The Effect of Alveolar Dead Space on the Measurement of End-Expiratory Lung Volume by Modified Nitrogen Wash-Out/Wash-In in Lavage-Induced Lung Injury

Rui Tang MD, Yingzi Huang MD, Qiuhua Chen MD, Xia Hui MD, Yang Li MD, Qing Yu MD, Hongjie Zhao MD, Yi Yang MD PhD, and Haibo Qiu MD PhD

BACKGROUND: The accuracy of end-expiratory lung volume measurement by the modified nitrogen wash-out/wash-in method (EELV-N_2) depends on the precise determination of carbon dioxide elimination ($\dot{V}_{CO_2}$), which is affected by alveolar dead space ($V_{D\text{-}alv}$). The purpose of this study was to investigate the influence of $V_{D\text{-}alv}$ on EELV-N_2. METHODS: Six piglets with lavage-induced acute lung injury were mechanically ventilated in a decremental PEEP trial that was reduced from 20 to 4 cm H_2O in steps of 4 cm H_2O every 10 min. EELV was measured by the modified EELV-N_2 method and computed tomography scan (EELV-CT), volumetric capnography, blood gas measurements, and hemodynamic data were recorded at each PEEP level. The data were divided into higher and lower PEEP groups. RESULTS: During the decremental PEEP trial, EELV-N_2 exhibited a high correlation (r^2 = 0.86, *P* < .001) with EELV-CT, with a bias of −48.6 ± 150.7 mL (1 ± 18%). In the higher PEEP group, EELV-N_2 was not correlated with EELV-CT, with a bias of –168.1 ± 171.5 mL (−14 ± 14%). However, in the lower PEEP group, EELV-N_2 exhibited a high correlation (r^2 = 0.86, *P* < .001) with EELV-CT, with a bias of 11.2 ± 97.2 mL (6 ± 17%). The measurement bias was negatively correlated with $V_{D\text{-}alv}$ (r^2 = 0.44, *P* = .04) and $\dot{V}_{CO_2}$ (r^2 = 0.47, *P* = .03) in the higher PEEP group. CONCLUSIONS: In this surfactant-depleted model, EELV measurement by the modified EELV-N_2 method reveals a systematic underestimation at high PEEP levels that is partly due to an increase in $V_{D\text{-}alv}$. *Key words: end-expiratory lung volume; nitrogen wash-out; alveolar dead space; PEEP; mechanical ventilation.* [Respir Care 2012;57(12):2074–2081. © 2012 Daedalus Enterprises]

Introduction

Determination of end-expiratory lung volume (EELV) can help to monitor severity of acute lung injury[1]; to assess respiratory mechanics, such as specific lung compliance,[2] lung strain,[3,4] and alveolar recruitment[5–7]; to guide lung-protective ventilation[8–10]; and to identify patients who profit from recruitment maneuver after endotracheal suctioning.[11]

Despite its critical role in the management of critically ill patients, EELV measurement is not without difficulties, especially in ventilated patients. Quantitative analysis of pulmonary computed tomography (CT) at end-expiration is the gold standard for EELV measurement.[12] However, the repeated measurements of EELV by pulmonary CT are obviously impractical because of radiation exposure, arduous analysis process, and the unavailability of the CT scan at the bedside. Recently, multiple breath wash-out methods, such as the modified nitrogen wash-out/wash-in technique (EELV-N_2),[13] have enabled EELV determination in ventilated patients without the need to interrupt mechanical ventilation. Previous studies demonstrated that

The authors are affiliated with the Department of Critical Care Medicine, Zhong-Da Hospital, Southeast University School of Medicine, Nanjing, China.

This study was funded by project of the National Key Clinical Specialty Construction (2100299) and Jiangsu Key Medical Discipline (889-KJXW11.3). The authors have disclosed no conflicts of interest.

Correspondence: Haibo Qiu MD PhD, Department of Critical Care Medicine, Zhong-Da Hospital, Southeast University School of Medicine, Nanjing 210009, China. E-mail: haiboq2000@yahoo.com.cn.

DOI: 10.4187/respcare.01800

the EELV-N_2 method is highly accurate in patients with acute respiratory failure,[13,14] ventilated pediatric patients,[15] and in an animal model of unilateral pleural effusion.[16]

Although the EELV-N_2 technique is now commercially available and can be performed easily, a potential problem in using this method is alveolar dead space ($V_{D\text{-}alv}$), which can affect the accuracy. According to the algorithm of the method, the volume of nitrogen wash-out/wash-in is not measured directly but is calculated by determining oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide elimination ($\dot{V}_{CO_2}$), and inspiratory and end-tidal concentrations of oxygen and carbon dioxide (P_{ETCO_2}).[13] Alveolar tidal volume ($V_{T\text{-}alv}$) is an important variable to calculate the volume of nitrogen in this method, and is computed according to the Bohr formula:

$$V_{T\text{-}alv} = \dot{V}_{CO_2}/P_{ETCO_2}$$

Previous studies showed that an increase in $V_{D\text{-}alv}$ that is induced by PEEP leads to impaired $\dot{V}_{CO_2}$ in both healthy and injured lungs,[17–19] which can cause an underestimation of $V_{T\text{-}alv}$ and EELV. Furthermore, in order to solve the synchronization problems about gas flow and concentration measurements, P_{ETCO_2} is used to calculate $V_{T\text{-}alv}$. However, P_{ETCO_2} is higher than the alveolar partial pressure of CO_2 in acute lung injury, as the phase III slope for volumetric capnography is not always a plateau, but can be positive.[20–22] Thus, $V_{T\text{-}alv}$ may be underestimated when calculated using P_{ETCO_2} instead of alveolar CO_2 concentration, which can potentially lead to errors in EELV measurements.

In light of the above reasons, the purposes of this study were to evaluate the effect of $V_{D\text{-}alv}$ on the accuracy of measuring EELV-N_2 in lavage-induced lung injury, and to determine whether an increase in $V_{D\text{-}alv}$ at high PEEP induces an underestimation of EELV.

QUICK LOOK

Current knowledge

The accuracy of end-expiratory lung volume measurement by modified nitrogen wash-out/wash-in requires precise measurement of carbon dioxide production ($\dot{V}_{CO_2}$). While $\dot{V}_{CO_2}$ measurement is straightforward, the accuracy can be affected by alveolar dead space.

What this paper contributes to our knowledge

In a surfactant-depleted porcine model of acute respiratory distress, the accuracy of end-expiratory lung volume (EELV) measurements is affected by an increase in alveolar dead space caused by excessive PEEP. EELV measurements underestimate actual volumes at high PEEP.

Methods

Animal Preparation

This study was conducted at Southeast University School of Medicine, Nanjing, China, after approval by the institutional animal ethics committee. Six healthy piglets (2 male, 4 female) weighing 33.3 ± 1.6 kg were premedicated with intramuscular midazolam (0.3 mg/kg) and ketamine (10 mg/kg). The animals were subsequently anesthetized by a continuous infusion of pentobarbital (10–20 mg/kg/h), fentanyl (3–6 μg/kg/h), and pancuronium (0.5 mg/kg/h).

The animals were tracheotomized and mechanically ventilated in the supine position via an 8-mm inner diameter endotracheal tube (Mallinckrodt/Covidien, Mansfield, Massachusetts) using a constant flow volume controlled mode (Engström CareStation, Datex, GE Healthcare, Madison, Wisconsin). Throughout the experiment the animals were ventilated with a V_T of 6 mL/kg, a respiratory rate of 30 breaths/min, an inspiratory/expiratory ratio of 1:2, and an F_{IO_2} of 0.5.

Lung Lavage Procedure

Lung injury was induced by surfactant depletion after lung lavage with warmed normal saline (30 mL/kg at 37–39°C). Lung lavages were performed every 5 min until P_{aO_2} was below 150 mm Hg on pure oxygen and PEEP of 0 cm H_2O. The injury was then allowed to stabilize over the following 60 min on baseline ventilator settings.

Protocol

After stabilization of the lung injury, the animals were transferred to the CT scan room. A 2-min recruitment maneuver was performed in the pressure control mode with a PEEP of 20 cm H_2O, a peak inspiratory pressure of 50 cm H_2O, respiratory rate of 20 breaths/min, inspiratory/expiratory ratio of 1:1, and F_{IO_2} of 1.0. Thereafter the ventilator was changed back to the previous settings, and PEEP was reduced in 4 cm H_2O steps, from 20 cm H_2O to 4 cm H_2O. Each PEEP level was maintained for 10 min before data acquisition. At the end of the study, all experimental animals were euthanized by an intravenous overdose of potassium chloride solution.

Hemodynamic Monitoring and Blood Gas Measurements

Central venous and pulmonary artery pressures were measured using a 7.5 French pulmonary artery catheter

(Arrow, Teleflex Medical, Reading Pennsylvania) that was advanced via the left internal jugular vein. The right femoral artery was cannulated with a 4 French, 8-cm catheter (PiCCO, Pulsion Medical Systems, Feldkirchen, Germany). For hemodynamic monitoring, an electrocardiogram monitor (PM-9000 Express, Mindray, Shenzhen, China) and a hemodynamic monitor (PiCCO plus, Pulsion Medical Systems, Feldkirchen, Germany) were used. Cardiac output was measured by the hemodynamic monitor system as the average of 3 repeat injections of 10 mL iced normal saline into the right atrial port of the pulmonary artery catheter. Arterial and mixed venous blood gases were measured using a blood gas analyzer (Critical Care Xpress, Nova Biomedical, Waltham, Massachusetts). The venous admixture was calculated using the formula (capillary oxygen content – arterial oxygen content)/(capillary oxygen content – mixed venous oxygen content). After establishing intravenous access, a continuous infusion of normal saline was delivered at a rate of 5 mL/kg/h. Body temperature (rectal) was maintained at 36–38°C with an electric blanket.

EELV-N_2 Method

EELV-N_2 was determined twice via the technique available on the Engström CareStation ventilator, E-COVX, which is an automated procedure with an F_{IO_2} step change of 0.1, as described previously by Olegård et al.[13] Air flow was measured with a flow sensor (Pedi-lite+, GE Healthcare, Madison, Wisconsin) with an accuracy of 6% or 4 mL and a dead space of 2.5 mL. At each time point, EELV was taken as the mean of the the wash-out and wash-in values. The absence of a circuit leak was confirmed by a lack of an obvious reduction in airway pressure during a 10-second end-inspiration pause.

EELV-CT Method

At each PEEP level, whole-lung CT scans were performed during end-expiratory breath-holding (Somatom Sensation 64, Siemens, Forchheim, Germany), using a 512 × 512 matrix, 120 KV, 120 mAs, an exposure time of 0.33 second per rotation, a pitch of 1.2, and a collimation of 0.6 mm. The images were reconstructed with 5-mm slice thickness, using a body reconstruction filter (Siemens notation, B80f). The voxel volume ranged from 0.44 × 0.44 × 5 mm to 0.60 × 0.60 × 5 mm (0.97 – 1.8 mm^3). The CT number characterizing each voxel was expressed in Hounsfield units (HU).

To analyze the images, commercially available software was used (Pulmo Option, Syngo, Siemens). All of the images were assessed at a window width of 1,600 HU and a window center of –600 HU, and only the lung parenchyma was selected as a region of interest, by excluding the chest wall, mediastinum, large vessels, and airways, by manual segmentation. The voxels of each CT slice were distributed into 10 compartments, ranging from –1,000 to 100 HU, with an interval of 100 HU. For each compartment of a known number of voxels, the lung, gas, and tissue volumes were calculated as follows[1]:

Lung volume = number of voxels × volume of the voxel
Gas volume = (mean CT/–1,000) × lung volume

where the volume of gas = 0 if the compartment considered had a CT number above 0, and

Tissue volume = lung volume – gas volume

The total volume of lung, gas (EELV-CT), and tissue was computed by summing the value of each volume of all slices. Different aerated lung regions were divided into 4 functional compartments, according to the following standard definition, based on HU[23]:

Non-aerated: 100 to –100 HU
Poorly aerated: −100 to –500 HU
Normally aerated: −500 to –900 HU
Hyperinflated −900 to –1,000 HU

Volumetric Capnography Analysis

Volumetric capnography was recorded using Ventrak 1550/Capnogard 1265 and Aplus Software (Novametrix, Wallingford, Connecticut). Air flow and airway opening pressure were measured using fixed-orifice differential pressure flow sensors (model 7222, Novametrix, Wallingford, Connecticut, with a dead space of 8 mL). CO_2 was measured using an infrared mainstream sensor (Capnostat, Philips Respironics, Murrysville, Pennsylvania, with a response time < 75 ms, an accuracy of ± 5% at values between 41–100 mm Hg, and ± 2 mm Hg below 40 mm Hg, a resolution of 1 mm Hg, and a dead space of the airway adapter of 5 mL). All 3 sensors (including the Pedi-lite+) were placed at the airway opening. The sensors were calibrated according to the manufacturer's instructions.

Physiologic dead space was calculated using the Enghoff modification of the Bohr formula.[24] Anatomical dead space was determined using the Fowler method.[25] $V_{D\text{-}alv}$ was computed by subtracting the anatomical dead space from the physiologic dead space. $V_{D\text{-}alv}/V_{T\text{-}alv}$ was then obtained by dividing $V_{D\text{-}alv}$ by $V_{T\text{-}alv}$ ($V_{T\text{-}alv} = V_T$ – anatomical dead space). $\dot{V}_{CO_2}$ (the CO_2 volume exhaled per minute) and P_{ETCO_2} were measured with the ventilator.

Statistical Analysis

Data are presented as mean ± SD unless specified otherwise. The EELV-N_2 and EELV-CT values were compared with the Bland-Altman technique,[26] using a linear regression model. The data were divided into the higher

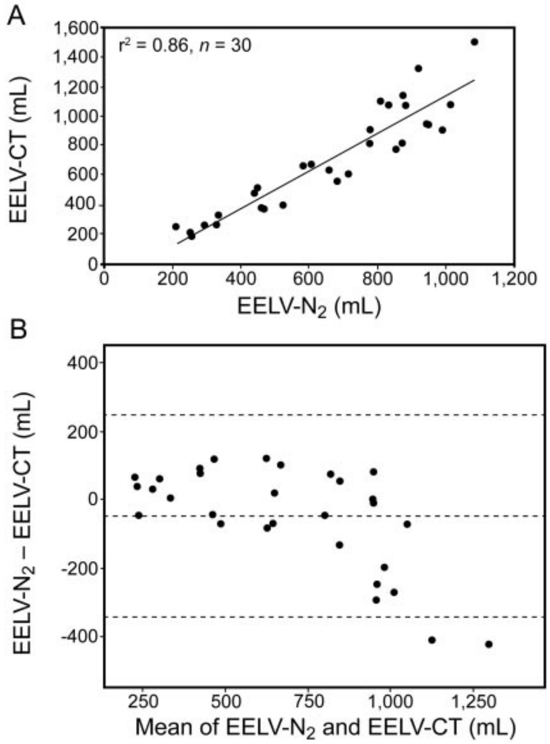

Fig. 1. Comparison of end-expiratory lung volume (EELV) measured by the modified nitrogen wash-out/wash-in method (EELV-N_2) and by computed tomography (CT) scan (EELV-CT) during the decremental PEEP protocol. A: EELV-N_2 was correlated with EELV-CT (r^2 = 0.86, $P < .001$). B: A Bland-Altman plot of the EELV-N_2 levels and EELV-CT (average difference −48.6 ± 150.7 mL, limits of agreement −344.0 to 246.8 mL).

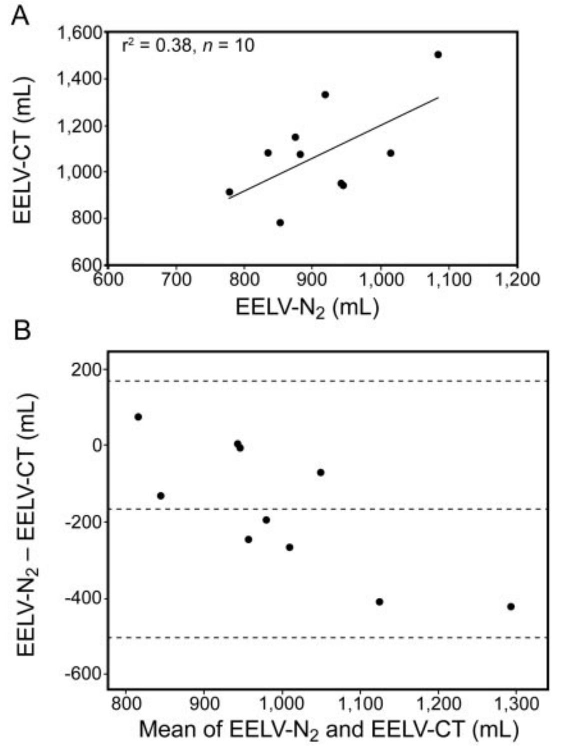

Fig. 2. Comparison of end-expiratory lung volume (EELV) measured by the modified nitrogen wash-out/wash-in method (EELV-N_2) and by computed tomography (CT) scan (EELV-CT) in the higher PEEP group. A: EELV-N_2 was not correlated with EELV-CT. B: A Bland-Altman plot of the EELV-N_2 and EELV-CT (average difference −168.1 ± 171.5 mL, limits of agreement −504.2 to 168.0 mL).

and lower PEEP group according to PEEP above or below and equal to PEEP at the lowest $V_{D\text{-alv}}/V_{T\text{-alv}}$. The reason for the division was that $V_{D\text{-alv}}/V_{T\text{-alv}}$ was useful for detecting lung collapse and for establishing open-lung PEEP in lavage-induced lung injury.[27] The difference between the higher and lower PEEP groups was compared using the Student *t* test or Mann-Whitney U test. Statistical comparisons of the data over time were conducted using a repeated-measures analysis of variance, followed by Bonferroni correction for multiple comparisons. The correlations between 2 variables were determined by a linear regression analysis or a Spearman correlation analysis. Differences with $P < .05$ were considered statistically significant. Statistics software (SPSS 16.0, SPSS, Chicago, Illinois) was used.

Results

During the decremental PEEP process, EELV-N_2 was strongly correlated with the EELV-CT (r^2 = 0.86, $P < .001$). A Bland-Altman plot of the data revealed a bias of −48.6 ± 150.7 mL (1 ± 18%) (Fig. 1).

The lowest $V_{D\text{-alv}}/V_{T\text{-alv}}$ value was at a PEEP of 13 ± 2 cm H_2O. In the higher PEEP group, EELV-N_2 was not correlated with the EELV-CT, with a bias of −168.1 ± 171.5 mL (−14 ± 14%) (Fig. 2). However, in the lower PEEP group, EELV-N_2 maintained a high correlation (r^2 = 0.86, $P < .001$) with EELV-CT, with a bias of 11.2 ± 97.2 mL (6 ± 17%) (Fig. 3).

The volumes of hyperinflated, normally, poorly and non-aerated lung regions and venous admixture were significantly different between the higher and lower PEEP groups. $V_{D\text{-alv}}$, $V_{D\text{-alv}}/V_{T\text{-alv}}$, and P_{ETCO_2} did not differ between the 2 groups (Table 1). However, $V_{D\text{-alv}}$ was correlated with the hyperinflated lung region in the higher PEEP group (r^2 = 0.47, P = .03), whereas $V_{D\text{-alv}}$ was correlated with venous admixture (Rho = 0.83, $P < .001$) and the non-aerated lung region (Rho = 0.81, $P < .001$) in the lower PEEP group. $\dot{V}_{CO_2}$ was negatively correlated with $V_{D\text{-alv}}$ in the higher PEEP group (r^2 = 0.42, P = .04), whereas $\dot{V}_{CO_2}$ was negatively correlated with $V_{D\text{-alv}}$ (Rho = −0.81, $P < .001$) and venous admixture (Rho = −0.53, P = .02) in the lower PEEP group.

During the decremental PEEP process, EELV-N_2 and EELV-CT values were progressively reduced. Compared

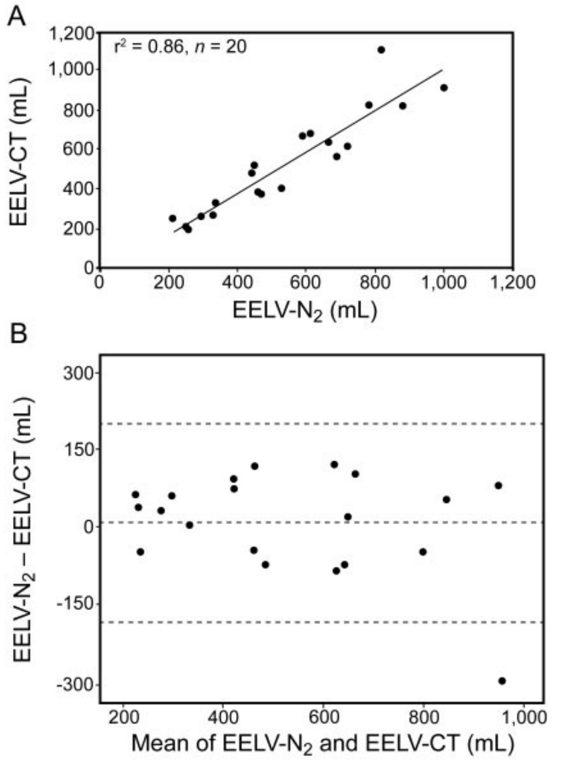

Fig. 3. Comparison of end-expiratory lung volume (EELV) measured by the modified nitrogen wash-out/wash-in method (EELV-N_2) and computed tomography (CT) scan (EELV-CT) in the lower PEEP group. A: EELV-N_2 was correlated with EELV-CT ($r^2 = 0.86$, $P < .001$). B: A Bland-Altman plot of the EELV-N_2 and EELV-CT (average difference 11.2 ± 97.2 mL, limits of agreement –179.4 to 201.8 mL).

with the PEEP levels ranging from 16 to 8 cm H_2O, there was a decreasing trend in $\dot{V}_{CO_2}$ and an increasing trend in $V_{D\text{-}alv}$ at PEEP of 20 cm H_2O and 4 cm H_2O. The measurement bias changed from the minor overestimation to systematic underestimation along with the increase of lung volume (Table 2). The measurement bias was negatively correlated with $V_{D\text{-}alv}$ ($r^2 = 0.44$, $P = .04$), hyperinflated lung region ($r^2 = 0.72$, $P = .002$), and carbon dioxide elimination ($r^2 = 0.47$, $P = .03$) in the higher PEEP group (Fig. 4). These relationships were not observed in the lower PEEP group.

Mean arterial pressure, mean pulmonary arterial pressure, and cardiac output were stable during the decremental PEEP process. However, mean arterial pressure and cardiac output were decreased at PEEP of 20 cm H_2O, although it did not reach statistical significance (Table 3).

Discussion

This study demonstrates that EELV can be accurately measured using the modified nitrogen wash-out/wash-in method in a swine model of acute lung injury, especially at low PEEP levels. However, an increase in $V_{D\text{-}alv}$ partly induces an underestimation of EELV at high PEEP levels.

The saline lavage model that was used in this study is characterized by increased $V_{D\text{-}alv}$, which is clearly affected by PEEP.[27] Thus, this model was suitable for our evaluation of the influence of $V_{D\text{-}alv}$ on EELV-N_2 measurements. In general, the modified EELV-N_2 method revealed an average lung volume underestimation of -48.6 ± 150.7 mL (1 ± 18%), compared with EELV-CT. The high variation in accuracy was due to the minor overestimation at low lung volumes and the obvious underestimation at high lung volumes. However, the accuracy of the modified method was as high as 1%, and the average measurement bias was only about 50 mL. In fact, the respiratory pattern of the small V_T and high respiratory rate adopted in our study, which conformed to lung-protective ventilation in acute lung injury, was unfavorable to this method, due to a possible insufficient wash-out/wash-in time. Despite the aforementioned disadvantages, the modified EELV-N_2 method provides acceptable accuracy for measuring EELV in acute lung injury.

As a multiple breath wash-out method, the volume that is measured by the modified EELV-N_2 method is in fact "accessible pulmonary gas volume."[12] However, the difference between the traditional nitrogen wash-out/wash-in method[28,29] and the modified method lies in how the volume of nitrogen is measured. In the modified method, nitrogen is not measured using a mass spectrometer technique, but is calculated by determining $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. As a result, lung volume, as determined by the modified method, is not only accessible but also should take part in gas exchange. Previous studies showed that increased $V_{D\text{-}alv}$ caused by PEEP impaired $\dot{V}_{CO_2}$ in both healthy and injured lungs,[17–19] and this may have led to an underestimation of EELV by the modified method. Our results demonstrate that in the higher PEEP group, EELV-N_2 is systemically lower than the EELV-CT and is no longer correlated with EELV-CT. The accuracy of the measurements was lowered to –14%. Thus, the underestimated measurement values at high PEEP levels merit attention. However, in the lower PEEP group, EELV-N_2 maintained a significant linear relationship with EELV-CT, and the accuracy of the measurement was sufficient for clinic use. In fact, in previous studies that demonstrated a high accuracy of EELV measurements using the modified method, the PEEP level did not exceed 10 cm H_2O.[14–16]

The CO_2 elimination by the lung is influenced by cardiac output, effective alveolar surface area, and alveolar ventilation.[17,30] Because of the mechanical heterogeneity of the acutely injured lung, $V_{D\text{-}alv}$ was significantly increased in the higher PEEP group, which was induced by hyperinflated lung region. Hence, the reduction of $\dot{V}_{CO_2}$ at high PEEP levels was partially due to an increased $V_{D\text{-}alv}$ and hyperinflated lung region. Furthermore, the measure-

Table 1. Dead-Space Variables, Lung Morphology, and Venous Admixture in the Higher and Lower PEEP Groups

	Higher PEEP Group ($n = 10$)	Lower PEEP Group ($n = 20$)	P
$V_{D\text{-alv}}$, mL	32.3 ± 8.7	38.4 ± 15.6	.26
$V_{D\text{-alv}}/V_{T\text{-alv}}$	0.23 ± 0.06	0.24 ± 0.10	.90
P_{ETCO_2}, mm Hg	42.3 (37.8–51.2)	38.0 (35.5–43.5)	.07
Volume hyperinflated, mL	68.5 (36.3–104.8)	22.4 (10.2–39.8)	.004
Volume normally aerated, mL	1309.1 ± 210.6	552.2 ± 357.5	< .001
Volume poorly aerated, mL	244.9 ± 99.7	389.2 ± 141.6	.008
Volume non-aerated, mL	20.9 (13.8–39.7)	107.7 (52.8–215.9)	< .001
Venous admixture	0.04 (0.04–0.05)	0.14 (0.07–0.29)	< .001

The data are expressed as mean ± SD if normally distributed or as median (IQR) if not normally distributed.
$V_{D\text{-alv}}$ = alveolar dead space
$V_{T\text{-alv}}$ = alveolar tidal volume
P_{ETCO_2} = end-tidal partial pressure of CO_2

Table 2. EELV Measurement, Alveolar Dead Space, Carbon Dioxide Elimination, and Measurement Bias at Each PEEP Level

PEEP, cm H_2O	EELV-CT, median (IQR), mL	EELV-N_2, median (IQR), mL	$V_{D\text{-alv}}$, mean ± SD, mL	$\dot{V}_{CO_2}$, mean ± SD, mL/min	Measurement Bias, mean ± SD, mL
20	1,082 (949–1,236)	944 (880–1,032)	35.9 ± 6.8	125 ± 22	−161.1 ± 167.1
16	911 (810–1,143)*	864 (820–937)*	27.8 ± 9.7*	140 ± 25*	−96.6 ± 202.8
12	657 (601–892)*	700 (646–785)*	30.4 ± 6.5	140 ± 23	−27.2 ± 150.8*
8	395 (364–529)*	464 (414–539)*	34.8 ± 12.2	130 ± 18	28.2 ± 80.4
4	260 (207–331)*	276 (241–359)*	55.0 ± 12.8	120 ± 21	13.7 ± 56.9

* $P < .05$ compared with PEEP 20 cm H_2O.
EELV-CT = end-expiratory lung volume measured by thoracic computed tomography
EELV-N_2 = end-expiratory lung volume measured by the modified nitrogen wash-out/wash-in method
$V_{D\text{-alv}}$ = alveolar dead space
$V_{T\text{-alv}}$ = alveolar tidal volume
$\dot{V}_{CO_2}$,= carbon dioxide elimination
Measurement bias = EELV-N_2 minus EELV-CT

ment bias was correlated with $V_{D\text{-alv}}$, hyperinflated lung region, and $\dot{V}_{CO_2}$ in the higher PEEP group. Thus, $V_{D\text{-alv}}$ played a role in the underestimation of EELV at high PEEP levels. In a recent study that assessed lung volume changes induced by PEEP in patients with ARDS, EELV was measured using the modified EELV-N_2 method.[7] Four of the 30 patients who were ventilated with the highest PEEP level used in the study (> 16 cm H_2O) were excluded from the analysis due to a measurement error that the researchers attributed to a possible circuit leak. However, we propose another explanation for this error, namely, an increase in $V_{D\text{-alv}}$ that was caused by high PEEP.

There were significant differences between the higher and lower PEEP groups, including hyperinflated, normally, poorly and non-aerated lung regions. However, $V_{D\text{-alv}}$ and $V_{D\text{-alv}}/V_{T\text{-alv}}$ did not differ between the 2 groups because the venous admixture had a substantial influence on the calculation of $V_{D\text{-alv}}$, as $V_{D\text{-alv}}$ was calculated according to the Enghoff modification of the Bohr equation.[31] Thus, $V_{D\text{-alv}}$ in the lower PEEP group was highly correlated with the venous admixture and was more suitably interpreted as "shunt dead space,"[32] which is not a reflection of the true $V_{D\text{-alv}}$ (the ventilated alveoli without perfusion). Hence, the reduction in $\dot{V}_{CO_2}$ was partially due to higher $V_{D\text{-alv}}$ caused by hyperinflated lung region at higher PEEP levels, and was primarily due to higher $V_{D\text{-alv}}$ caused by alveolar collapse and venous admixture at lower PEEP levels. Accordingly, EELV measured by the modified method was accurate at low PEEP levels but not valid at high PEEP levels. Thus, when $V_{D\text{-alv}}$ is calculated according to the Enghoff modification of the Bohr equation, the increased $V_{D\text{-alv}}$ has a differential effect on EELV measurements, with the modified EELV-N_2 method between the higher and lower PEEP groups.

Limitations

There are several potential limitations to this study. First, the respiratory pattern of small V_T and fast respiratory rate that we used may have lowered the measurement accu-

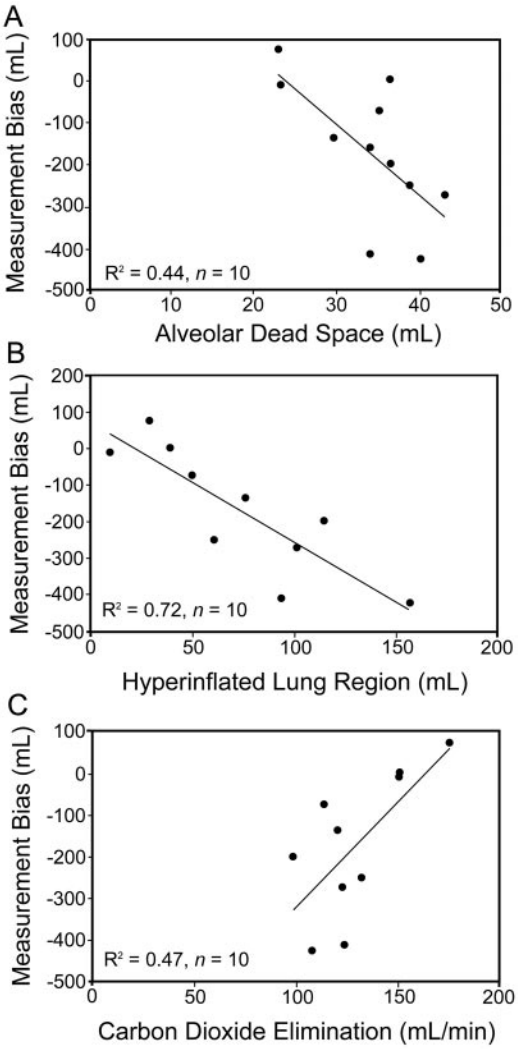

Fig. 4. Correlations between measurement bias, alveolar dead space, hyperinflated lung region, and carbon dioxide elimination at high PEEP levels. A: Measurement bias was negatively correlated with alveolar dead space (r^2 = 0.44, *P* = .04). B: Measurement bias was negatively correlated with hyperinflated lung region (r^2 = 0.72, *P* = .002). C: Measurement bias was correlated with carbon dioxide elimination (r^2 = 0.47, *P* = .03). Measurement bias = EELV-N_2 – EELV-CT.

Table 3. Hemodynamic Data at Each PEEP Level

PEEP, cm H_2O	Mean Arterial Pressure (mm Hg)	Mean Pulmonary Arterial Pressure (mm Hg)	Cardiac Output (L/min)
20	95.2 ± 3.8	25.3 ± 3.0	4.6 ± 1.0
16	97 ± 15.5	24.6 ± 2.8	5.4 ± 1.5
12	107.1 ± 15.0	24.0 ± 3.5	5.6 ± 1.7
8	116.8 ± 11.6	26.3 ± 6.6	5.5 ± 1.6
4	124.3 ± 15.2	32.8 ± 11.6	5.5 ± 1.5

The data are expressed as mean ± SD.

racy, as each wash-out/wash-in time may not have been sufficient. However, the respiratory pattern was not changed during the study protocol, and the underestimation of EELV was not found in the lower PEEP group. Accordingly, high respiratory rate is not the reason for the EELV measurement error at high PEEP levels. Second, the volume control mode that we used differed from partial ventilatory support, as variable V_T during spontaneous breathing may lower the accuracy of the modified method. Third, the surfactant-depletion model that was used in this study may not adequately represent the complex set of conditions that exists in actual patients. Therefore, caution should be applied when interpreting our results. Fourth, the sample size was small, thereby limiting the power of the statistical analysis.

Conclusions

In this surfactant-depleted model, the modified EELV-N_2 method can be used to measure EELV with acceptable accuracy, particularly at low PEEP levels. However, partly due to high $V_{D\text{-}alv}$, EELV is underestimated at high PEEP levels. Thus, clinicians should be cautious of the potential EELV measurement errors at high PEEP levels.

REFERENCES

1. Puybasset L, Cluzel P, Gusman P, Grenier P, Preteux F, Rouby JJ. Regional distribution of gas and tissue in acute respiratory distress syndrome. I. Consequences for lung morphology. CT Scan ARDS Study Group. Intensive Care Med 2000;26(7):857-869.
2. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure: computed tomographic scan study. Am J Respir Crit Care Med 1987; 136(3):730-736.
3. Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. Am J Respir Crit Care Med 2008;178(4):346-355.
4. Mattingley J, Holets S, Oeckler R, Stroetz R, Buck C, Hubmayr R. Sizing the lung of mechanically ventilated patients. Crit Care 2011; 15(1):R60.
5. Rylander C, Högman M, Perchiazzi G, Magnusson A, Hedenstierna G. Functional residual capacity and respiratory mechanics as indicators of aeration and collapse in experimental lung injury. Anesth Analg 2004;98(3):782-789.
6. Patroniti N, Bellani G, Cortinovis B, Foti G, Maggioni E, Manfio A, et al. Role of absolute lung volume to assess alveolar recruitment in acute respiratory distress syndrome patients. Crit Care Med 2010; 38(5):1300-1307.
7. Dellamonica J, Lerolle N, Sargentini C, Beduneau G, Di Marco F, Mercat A, et al. PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. Intensive Care Med 2011;37(10):1595-1604.
8. Lambermont B, Ghuysen A, Janssen N, Morimont P, Hartstein G, Gerard P, et al. Comparison of functional residual capacity and static compliance of the respiratory system during a positive end-expiratory pressure (PEEP) ramp procedure in an experimental model of acute respiratory distress syndrome. Crit Care 2008;12(4):R91.

9. Bikker IG, van Bommel J, Reis Miranda D, Bakker J, Gommers D. End-expiratory lung volume during mechanical ventilation: a comparison with reference values and the effect of positive end-expiratory pressure in intensive care unit patients with different lung conditions. Crit Care 2008;12(6):R145.
10. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, et al. Lung stress and strain during mechanical ventilation: any safe threshold? Am J Respir Crit Care Med 2011;183(10):1354-1362.
11. Heinze H, Eichler W, Karsten J, Sedemund-Adib B, Heringlake M, Meier T. Functional residual capacity-guided alveolar recruitment strategy after endotracheal suctioning in cardiac surgery patients. Crit Care Med 2011;39(5):1042-1049.
12. Heinze H, Eichler W. Measurements of functional residual capacity during intensive care treatment: the technical aspects and its possible clinical applications. Acta Anaesthesiol Scand 2009;53(9):1121-1130.
13. Olegård C, Söndergaard S, Houltz E, Lundin S, Stenqvist O. Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. Anesth Analg 2005;101(1):206-212.
14. Chiumello D, Caironi PC, Monica, Tallarini F, Botticelli M, Berto V, Mietto C, et al. Nitrogen washout/washin, helium dilution and computed tomography in the assessment of end expiratory lung volume. Crit Care 2008;12(6):R150.
15. Bikker IG, Scohy TV, Bogers AJ, Bakker J, Gommers D. Measurement of end-expiratory lung volume in intubated children without interruption of mechanical ventilation. Intensive Care Med 2009; 35(10):1749-1753.
16. Graf J, Santos A, Dries D, Adams AB, Marini JJ. Agreement between functional residual capacity estimated via automated gas dilution versus via computed tomography in a pleural effusion model. Respir Care 2010;55(11):1464-1468.
17. Breen PH, Mazumdar B. How does positive end-expiratory pressure decrease CO_2 elimination from the lung? Respir Physiol 1996;103(3): 233-242.
18. Tusman G, Bohm SH, Suarez-Sipmann F, Scandurra A, Hedenstierna G. Lung recruitment and positive end-expiratory pressure have different effects on CO_2 elimination in healthy and sick lungs. Anesth Analg 2010;111(4):968-977.
19. Johnson JL, Breen PH. How does positive end-expiratory pressure decrease pulmonary CO_2 elimination in anesthetized patients? Respir Physiol 1999;118(2-3):227-236.
20. Tusman G, Sipmann F, Borges J, Hedenstierna G, Bohm S. Validation of Bohr dead space measured by volumetric capnography. Intensive Care Med 2011;37(5):870-874.
21. Blanch L, Lucangelo U, Lopez-Aguilar J, Fernandez R, Romero PV. Volumetric capnography in patients with acute lung injury: effects of positive end-expiratory pressure. Eur Respir J 1999;13(5):1048-1054.
22. Tusman G, Suarez-Sipmann F, Bohm SH, Borges JB, Hedenstierna G. Capnography reflects ventilation/perfusion distribution in a model of acute lung injury. Acta Anaesthesiol Scand 2011; 55(5):597-606.
23. Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med 2001;164(9):1701-1711.
24. Englhoff H. Volumen inefecax. Bemerkungen zur Frage des schaedlichen Raumes. Uppsala Läk För Förh 1938;44:191-218. *Article in German.*
25. Fowler WS. Lung function studies; the respiratory dead space. Am J Physiol 1948;154(3):405-416.
26. Martin Bland J, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 327(8476):307-310.
27. Tusman G, Suarez-Sipmann F, Bohm SH, Pech T, Reissmann H, Meschino G, et al. Monitoring dead space during recruitment and PEEP titration in an experimental model. Intensive Care Med 2006; 32(11):1863-1871.
28. Wrigge H, Sydow M, Zinserling J, Neumann P, Hinz J, Burchardi H. Determination of functional residual capacity (FRC) by multibreath nitrogen washout in a lung model and in mechanically ventilated patients. Intensive Care Med 1998;24(5):487-493.
29. Zinserling J, Wrigge H, Varelmann D, Hering R, Putensen C. Measurement of functional residual capacity by nitrogen washout during partial ventilatory support. Intensive Care Med 2003;29(5):720-726.
30. Anderson CT, Breen PH. Carbon dioxide kinetics and capnography during critical care. Crit Care 2000;4(4):207-215.
31. Niklason L, Eckerstrom J, Jonson B. The influence of venous admixture on alveolar dead space and carbon dioxide exchange in acute respiratory distress syndrome: computer modelling. Crit Care 2008; 12(2):R53.
32. Hedenstierna G, Sandhagen B. Assessing dead space: a meaningful variable? Minerva Anestesiol 2006;72(6):521-528.