressure control ventilation (PCV) peak pressure, 35 cm H_2O; PEEP, 20 cm H_2O; inspiratory time, 0.6 sec; rate, 40/min and FiO_2 1.0. The PEEP was then set to 20 cm H_2O and pressure control set to a peak airway pressure of 40 cm H_2O. These settings were maintained for 2 min, followed by a 15-min stabilization period with a peak pressure 35 cm H_2O. Data were gathered if PAO_2 + $PaCO_2$ was >400 mmHg. If PAO_2 + $PaCO_2$ was <400 mmHg, the PEEP setting remained unchanged and pressure control was increased to obtain a peak airway pressure of 45 cm H_2O. This pattern was sustained for 2 min, followed by a 15-min stabilization period with peak pressure 35 cm H_2O. If PAO_2 + $PaCO_2$ was >400 mmHg, the lung recruitment was considered complete (22,23).

PEEP titration. When the sum of PAO_2 and $PaCO_2$ was >400 mmHg, all swine underwent a decremental PEEP titration in volume control mode. PEEP was decreased in 2 cm H_2O steps (from 20 to 0 cm H_2O) and was maintained at each level for 10 min. Cdyn was measured at each step using a VT of 8 ml/kg and a frequency of 40/min. Additionally, the physiological data including Cdyn, VD/VT and P/F were gathered following each step. The optimal open-lung PEEP was identified by the lowest VD/VT method, which was achieved as determined by a reduction in VD/VT and then a rise with each PEEP step.

The study consisted of the following seven experimental periods: i) Pre-injury period, which involved introduction of catheters and mechanical ventilation using the initial parameters; ii) injury period, when ARDS was induced by the

intravenous administration of oleic acid; iii) PEEP period 1 (Po-4), 4 cm H_2O below the optimal PEEP; iv) PEEP period 2 (Po-2), 2 cm H_2O below the optimal PEEP; v) PEEP period 3 (Po), optimal PEEP; vi) PEEP period 4 (Po+2), 2 cm H_2O above the optimal PEEP; vii) PEEP period 5 (Po+4). 4 cm H_2O above the optimal PEEP.

Statistical analysis. All data were analyzed using IBM-SPSS version 19.0 statistics software (IBM SPSS, Armonk, NY, USA) and were expressed as mean ± standard deviation. Analysis of non-parametric repeated-measures ANOVA test was used for comparison of all variables collected during the seven assessment periods. P<0.05 was considered to indicate a statistically significant difference.

Results

Optimal PEEP. The optimal PEEP identified by the lowest VD/VT method was 13.25±1.36 cm H_2O.

VD/VT changes induced by different PEEP levels. There was a significant (P<0.05) increase in VD/VT from the pre-injury period (0.35±0.11) to the injury period (0.68±0.10). Following the RM, VD/VT decreased to the lowest value of 0.44±0.08 (vs. injury, P<0.05) at the optimal PEEP. When PEEP decreased to Po-4 cm H_2O, VD/VT significantly increased to 0.60±0.07 (P<0.05). However, at the Po+4 cm H_2O, VD/VT was higher (0.64±0.10; Fig. 1 and Table I).

Changes of P/F during PEEP decrement. There was a statistically significant (P<0.05) reduction in P/F from the pre-injury period (562±162 mmHg) to the injury period (75±21 mmHg). Following the RM, P/F values significantly increased from 166±109 to 365±133 mmHg when the PEEP increased from the Po-4 cm H_2O to Po+2 cm H_2O. However, P/F decreased again at Po+4 cm H_2O (Fig. 2 and Table I).

Changes of Cdyn and Qs/Qt during PEEP decrement. At all periods after injury, the Cdyn values were decreased compared with the pre-injury value (P<0.05), but the highest post-RM values were observed at the pressure level of optimal PEEP. However, Qs/Qt values were significantly (P<0.05) lower at the pressure level of optimal PEEP compared with the levels at the injury period (Figs. 3 and 4 and Table I).

Hemodynamic changes induced by different PEEP levels. The CI, ITBI, GEDI and SVRI did not change significantly during the pre-injury, injury and variable PEEP periods, although a downtrend was observed in CI with the increase of PEEP. For CVP, a significant (P<0.05) increment was observed during the variable PEEP period relative to the pre-injury and injury period. In addition, CVP increased markedly as PEEP increased. In comparison with the pre-injury period, EVLWI values were significantly higher during the injury and variable PEEP periods (P<0.05; Table II).

Discussion

Currently, many methods exist in the literature for identifying the PEEP to set in patients with ARDS following a lung RM.

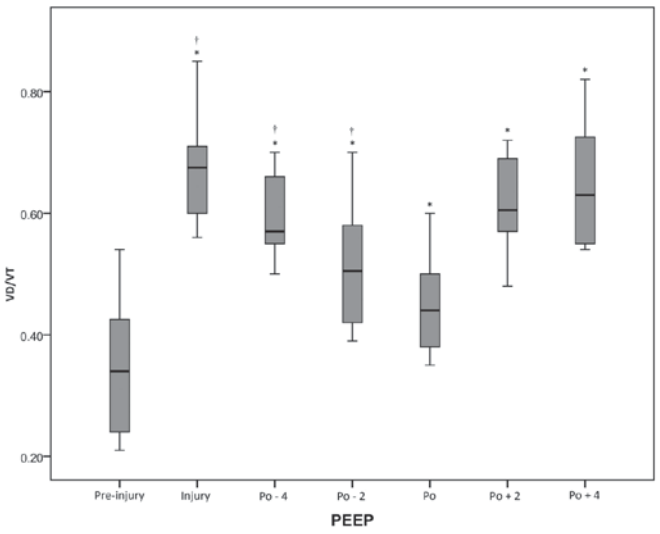

Figure 1. VD/VT of the acute respiratory distress syndrome swine model under different conditions. *P<0.05 vs. pre-injury; †P<0.05 vs. injury. VD/VT, ratio of dead space volume to tidal volume (dead space fraction); PEEP, positive end-expiratory pressure; Po, optimal PEEP; -n, n cm Hg below Po; +n; n cm Hg above Po.

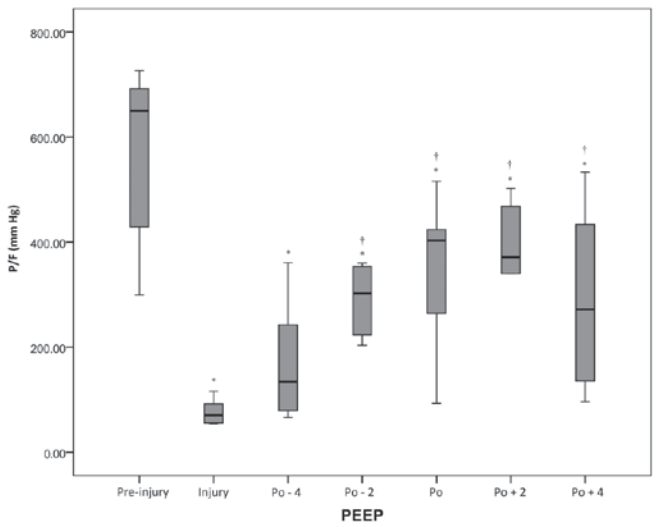

Figure 2. P/F ratio of the acute respiratory distress syndrome swine model under different conditions. *P<0.05 vs. pre-injury; †P<0.05 vs. injury. P/F, alveolar partial pressure of oxygen/fraction of inspiration oxygen (oxygenation index); PEEP, positive end-expiratory pressure; Po, optimal PEEP; -n, n cm Hg below Po; +n; n cm Hg above Po.

The detection parameters include Cdyn, PAO_2, maximum PAO_2 + $PaCO_2$, as well as the inflation lower inflection point (Pflex) and deflation upper Pflex on the pressure-volume curve (22). However, controversy over the approach for setting PEEP has existed since 1967 when Ashbaugh *et al* (24) first used PEEP to manage ARDS. A previous study has reported that an increased VD/VT ratio is one of the markers of early ARDS, and furthermore, an elevated VD/VT ratio is associated with an increased risk of mortality (10). In the present study, a decremental PEEP procedure was performed following an RM in swine with ARDS. It was observed that PEEP caused significant changes of VD/VT, Qs/Qt, Cdyn and P/F. The results indicated that in cases of recruitment maneuver and

Table I. Respiration parameters of the acute respiratory distress syndrome swine model under different conditions (mean ± standard deviation).

Parameter	Pre-injury	Injury	Po-4	Po-2	Po	Po+2	Po+4
VD/VT	0.35±0.11	0.68±0.10[a]	0.60±0.07[a,b]	0.52±0.11[a,b]	0.44±0.08[a,b]	0.61±0.08[a]	0.64±0.10[a]
$PaCO_2$ (mmHg)	34.80±6.73	43.81±8.02[a]	47.73±10.33[a]	49.05±12.47[a]	49.19±11.82[a]	47.71±12.28[a]	47.62±12.89[a]
SaO_2 (%)	99.86±0.05	88.40±11.25[a]	96.79±1.52[b]	98.58±0.48[b]	98.75±2.55[b]	97.78±0.96[b]	96.34±2.50[b]
Qs/Qt (%)	1.88±1.14	21.06±15.62[a]	7.50±4.14[a,b]	5.01±1.53[b]	2.77±2.53[b]	6.68±2.86[b]	9.55±5.85[a,b]
P/F (mmHg)	562±162	75±21[a]	166±109[a]	291±62[a,b]	342±144[a,b]	365±133[a,b]	294±170[a,b]
Cdyn (ml/cm H_2O)	38.17±6.97	15.17±5.37[a]	17.83±3.81[a]	18.00±4.97[a]	20.67±5.58[a,b]	19.33±4.44[a,b]	17.50±3.34[a]

[a]P<0.05 vs. pre-injury; [b]P<0.05 vs. injury. VD/VT, dead space volume/tidal volume (dead space fraction); $PaCO_2$, alveolar partial pressure of carbon dioxide; SaO_2, arterial oxygen saturation; Qs/Qt, intrapulmonary shunt fraction; P/F, alveolar partial pressure of oxygen/fraction of inspiration oxygen (oxygenation index); Cdyn, dynamic tidal respiratory compliance; Po, optimal positive end-expiratory pressure; -n, n cm Hg below Po; +n; n cm Hg above Po.

Table II. Hemodynamics parameters of the acute respiratory distress syndrome swine model under different conditions (mean ± standard deviation).

Parameter	Pre-injury	Injury	Po-4	Po-2	Po	Po+2	Po+4
CVP (mmHg)	6.58±2.08	8.67±2.84[a]	10.67±1.72[a,b]	10.83±2.67[a,b]	10.75±2.83[a,b]	11.33±2.06[a,b]	11.83±1.90[a,b]
CI (l/min/m^2)	4.84±2.08	3.36±1.62	3.80±1.86	3.75±2.00	3.75±2.09	2.96±1.46	2.67±1.22
ITBI (ml/m^2)	694±219	664±201	561±240	690±229	611±202	597±201	590±130
GEDI (ml/m^2)	555±175	532±161	449±192	552±183	488±162	478±160	472±104
EVLWI (ml/kg)	10.69±4.01	17.61±5.71[a]	15.33±3.00[a]	17.14±7.13[a]	16.85±6.05[a]	16.69±4.97[a]	16.94±4.81[a]
SVRI (dyn.sec.cm^{-5}.m^2)	1,430±590	2,113±1,012	2,469±948	2,541±1,366	2,179±1,439	2,152±1,532	1,970±1,237

[a]P<0.05 vs. pre-injury; [b]P<0.05 vs. injury. CVP, central venous pressure; CI, cardiac output index; ITBI, intra-thoracic blood volume index; GEDI, global end-diastolic volume index; ELWI, extravascular lung water index; SVRI, systemic vascular resistance index; Po, optimal positive end-expiratory pressure; -n, n cm Hg below Po; +n; n cm Hg above Po.

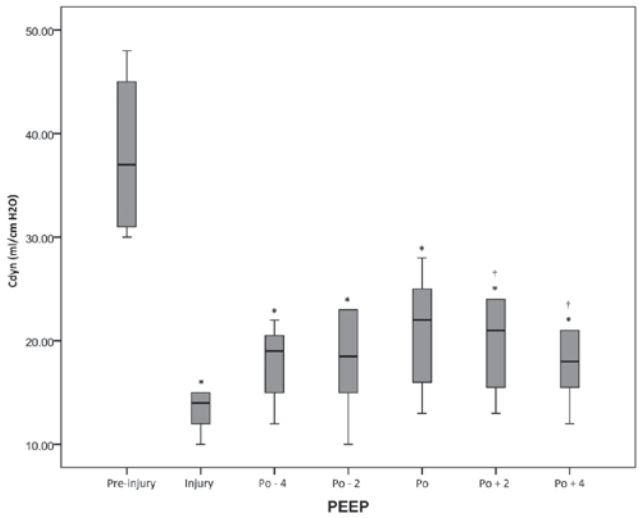

Figure 3. Cdyn of the acute respiratory distress syndrome swine model under different conditions. *P<0.05 vs. pre-injury; †P<0.05 vs. injury. Cdyn, dynamic tidal respiratory compliance; PEEP, positive end-expiratory pressure; Po, optimal PEEP; -n, n cm Hg below Po; +n; n cm Hg above Po.

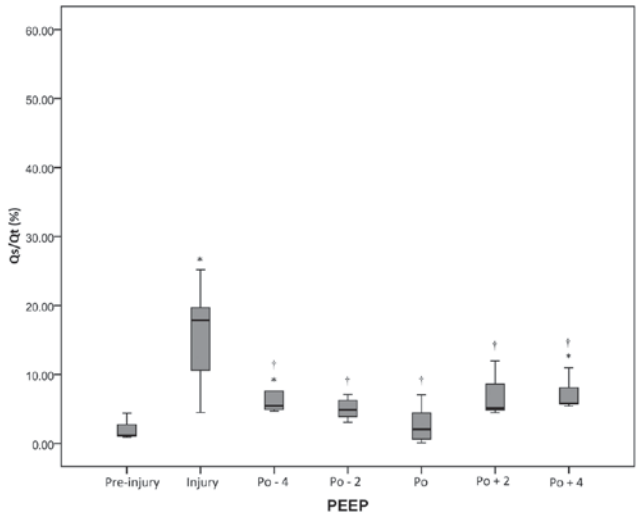

Figure 4. Qs/Qt of the acute respiratory distress syndrome swine model under different conditions. *P<0.05 vs. pre-injury; †P<0.05 vs. injury. Qs/Qt, intrapulmonary shunt ratio; PEEP, positive end-expiratory pressure; Po, optimal PEEP; -n, n cm Hg below Po; +n; n cm Hg above Po.

a PEEP titration procedure, VD/VT might become a clinically useful tool for assessing collapsed alveolar opening and titrating the optimal PEEP in ARDS.

A markedly elevated VD/VT may be detected in early ARDS, which is suggested to be due to the obstruction of pulmonary blood flow in the extra-alveolar pulmonary circulation (25), and increasing areas with a low ventilation (26). Importantly, injury of pulmonary capillaries by inflammation and thrombus can also result in increased VD/VT (27,28). As shown in Fig. 1, VD/VT was significantly higher during the injury period than during the pre-injury period, which was in accordance with results from previous studies (29,30). In addition, the results showed that different PEEP levels following RM caused significant changes in VD/VT, which was in agreement with the findings of Maisch *et al* (31), who showed that different PEEP levels after RM caused significant changes in VD/VT and P/F, as well as compliance in patients with ARDS. With the increase of PEEP, VD/VT showed a trend of decline. However, higher PEEP may lead to an increase of the VD/VT ratio, which might be caused by the regional over-distention of well-ventilated alveoli (26) or by a reduction in cardiac output (32). As can be seen from the formula used to calculate VD/VT, VD/VT is inversely related to CO_2 elimination. The elimination of CO_2 by the lung is influenced by effective alveolar surface area, alveolar ventilation and cardiac output (33,34). Following the RM and optimal PEEP, the CO_2 elimination capacity of the lung is increased, because alveolar ventilation is markedly increased. The present study also showed that in the PEEP levels ranging from Po-4 to Po, VD/VT was gradually reduced. However, when the PEEP levels ranged from Po+2 to Po+4 cm H_2O, VD/VT increased again. A previous study demonstrated that VD was significantly increased in piglets with higher PEEP (20 cm H_2O), which was induced by hyperinflation of the lung region (35).

In ARDS, the alveolar collapse causes a deficiency of alveolar ventilation while the blood flow does not significantly decrease and VD/VT increases, which leads to a decline of the ventilation and blood flow and increase of Qs/Qt. In the present study, the Qs/Qt ratio achieved its maximum value with the increase of VD/VT in ARDS conditions. Under the application of PEEP, the Qs/Qt ratio showed a trend of decline to approach the base value with the reduction of VD/VT. Furthermore, Qs/Qt reached its minimum under the optimal PEEP state.

Higher PEEP increases VD/VT via a reduction in cardiac output (32,36). In the present study, following the application of PEEP, CVP increased as the PEEP increased, indicating that PEEP significantly affected the loading conditions of the right atrium to reduce the volume of returned blood. The increase of CVP might be due to the augmentation of intrapleural pressure and vena cava reflux resistance that were induced by the high PEEP levels. Moreover, the reduction of returned blood volume gives rise to a reduction of left atrium cardiac output, which is in accordance with the present study's findings that the CI gradually declined with the increase of PEEP. Notably, CI had no evident significant difference among PEEP states, because the PEEP range in this study was <20 cm H_2O.

In conclusion, measurement of VD/VT is valuable in assessing the effects of lung recruitment. The minimal VD/VT can be used as one of many options for the assessment of PEEP titration in ARDS. In the context of RM and a PEEP titration procedure, a reduction in VD/VT and Qs/Qt, and an increase in Cdyn and P/F indicate a maximum amount of effectively expanded alveoli. The VD/VT may be prospectively used in future clinical trials, particularly when the goal is to evaluate the benefit of an open-lung protective ventilation strategy in patients with ARDS.

However, there are certain limitations to the present study. In the context of RM and PEEP, alveolar ventilation volume could not be assessed by direct computed tomography methods. In addition, PEEP was not evaluated at >20 cm H_2O after RM in the ARDS model, so it is impossible to comment on the effect of higher PEEP on VD/VT and Qs/Qt under those circumstances. Finally, the sample size of 12 swine

is relatively small, and arguably underpowered to detect an important effect.

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