

## ORIGINAL RESEARCH

## Effect of tidal volume and positive end-expiratory pressure on expiratory time constants in experimental lung injury

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### Abstract

We utilized a multicompartment model to describe the effects of changes in tidal volume ( $V_T$ ) and positive end-expiratory pressure (PEEP) on lung emptying during passive deflation before and after experimental lung injury. Expiratory time constants ( $\tau_E$ ) were determined by partitioning the expiratory flow–volume ( $\dot{V}_E V$ ) curve into multiple discrete segments and individually calculating  $\tau_E$  for each segment. Under all conditions of PEEP and  $V_T$ ,  $\tau_E$  increased throughout expiration both before and after injury. Segmented  $\tau_E$  values increased throughout expiration with a slope that was different than zero ( $P < 0.01$ ). On average,  $\tau_E$  increased by 45.08 msec per segment. When an interaction between injury status and  $\tau_E$  segment was included in the model, it was significant ( $P < 0.05$ ), indicating that later segments had higher  $\tau_E$  values post injury than early  $\tau_E$  segments. Higher PEEP and  $V_T$  values were associated with higher  $\tau_E$  values. No evidence was found for an interaction between injury status and  $V_T$ , or PEEP. The current experiment confirms previous observations that  $\tau_E$  values are smaller in subjects with injured lungs when compared to controls. We are the first to demonstrate changes in the pattern of  $\tau_E$  before and after injury when examined with a multiple compartment model. Finally, increases in PEEP or  $V_T$  increased  $\tau_E$  throughout expiration, but did not appear to have effects that differed between the uninjured and injured state.

## Introduction

Acute respiratory distress syndrome (ARDS) is a lung injury characterized by hypoxia and impaired pulmonary mechanics. The associated histological changes, such as alveolar flooding and collapse, airway edema, and altered

surfactant function, are heterogeneous in distribution within the lungs (Dakin et al. 2011). Because of this heterogeneity, some lung units have abnormal values of resistance ( $R$ ) and/or elastance ( $E$ ), while others have values that are similar to those found in healthy lung (Eissa et al. 1991b; Schiller et al. 2001; Otto et al. 2008; Mertens

et al. 2009; Kaczka et al. 2011a,b). The  $R$  and  $E$  of a lung unit determine its time constant ( $\tau$ ), which is defined as the time required to inflate or deflate 63% of the volume of a given lung unit. The regional variation in  $R$  and  $E$  of lung tissue implies that there is regional heterogeneity in expiratory time constants ( $\tau_E$ ).

Currently, there is scant information regarding the extent to which the pattern of  $\tau_E$  is altered by the development of lung injury in a given subject. We have recently demonstrated that the  $\tau_E$  pattern of lung passive expiration in the same subject differs with injury status and that these patterns can be altered by manipulating the density of the ventilating gas (Henderson et al. 2015). Kondili and colleagues have examined changes in  $\tau_E$  due to manipulation of positive end-expiratory pressure (PEEP) following lung injury (Kondili et al. 2002). They found that in patients with ARDS at zero PEEP,  $\tau_E$  increased throughout expiration due to progressive increases in respiratory system resistance ( $R_{RS}$ ). The application of PEEP decreased  $R_{RS}$  (primarily in late expiration), resulting in  $\tau_E$  values that were smaller and less varied throughout lung emptying. Similarly, Kondili and colleagues found that the addition of PEEP increased respiratory system elastance ( $E_{RS}$ ) and  $\tau_E$  during the early portion of expiration.

No studies have documented the role of altering PEEP or tidal volume ( $V_T$ ) on the pattern of  $\tau_E$  in the same subject before and after injury. This is relevant, as a more complete understanding of how PEEP and  $V_T$  interact with injury status may alter mechanical ventilation strategies. For example, the optimal combination of PEEP and  $V_T$  may differ in the same patient as lung injury evolves and resolves. Recognition of these changes may allow clinicians to optimize the pattern of lung emptying and minimize the risk of new ventilator-induced lung injury.

We reasoned that interventions that alter regional  $E$  and  $R$ , such as alterations in  $V_T$  or PEEP, should alter  $\tau_E$  values and the pattern of passive expiration. We hypothesized that the effects of both PEEP and  $V_T$  on  $\tau_E$  would differ between the uninjured and injured states. To this end, we undertook to characterize the effects of changes in PEEP and  $V_T$  on  $\tau_E$ ,  $R_{RS}$ , and  $E_{RS}$  before and after the induction of an experimental model of lung injury.

## Methods

### Animals and instrumentation

The Animal Research Committee of the University of British Columbia (certificate #: A12-0272) reviewed and approved the experimental procedures. Anesthesia was induced with inhaled isoflurane (3–5% in oxygen) after sedation with telazol (4–6 mg/kg intramuscular injection)

in six adult female Yorkshire X pigs (weight,  $31.42 \pm 5.42$  kg). After tracheal intubation, inhalational anesthesia was discontinued once total intravenous anesthesia was established with midazolam (0.1 mg/kg intravenous) and a propofol infusion (200  $\mu$ g/kg/min and adjusted to between 150 and 300  $\mu$ g/kg/min). The adequacy of anesthesia was assessed every 15 min using assessment of vital signs, physical examination, and electrocardiography. The animals were mechanically ventilated (Puritan-Bennett 7200, Covidien, Ireland) with 0 cm H<sub>2</sub>O of PEEP using an inspired oxygen fraction (FiO<sub>2</sub>) of 0.5 and  $V_T$  of 10 cc/kg. Breathing frequency was initially set at 15 breaths/min, and was adjusted to maintain end-tidal CO<sub>2</sub> between 35 and 45 mmHg with an inspiratory flow of 45 L/min. A right femoral artery catheter was used to collect arterial blood samples into preheparinized syringes, which were immediately analyzed by calibrated blood gas analyzer (ABL 80 CO-OX Flex). Neuromuscular blockade was induced when needed prior to all measurements of pulmonary mechanical parameters using pancuronium (0.05–0.1 mg/kg intravenous) after a bolus of intravenous midazolam (0.1 mg/kg). Paralysis was monitored by assessment of response to train-of-four stimulation using a peripheral nerve stimulator on the palmar side of the forelimb. At the end of the experiment, euthanasia was achieved with pentobarbital sodium (120 mg/kg intravenous). Death was confirmed by the absence of a pulse and cardiac electrical activity on continuous surface electrocardiography.

### Induction of lung injury

We used a previously published method (Henderson et al. 2014) of lung injury that satisfies the current American Thoracic Society's guidelines for a high-quality model of ARDS and that demonstrates a profound neutrophilic alveolitis with diffuse alveolar damage (Matute-Bello et al. 2011). Sodium polyacrylate gel (1%) in aqueous solution was injected through the endotracheal tube and was manually dispersed throughout the lungs by bagging. One 5-mL aliquot was given every 5 min until an arterial oxygen tension (PaO<sub>2</sub>) of less than 150 mmHg, while receiving a fraction of inspired oxygen (FiO<sub>2</sub>) of 0.5 was observed. The animals required  $3 \pm 1.4$  h after injury to achieve this degree of hypoxia. The ratio of PaO<sub>2</sub>/FiO<sub>2</sub> less than 300 was chosen to be consistent with current definitions of ARDS (Ranieri et al. 2012).

### Interventions

Prior to and subsequent to experimental lung injury, animals were ventilated in a computer-generated random order with six different combinations of  $V_T$  and PEEP:

$V_T$  of 5, 10, 12, and 15 cc/kg all at 0 cm H<sub>2</sub>O PEEP along with 5 and 10 cm H<sub>2</sub>O PEEP at 12 cc/kg. PEEP and  $V_T$  levels were chosen to allow the assessment of a range of clinically relevant PEEP and  $V_T$  values and reflect those used in recent similar studies (Pelosi *et al.* 2001; Kondili *et al.* 2002). Prior to each set of measurements, the animals were ventilated for 20 min at each combination of  $V_T$  and PEEP to eliminate the effect of volume history.

### Measurement of pulmonary mechanics

All data were collected and recorded digitally (PowerLab/16SP model ML 795 and Chart v7, ADI, Colorado Springs, CO). Data sampling occurred at a frequency of 1000 Hz. Using heated pneumotachographs (Model 3813, Hans Rudolph, Kansas City, MO), inspiratory and expiratory flows ( $\dot{V}_I$  and  $\dot{V}_E$ ) were measured and subsequently integrated using a trapezoidal technique to determine inspiratory and expiratory volumes ( $V_I$  and  $V_E$ ). Each analog input was fitted with a fixed 25-kHz low-pass filter which functions as the antialiasing feature.

Airway pressure ( $P_{AW}$ ) was measured at a port distal to the ventilator wye and pleural pressure was assumed to be approximated by the measurement of esophageal pressure ( $P_{ES}$ ) with a balloon-tipped catheter (Ackrad Laboratory, Cranford, NJ). The catheter was positioned in the lower third of the esophagus and balloon position was verified by the presence of cardiac pulsation in the trace and the adequacy of waveform shape during mechanical ventilation (Baydur *et al.* 1982; Talmor *et al.* 2008). PVC pressure tubing (2 mm internal diameter, 3 mm outer diameter) with male and female Luer lock connections were used to connect all apparatus.  $P_{AW}$  and  $P_{ES}$  were referenced to atmospheric pressure and measured using calibrated pressure transducers (Raytech Instruments, Vancouver, BC, Canada).

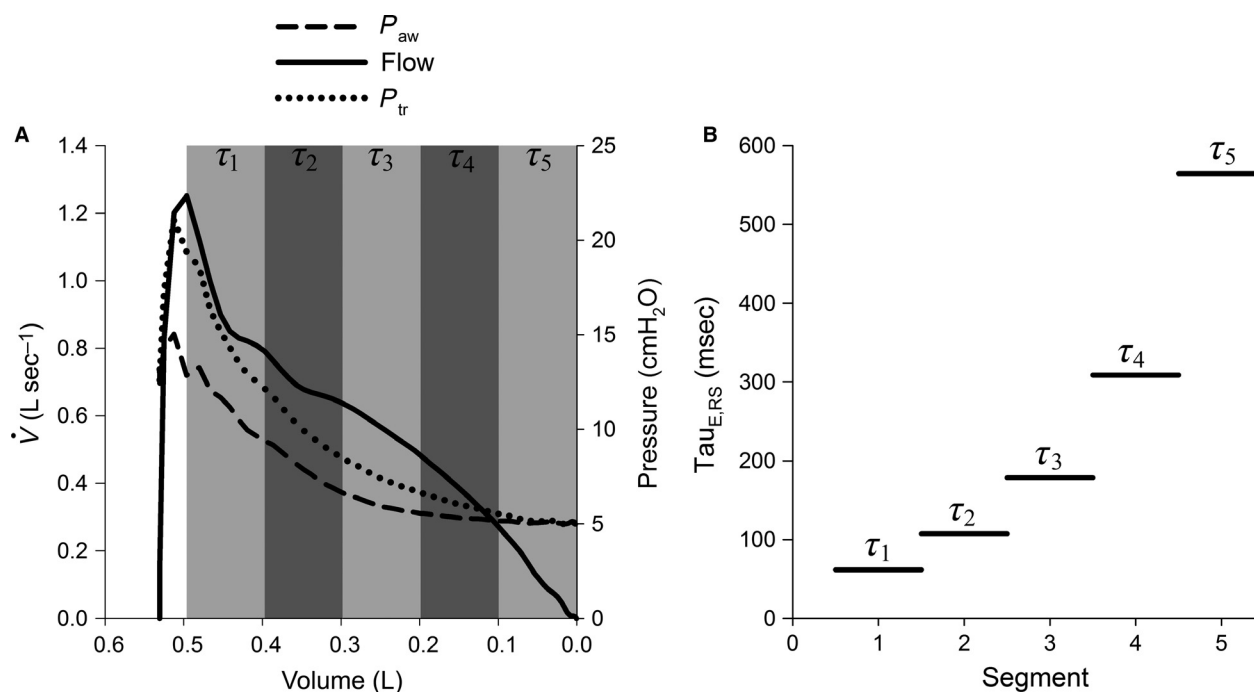
Tracheal pressure ( $P_{TR}$ ) is often assumed to be estimated by  $P_{AW}$ . This assumption may not be valid under dynamic conditions such as when flow-dependent resistance across the endotracheal tube creates a time-dependent pressure drop across the endotracheal tube ( $P_{ETTV(t)}$ ). The drop in pressure causes  $P_{TR}$  to differ significantly from  $P_{AW}$  (Uchiyama *et al.* 2009). To overcome this,  $P_{TR}$  at a specific time ( $P_{TRV(t)}$ ) may be measured directly or calculated at any time point given that ( $P_{TRV(t)} = P_{AW(t)} - (P_{ETTV(t)})$ ) (Guttman *et al.* 1993). To calculate  $P_{TRV(t)}$ , we used a previously validated multifactor formula that estimates the pressure drop across the endotracheal tube from three known values: the endotracheal tube length and diameter,  $\dot{V}_E$  and  $P_{AW}$  (Guttman *et al.* 1993, 1995). The model is defined as:  $P_{TRV(t)} = P_{AW(t)} - K_1 \dot{V}_E^{K_2}$ , where  $K_1$  and  $K_2$  are empirically derived values from previous work (Guttman *et al.* 1993).

Elastance of the respiratory system ( $E_{RS}$ ), that is, without the interposition of the endotracheal tube or ventilator apparatus for the entire expiration, was calculated as  $\Delta P_{TR}/\Delta V$ . Lung elastance ( $E_L$ ) was calculated as  $\Delta (P_{TR} - P_{ES})/\Delta V$ . Chest wall elastance ( $E_{CW}$ ) was calculated as  $\Delta P_{ES}/\Delta V$ . Descriptive  $E_{RS}$ ,  $E_L$ , and  $E_{CW}$  data (as opposed to that used to calculate  $\tau_E$ ) were collected during end-inspiratory plateau conditions. As the flow-dependent resistance of the endotracheal tube and ventilator apparatus alters values of  $R$  measured distal to the endotracheal tube (Wright and Bernard 1989; Guttman *et al.* 1993), we calculated the resistance of the respiratory system without the effect of the endotracheal tube and ventilator ( $R_{RS}$ ) as  $\Delta P_{TR}/\Delta \dot{V}_E$ . Transpulmonary pressure ( $P_{TP}$ ) was defined as  $P_{TR} - P_{ES}$  and lung resistance ( $R_L$ ) was calculated as  $\Delta P_{TP}/\Delta \dot{V}_E$ . Chest wall resistance ( $R_{CW}$ ) was calculated as  $\Delta P_{ES}/\Delta \dot{V}_E$ . Functional residual capacity (FRC) was measured before and after injury using a previously described helium dilution method (Patroniti *et al.* 2004). Arterial blood gas analysis was performed prior to injury, after injury, and at the end of the experimental session.

### Calculation of expiratory time constants

Calculating a single value for  $\tau_E$  assumes that all lung units inflate and deflate as a single compartment and does not allow differentiation between fast and slow filling/emptying units (McIlroy *et al.* 1963; Brunner *et al.* 1995; Aerts *et al.* 1999). The assumption that a single all lung units have identical  $\tau_E$  may have important consequences; heterogeneous rates of alveolar filling/emptying can create localized areas of high tissue strain, which may cause new lung injury and/or exacerbate existing injury (Protti *et al.* 2011). To address this issue, we and others have utilized a multicompartiment model to describe lung emptying during passive deflation by partitioning the expiratory flow-volume ( $\dot{V}_E V$ ) curve into multiple discrete segments and individually calculating  $\tau_E$  for each these segments (Guttman *et al.* 1995; Lourens *et al.* 2000; Kondili *et al.* 2002, 2004; Henderson *et al.* 2015). The multisegment method allows a more nuanced description of the changes in  $\tau_E$  throughout expiration, and therefore facilitates better understanding of the physiology of passive expiration than does a single-compartment model.

We combined 10 individual  $\dot{V}_E V$  and pressure-volume (PV) traces taken at the end of 20 min of ventilation at each PEEP and  $V_T$  combination using methods described by Guttman (Guttman *et al.* 1995) and Kondili (Kondili *et al.* 2002). From these data, we created ensemble  $\dot{V}_E V$  and PV curves for each animal for all combinations of injury state, each combination of  $V_T$  and PEEP. From these data, we calculated values for  $\tau_E$  of the respiratory



**Figure 1.** Graphical representation of the method used to derive segmental expiratory time constants ( $\tau_E$ ) values. (A) Flow–volume ( $\dot{V}V$ ) curve (black line), a pressure–volume (PV) curve using pressures measured at the ventilator wye and including the effects of the endotracheal tube and ventilator apparatus (dashed line), and a PV curve using tracheal pressures excluding the effects of the endotracheal tube and ventilator apparatus (dotted line) were created for each animal. Each ensemble from maximum expiratory flow to end expiration was divided into five equivolometric segments. (B) For each segment the expiratory  $\dot{V}V$  curve was replaced by a least squares fitted straight line. (C) The slope of each segment provides the  $\tau_E$  for that segment. In this figure, only the expiratory time constant of the respiratory system ( $\tau_{E,RS}$ ) is displayed.

system *excluding* the endotracheal tube and ventilator apparatus using  $P_{TR}$ . To allow the assessment of  $\tau_E$  heterogeneity, the  $V_E$  from the point of maximum  $\dot{V}_E$  to the end of expiration (defined as  $\dot{V}_E$  less than 0.05 L/sec) for each ensemble was divided into five equal volume segments ( $V_{E1} - V_{E5}$ ). We chose to use five segments in keeping with methods from similar studies (Guttmann et al. 1995; Kondili et al. 2002). Each of the five  $V_E$  segments was assumed to have  $E$  and  $R$  values that did not vary throughout the duration of the segment. Therefore for each  $V_E$  segment, the  $\tau_E$  was calculated as the quotient of  $R_{RS}$  and  $E_{RS}$ .  $R_{RS}$  was calculated as  $(P_{TR} - P_{ATM}) / \dot{V}_E$  and  $E_{RS}$  as  $\Delta P_{TR} / \Delta V_E$  for the  $V_E$  segment in question. This method allowed the calculation of unique respiratory system time constants for each of the five  $V_E$  segments (named  $\tau_{E1}$  through  $\tau_{E5}$ ) from the point of maximum  $\dot{V}_E$  to end expiration (Fig. 1).

### Statistical analyses and model

Descriptive statistics are displayed as mean  $\pm$  standard deviation. Other values are displayed as mean and 95% confidence intervals (CI). Continuous variables were analyzed using paired  $t$  tests (within animal) or two-sample  $t$

tests (between animals), where appropriate. All tests were two-sided and the statistical significance was defined at  $P < 0.05$ . Statistical analyses were performed using STATA 10.0 Statistical Software (StataCorp, College Station, TX) and SAS (SAS Institute, Inc., NC).

Expired time constants values were analyzed by linear mixed-effect model, including a random effect for each animal and fixed effects for segment, PEEP,  $V_T$ , and pre-post injury.

Significance of model coefficient estimates, least squares means, and differences in least squares means were determined by  $T$  test. Main effects and interactions were confirmed by use of  $F$  tests with type III sums of squares. All tests were performed at the 0.05 significance level. Differences in least squares means were adjusted for multiple testing using the Tukey–Kramer adjustment.

### Results

Before lung injury, the animals demonstrated a  $PaO_2$  of  $197 \pm 51$  mmHg while ventilated with a  $V_T$  of 10 cc/kg, 0 cm H<sub>2</sub>O PEEP and an  $FiO_2$  of 0.5. Thirty minutes after injury,  $PaO_2$  decreased to  $68 \pm 10$  mmHg and was  $69 \pm 19$  mmHg prior to euthanasia ( $P < 0.01$  for both

time points compared to preinjury values). During the same preinjury ventilation conditions, FRC was  $14.3 \pm 2.5$  mL/kg and decreased to  $9 \pm 2.9$  mL/kg after injury ( $P < 0.01$ ).  $E_{RS}$  and  $R_{RS}$  both increased with experimental injury due to significant increases in both  $E_L$  and  $R_L$  ( $P < 0.01$  for both) and no changes in  $E_{CW}$  or  $R_{CW}$  ( $P > 0.05$ ). Descriptive pulmonary mechanical data are presented in Table 1.

### Effect of injury status, PEEP, and tidal volume on expiratory time constants

Under all conditions of PEEP and  $V_T$ ,  $\tau_E$  increased throughout expiration both before and after injury (Table 2 and Fig. 2). Segmented  $\tau_E$  values increased throughout expiration with a slope that was different than zero ( $P < 0.01$ ). The expired time constant increased by an average of 45.08 msec per segment when  $\tau_E$  segment was treated as a continuous variable (36.07, 54.08; 95% CI). The model used for this analysis included an interaction between segment and injury. The main effect of segment as a continuous covariate was significant with and without interaction terms. Congruent with these findings,  $\tau_{E1}$  and  $\tau_{E2}$  were significantly smaller than  $\tau_{E4}$  and  $\tau_{E5}$ ,  $\tau_{E3}$  showed significant difference from  $\tau_{E4}$  and  $\tau_{E5}$ , and there was a difference between  $\tau_{E4}$  and  $\tau_{E5}$  ( $P < 0.01$  for all comparisons). When an interaction between injury status and  $\tau_E$  segment was included in the model, it was found to be significant ( $P < 0.05$ ), indicating that later

segments ( $\tau_{E4}$  and  $\tau_{E5}$ ) had higher values post injury compared to before injury.

Higher PEEP and  $V_T$  values were associated with higher  $\tau_E$  values (Figs. 3 and 4). The increase in  $\tau_E$  per 1 mL/kg increase in  $V_T$  and 1 cm H<sub>2</sub>O increase in PEEP and were 5.97 msec (3.23, 8.70; 95% CI) and 4.53 msec (2.34, 6.72; 95% CI), respectively. No evidence was found for an interaction between injury status and  $V_T$ , or between injury status and PEEP. The raw segment values for  $R_{RS}$ ,  $E_{RS}$ , and  $\tau_E$  are shown in Appendix.

### Effect of injury status, PEEP, and tidal volume on resistance and elastance

To further clarify the causative factors behind changes in  $\tau_E$  segments throughout expiration, we analyzed  $R_{RS}$  and  $E_{RS}$  on a per segment basis using the same methods applied to  $\tau_E$  segments  $\tau_{E1}$  to  $\tau_{E5}$ . Both  $R_{RS}$  and  $E_{RS}$  were significantly increased after injury compared to before injury in early  $V_E$  segments (Tables 3 and 4). Segment values for  $R_{RS}$  and  $E_{RS}$  after injury were statistically similar to values before injury ( $P > 0.05$ ).

The differing values for  $R_{RS}$  and  $E_{RS}$  between pre- and post injury status was confirmed by the presence of a significant interaction effect between injury status and segment ( $P < 0.01$ ). The effect of segment on  $R_{RS}$  as a continuous variable was not significant. However, segment as a categorical covariate was significant ( $P < 0.01$ ) in determining the value of  $R_{RS}$ . The estimated slope of

**Table 1.** Pulmonary mechanical data before and after experimental lung injury.

	$E_{RS}$ (cm H <sub>2</sub> O/L)	$R_{RS}$ (cm H <sub>2</sub> O/L/sec)	$E_L$ (cm H <sub>2</sub> O/L)	$R_L$ (cm H <sub>2</sub> O/L/sec)	$E_{CW}$ (cm H <sub>2</sub> O/L)	$R_{CW}$ (cm H <sub>2</sub> O/L/sec)
Before injury	$37.6 \pm 11.9$	$7.1 \pm 1.6$	$25.5 \pm 10.0$	$6.1 \pm 1.6$	$12.1 \pm 4.7$	$1.0 \pm 0.3$
After injury	$65.6 \pm 27.6$	$18.2 \pm 5.7$	$55.4 \pm 27.8$	$16.9 \pm 5.4$	$10.2 \pm 3.3$	$1.3 \pm 1.0$
<i>P</i> value	0.010	0.0026	0.011	0.0024	0.16	0.29

$E_{RS}$ , elastance of the respiratory system;  $E_L$ , elastance of the lung;  $E_{CW}$ , elastance of the chest wall;  $R_{RS}$ , resistance of the respiratory system;  $R_L$ , resistance of the lung;  $R_{CW}$ , resistance of the chest wall. Elastance data for this table were collected during end-inspiratory plateau conditions.

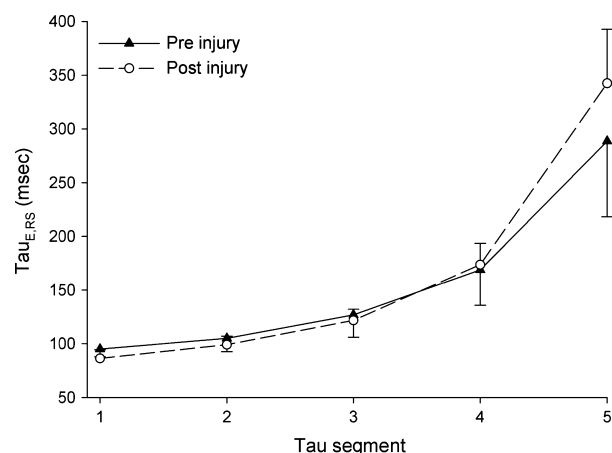
All data are presented as mean and 95% confidence intervals. *P* value compares the before and after injury values.

**Table 2.** Effect of injury by expired volume segment on  $\tau_E$ .

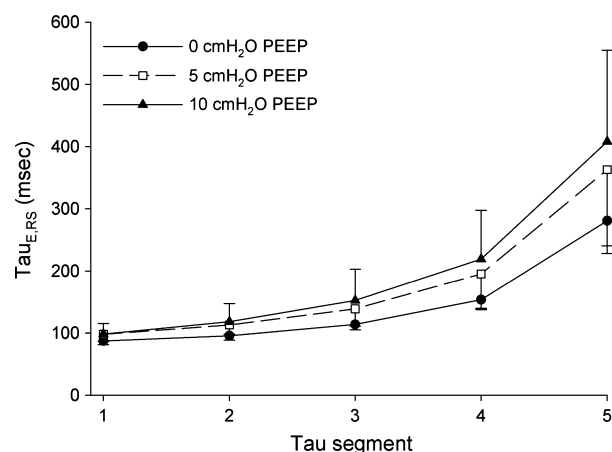
	$\tau_{E,RS1}$ (msec)	$\tau_{E,RS2}$ (msec)	$\tau_{E,RS3}$ (msec)	$\tau_{E,RS4}$ (msec)	$\tau_{E,RS5}$ (msec)
Before injury	95.1 (46.6, 143.7)	105.1 (56.5, 153.7)	126.9 (78.3, 175.4)	168.9 (120.4, 217.5)	288.6 (240.1, 337.2)
After injury	86.4 (37.9, 135.0)	99.1 (50.6, 147.7)	121.8 (73.2, 170.3)	173.7 (125.2, 222.3)	342.4 (298.9, 391.0)
Difference	-8.7 (-67.8, 50.4)	-6.0 (-65.1, 53.1)	-5.1 (-64.2, 53.9)	4.8 (-54.2, 63.9)	53.8 (-5.3, 112.9)

$\tau_{E,RS1-5}$ , expiratory time constant for expired volume slice 1 through 5; msec, milliseconds. All data are presented as mean and 95% confidence intervals.

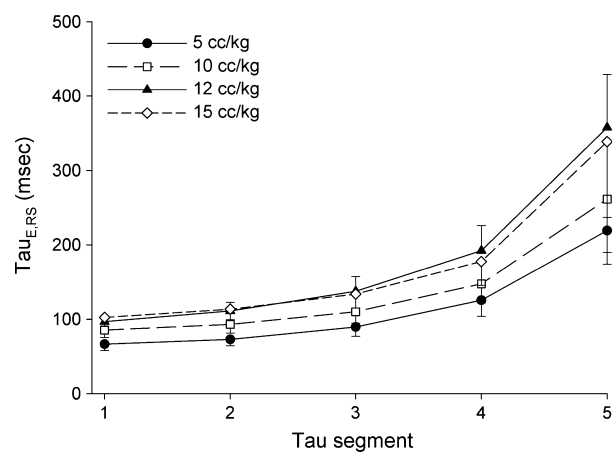




**Figure 2.** Values for  $\tau_{E,RS1}$  to  $\tau_{E,RS5}$  before and after injury are displayed as mean values  $\pm$  95% confidence interval.



**Figure 3.** Values for  $\tau_{E,RS1}$  to  $\tau_{E,RS5}$  at each positive end-expiratory pressure (PEEP) setting are displayed as mean values  $\pm$  95% confidence interval.



**Figure 4.** Values for  $\tau_{E,RS1}$  to  $\tau_{E,RS5}$  at each tidal volume ( $V_T$ ) setting are displayed as mean values  $\pm$  95% confidence interval.

$E_{RS}$  by segment was  $-6.76$  ( $-10.14, -3.38$ ; 95% CI) and was significant ( $P < 0.01$ ). Segment remained a significant continuous covariate when included in the model for  $E_{RS}$  without an interaction term. No evidence of other interactions was found.

Relative values (comparing postinjury to preinjury state) for  $R_{RS}$  and  $E_{RS}$  for each volume segment are shown in Figure 5, while raw values are shown in Appendix. Over both states of injury,  $R_{RS1}$  is significantly different from all subsequent segments except for  $R_{RS5}$  ( $P < 0.01$ ), as is the difference between  $R_{RS5}$  and  $R_{RS1} - R_{RS4}$  ( $P < 0.01$ ). However, the differences in  $R_{RS}$  by segment may have been driven by postinjury values, as no significant differences were found between  $R_{RS}$  segments preinjury. Post injury,  $R_{RS1}$  differs from all other segments post injury ( $P < 0.01$ ). For  $E_{RS}$ ,  $E_{RS1}$  and  $E_{RS2}$  were significantly different from  $E_{RS3}$ ,  $E_{RS4}$ , and  $E_{RS5}$  ( $P < 0.01$ ), as is the  $E_{RS3}$  from  $E_{RS4}$  and  $E_{RS5}$  ( $P < 0.01$ ). Within injury state, postinjury differences again outnumbered the preinjury segment differences; Post injury,  $E_{RS1}$  is different from all others ( $P < 0.01$ ),  $E_{RS2}$  is significantly different from  $E_{RS3}$ ,  $E_{RS4}$ , and  $E_{RS5}$  ( $P < 0.01$ ), and  $E_{RS3}$  and  $E_{RS5}$  are different ( $P < 0.01$ ). Pre injury, only  $E_{RS1}$  is significantly different from  $E_{RS4}$  and  $E_{RS5}$  ( $P < 0.05$ ).

Finally, we found that changes in PEEP or  $V_T$  altered  $R_{RS}$  and  $E_{RS}$ . A 1 cm H<sub>2</sub>O increase in PEEP increased  $R_{RS}$  by 0.21 cm H<sub>2</sub>O/L/sec (0.09, 0.33; 95% CI), and increased  $E_{RS}$  by 1.21 cm H<sub>2</sub>O/L (0.34, 2.08; 95% CI). A 1 mL/kg increase in  $V_T$  increased  $R_{RS}$  by 0.24 cm H<sub>2</sub>O/L/sec (0.09, 0.38; 95% CI), but did not have any significant effect on  $E_{RS}$ .

## Discussion

The current study has three main findings. First, consistent with our previous work (Henderson et al. 2015),  $\tau_E$  increased throughout expiration, and injury increased the difference between late and early  $\tau_E$  segments compared to before injury. These changes were due to increases in both  $R_{RS}$  and  $E_{RS}$ . Second, we found that manipulating PEEP or  $V_T$  did not have a differential effect on  $\tau_E$  between injured and uninjured states in a segmented model of expiration. Third, increases in both PEEP and  $V_T$  increased  $R_{RS}$ , a finding that has potential clinical implications for the choice of mechanical ventilation strategy in patients with ARDS or lung injury.

## Injury and time constants

Using a single-compartment model rather than a segmented model, we observed that injury decreased average  $\tau_E$  values compared with before injury (Table 2). The decreased  $\tau_E$  observed in the postinjury state is related to a

**Table 3.** Effect of injury by expired volume segment on  $R_{RS}$ .

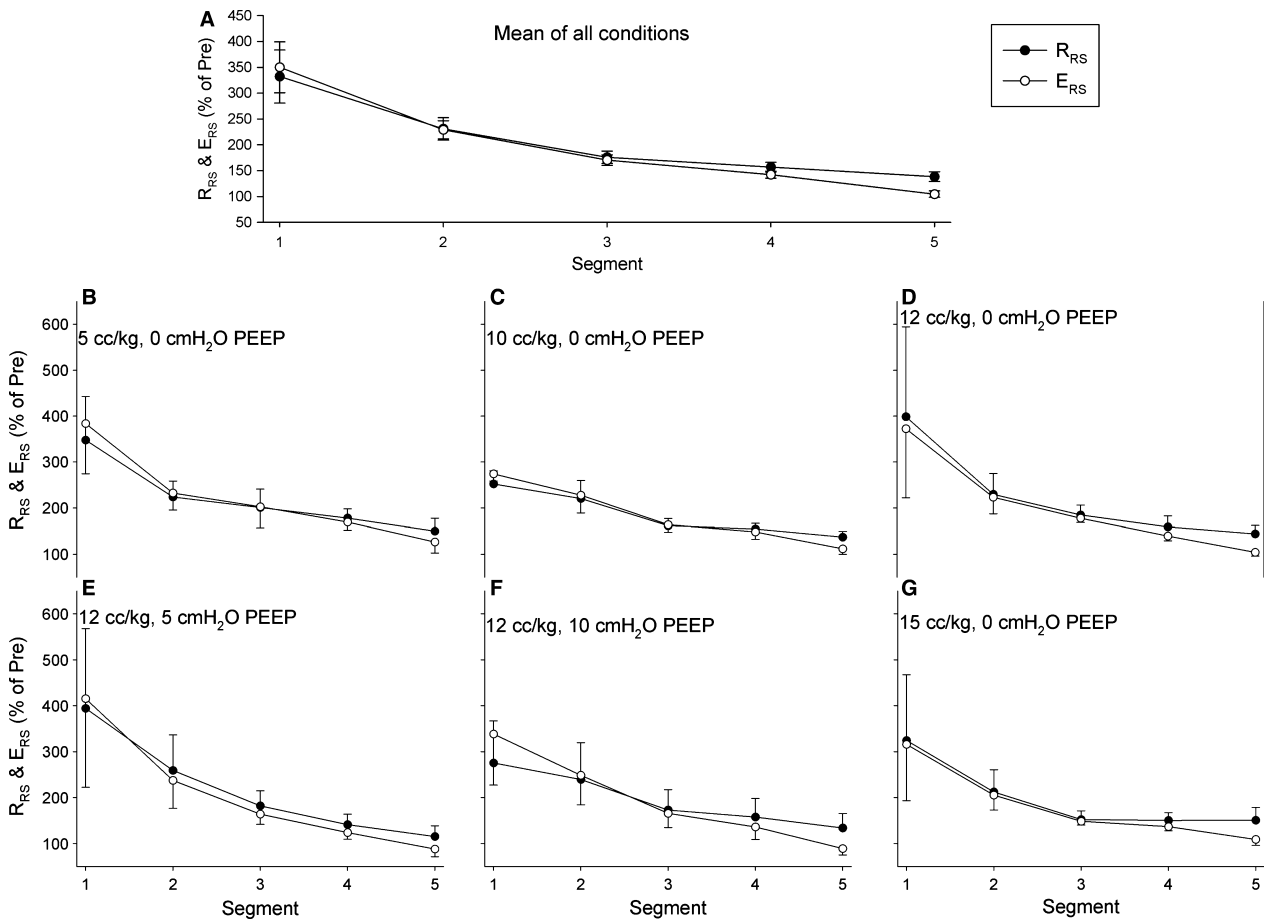
	$R_{RS1}$ (cm H <sub>2</sub> O/L/sec)	$R_{RS2}$ (cm H <sub>2</sub> O/L/sec)	$R_{RS3}$ (cm H <sub>2</sub> O/L/sec)	$R_{RS4}$ (cm H <sub>2</sub> O/L/sec)	$R_{RS5}$ (cm H <sub>2</sub> O/L/sec)
Before injury	5.3 (3.6, 7.0)	4.6 (2.9, 6.4)	4.4 (2.7, 6.1)	4.8 (3.0, 6.5)	7.4 (5.7, 9.1)
After injury	14.3 (12.6, 16.1)	9.4 (7.7, 11.2)	7.0 (5.3, 8.7)	6.9 (5.1, 8.6)	8.5 (6.7, 10.2)
Difference	9.1 (5.9, 12.2)	4.8 (1.7, 7.9)	2.6 (-0.5, 5.7)	2.1 (-1.0, 5.2)	1.1 (-2.0, 4.2)

$R_{RS1-5}$ , respiratory system resistance for expired volume slice 1 through 5. All data are presented as mean and 95% confidence intervals.

**Table 4.** Effect of injury by expired volume segment on  $E_{RS}$ .

	$E_{RS1}$ (cm H <sub>2</sub> O/L)	$E_{RS2}$ (cm H <sub>2</sub> O/L)	$E_{RS3}$ (cm H <sub>2</sub> O/L)	$E_{RS4}$ (cm H <sub>2</sub> O/L)	$E_{RS5}$ (cm H <sub>2</sub> O/L)
Before injury	54.1 (39.6, 68.5)	45.1 (30.6, 59.5)	36.5 (22.0, 50.9)	30.5 (16.0, 44.9)	27.6 (13.1, 42.0)
After injury	159.8 (145.4, 174.3)	96.1 (81.7, 110.6)	60.6 (46.1, 75.0)	42.8 (28.4, 57.3)	27.5 (13.0, 41.9)
Difference	105.8 (82.3, 129.2)	51.0 (27.6, 74.5)	24.1 (0.6, 47.5)	12.3 (-11.1, 35.8)	0.1 (-23.4, 23.5)

$E_{RS1-5}$ , elastance for expired volume slice 1 through 5. All data are presented as mean and 95% confidence intervals.



**Figure 5.** Relative values (comparing postinjury to preinjury state) for  $R_{RS}$  and  $E_{RS}$  for each equivolumic segment. Values are displayed as the mean of all positive end-expiratory pressure (PEEP) and tidal volume ( $V_T$ ) values (A), and for individual combinations of PEEP and  $V_T$  (B–G).

relative decrease in  $R_{RS}$  compared to  $E_{RS}$ . Following lung injury, we found that increases in  $R_{RS}$  and  $E_{RS}$  were driven by increases in  $R_L$  and  $E_L$  with no significant changes in  $R_{CW}$  and  $E_{CW}$ . Accordingly, the absence of mechanical alterations to the chest wall suggests that the injury used in this model was confined to the lungs (Table 1). When assessed from the perspective of a single compartment (i.e., not segmented), increases in  $E_L$  were greater than those in  $R_L$  and therefore  $\tau_E$  decreased after injury.

Many methods of calculating  $\tau_E$  assume that all lung units inflate and deflate as a single compartment and are thus unable to distinguish between units that fill/empty quickly and units that require greater time. We therefore employed a segmental method that can be used to more accurately describe the pattern of lung emptying during passive expiration, potentially providing more insight into the degree of pulmonary mechanical heterogeneity than is afforded by a single-compartment model (Guttmann et al. 1995; Lourens et al. 2000; Kondili et al. 2002, 2004; Henderson et al. 2015). When a segmented model was used to analyze our data, we were able to observe the mechanical properties of passive expiration with a higher degree of resolution than is afforded by the single-compartment model. In a segmented model, injury increased the difference between later versus earlier segment  $\tau_E$  values – that is, injury decreased the average  $\tau_E$  in early segments, and increased the average  $\tau_E$  for later segments compared to the uninjured state (Table 2 and Fig. 2).

When compared with uninjured values, both  $R_{RS}$  and  $E_{RS}$  after injury are roughly threefold higher at the beginning of expiration (Fig. 5A) before returning to values similar to those in uninjured lungs by the end of expiration. While both  $R_{RS}$  and  $E_{RS}$  increased postinjury, the increase in  $E_{RS}$  in absolute terms was greater, causing early  $\tau_E$  values (e.g.,  $\tau_{E1}$  in Table 2) to be smaller after injury compared to before injury. Throughout expiration, values of  $E_{RS}$  decreased more rapidly than  $R_{RS}$ , causing late  $\tau_E$  segment values to be higher (e.g.,  $\tau_{E5}$  in Table 2).

### PEEP and tidal volume

We found that increasing both PEEP and  $V_T$  increased  $\tau_E$ , but that these effects did not differ between the uninjured and injured states (Figs. 3 and 4). We demonstrated that increases in PEEP increased  $R_{RS}$  and increased  $E_{RS}$ , while increases in  $V_T$  increased  $R_{RS}$  alone. The independent effects of PEEP and  $V_T$  on  $\tau_E$  segments appeared consistent throughout expiration, that is, they were not confined to early or late  $\tau_E$  segments.

It is instructive to compare our results with those of other investigators. Kondili and colleagues reported effects of PEEP that differed from ours (Kondili et al. 2002). They found that in subjects with ARDS who were venti-

lated without PEEP,  $\tau_E$  and  $R_{RS}$  increased significantly in late expiration and that the addition of PEEP eliminated these findings. One result of the application of PEEP is that small airways are “splinted” open, and are less likely to close prematurely. The increased patency of small airways may allow more rapid exhalation, thereby resulting in smaller  $\tau_E$  values with higher PEEP, particularly in late expiration. This widely accepted concept supplies a satisfying explanation for the effect of PEEP in Kondili’s results. However, other authors have found patterns of expiration and effects of applied PEEP that are more similar to our results. Pesenti and colleagues found that PEEP increased  $R_{RS}$  in patients with ARDS and in normal controls (Pesenti et al. 1991). In patients with ARDS, Mols and colleagues observed that the pattern of  $\tau_{E1-5}$  and  $R_{RS1-5}$  was highly variable, with patients demonstrating steady increases, steady declines, or no discernible pattern during passive expiration (Mols et al. 2001). Similarly, other authors have demonstrated that increases in PEEP and  $V_T$  increase  $R_{RS}$  in subjects with lung injury or ARDS (Auler et al. 1990; Tantucci et al. 1992; Pelosi et al. 1995). Current management of ARDS often involves the use of high PEEP levels. In general, this improves oxygenation and may decrease new ventilator-associated lung injury (Gattinoni et al. 2012). However, our data suggest that increased PEEP or  $V_T$  may prolong expiration due to increased emptying time for lung units with long time constants. This may be of relevance in patients who develop ARDS in the context of lung disease that predisposes them to long time constants or gas trapping, such as COPD or asthma. In this subset of patients, a more conservative PEEP strategy may be warranted.

There are several possible explanations for the finding that increases in PEEP or  $V_T$  may increase  $R_{RS}$ . First, injured lung is characterized by inhomogeneity of distension, and high levels of PEEP could further overdistend some units, thereby increasing time constant inhomogeneity. Second, increased  $R_{RS}$  at higher PEEP or  $V_T$  values may in part be due to stress adaptation phenomena and specifically increases in viscoelastic resistance at higher PEEP values and lung volumes (Pesenti et al. 1991; Pelosi et al. 1995). Third, it has been suggested that the longitudinal stretching of airways at high PEEP and  $V_T$  levels may narrow their cross-sectional area and thus increase resistance to gas flow (Eissa et al. 1991a). Given these data, observation of the pattern of  $\tau_E$  during expiration may facilitate the choice of less injurious strategies of mechanical ventilation during the care of patients with ARDS or lung injury.

### Limitations

The current experiment reveals novel findings regarding the relationships between lung injury, the parameters of



mechanical ventilation, and the pattern of  $\dot{V}_E$ . However, several limitations must be considered. First, we did not measure  $P_{TR}$  directly in this experiment. Instead, like Guttman, we estimated  $P_{TR}$  from  $P_{AW}$  using a previously validated method (Guttman et al. 1993, 1995; Zhao et al. 2010). Guttman and colleagues measured  $P_{AW}$  at the ventilator wye and observed that the calculated  $\tau_E$  for sequential volume segments in mechanically ventilated ARDS patients were almost identical throughout expiration (Guttman et al. 1995). The similar  $\tau_E$  was due to the significant flow-dependent resistance of the endotracheal tube and ventilator ( $R_{AW}$ ) (Wright and Bernard 1989; Guttman et al. 1993). Given that flow is greatest at the onset of passive expiration, the relative contribution of  $R_{AW}$  on  $\tau_E$  is higher during early expiration and lower in late expiration, which masks the influence of  $R_L$  (Wright and Bernard 1989; Guttman et al. 1993). When they eliminated the effect of the endotracheal tube by estimating  $P_{TR}$  and used these values to calculate segmental values for  $\tau_E$ , Guttman and colleagues found a pattern of steadily increasing  $\tau_E$  throughout expiration. Similarly, our data demonstrate that  $\tau_E$  increases steadily throughout expiration when a segmented model that excludes the resistance of the endotracheal tube was used (Fig. 2). However, some caution is warranted when using the model of endotracheal tube resistance compensation such as that used in this experiment. Clinical patients with ARDS may have secretions that can alter endotracheal tube resistance in ways that are not modeled by benchtop testing.

## Appendix

### Raw values for selected pulmonary mechanical variables by expired volume segment.

$V_T$	PEEP (cm H <sub>2</sub> O)	Volume Segment	Pre			Post		
			$R_{RS}$ (cm H <sub>2</sub> O/L/sec)	$E_{RS}$ (cm H <sub>2</sub> O/L)	$\tau_E$ (msec)	$R_{RS}$ (cm H <sub>2</sub> O/L/sec)	$E_{RS}$ (cm H <sub>2</sub> O/L)	$\tau_E$ (msec)
5 mL/kg	0	1	2.80 ± 0.78	41.02 ± 12.76	70.39 ± 12.51	9.25 ± 4.48	143.01 ± 60.48	62.76 ± 11.61
		2	2.93 ± 0.67	39.58 ± 8.56	75.49 ± 13.32	6.28 ± 2.20	90.55 ± 33.48	70.29 ± 11.82
		3	3.45 ± 1.01	38.42 ± 8.20	91.35 ± 19.74	6.35 ± 2.34	74.13 ± 27.15	87.62 ± 16.56
		4	4.01 ± 0.86	34.15 ± 8.08	124.90 ± 38.10	7.00 ± 1.92	58.07 ± 18.76	126.16 ± 24.62
		5	5.47 ± 1.78	28.79 ± 9.36	203.46 ± 75.87	7.37 ± 2.09	33.58 ± 11.70	235.24 ± 53.06
10 mL/kg	0	1	3.97 ± 1.14	43.59 ± 9.64	90.02 ± 14.92	9.65 ± 2.68	116.61 ± 16.97	80.98 ± 13.73
		2	3.65 ± 0.87	39.42 ± 9.94	94.65 ± 17.13	7.51 ± 1.78	85.30 ± 23.93	91.18 ± 16.95
		3	3.99 ± 0.73	36.90 ± 5.81	110.96 ± 23.21	6.24 ± 0.89	60.46 ± 13.97	108.93 ± 21.88
		4	4.34 ± 0.89	31.50 ± 6.15	144.29 ± 39.92	6.47 ± 0.81	45.90 ± 10.33	150.71 ± 35.35
		5	6.31 ± 2.13	28.98 ± 5.92	238.36 ± 107.91	8.16 ± 1.82	31.82 ± 7.39	284.91 ± 100.36
12 mL/kg	0	1	4.79 ± 1.52	49.16 ± 14.25	96.79 ± 14.43	14.14 ± 7.69	149.95 ± 71.98	91.99 ± 13.97
		2	4.33 ± 1.30	43.62 ± 15.65	103.16 ± 18.40	9.21 ± 3.12	91.07 ± 27.21	101.98 ± 16.63
		3	3.89 ± 0.66	33.10 ± 6.27	121.45 ± 25.22	6.95 ± 1.09	59.02 ± 12.42	121.86 ± 18.84

(Continued)

## Conclusions

Our study provides several novel insights into the details of expiratory gas flow in animals before and after experimental lung injury. It has previously been observed that  $\tau_E$  values are smaller in subjects with injured lungs when compared to controls. However, we are the first to demonstrate this change within subjects and that  $\tau_E$  increased throughout expiration both before and after injury when examined with a multiple compartment model. Finally, we have demonstrated that increases in PEEP or  $V_T$  increased  $\tau_E$  throughout expiration, but did not appear to have effects that differed between the uninjured and injured state. Whether incorporating the pattern of  $\tau_E$  will improve strategies of mechanical ventilation in lung injury and ARDS needs to be assessed in future studies.

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## Conflict of Interest

None declared.

## Appendix. Continued.

$V_T$	PEEP (cm H <sub>2</sub> O)	Volume Segment	Pre			Post			
			$R_{RS}$ (cm H <sub>2</sub> O/L/sec)	$E_{RS}$ (cm H <sub>2</sub> O/L)	$\tau_E$ (msec)	$R_{RS}$ (cm H <sub>2</sub> O/L/sec)	$E_{RS}$ (cm H <sub>2</sub> O/L)	$\tau_E$ (msec)	
		4	4.60 ± 1.20	30.53 ± 6.70	156.62 ± 44.02	6.81 ± 1.05	41.89 ± 8.06	169.40 ± 32.67	
		5	7.02 ± 3.12	28.20 ± 6.36	266.85 ± 127.02	9.21 ± 2.85	28.92 ± 5.94	338.55 ± 114.55	
		5	1	5.89 ± 2.06	57.53 ± 19.26	101.23 ± 13.41	17.02 ± 8.87	176.77 ± 78.07	94.50 ± 19.94
		2	4.99 ± 1.39	45.84 ± 14.11	113.16 ± 27.05	10.85 ± 3.48	98.40 ± 31.72	112.23 ± 13.84	
		3	4.45 ± 1.39	34.34 ± 8.30	138.47 ± 53.03	7.33 ± 1.70	54.73 ± 14.47	138.95 ± 25.55	
		4	5.24 ± 2.29	29.66 ± 6.76	195.02 ± 106.88	6.53 ± 1.39	35.94 ± 9.40	194.97 ± 55.95	
		5	10.97 ± 8.69	30.06 ± 9.71	359.14 ± 252.48	7.75 ± 2.66	22.59 ± 5.16	366.49 ± 126.25	
		10	1	8.05 ± 2.39	75.98 ± 21.50	106.19 ± 22.35	18.52 ± 10.52	211.11 ± 84.45	89.93 ± 26.05
		2	6.87 ± 2.26	56.84 ± 15.54	129.55 ± 57.07	12.95 ± 4.26	122.80 ± 36.86	106.62 ± 16.74	
		3	6.08 ± 2.43	41.77 ± 11.06	165.48 ± 102.51	8.71 ± 2.10	64.25 ± 17.74	139.31 ± 20.17	
	15 mL/kg	0	4	5.81 ± 3.13	29.11 ± 6.42	221.92 ± 150.90	7.75 ± 3.05	36.93 ± 11.97	216.26 ± 64.67
			5	7.31 ± 4.39	22.53 ± 4.86	375.12 ± 271.56	8.39 ± 3.98	19.05 ± 5.50	440.72 ± 139.74
			1	6.17 ± 2.01	57.13 ± 14.99	106.23 ± 15.33	17.41 ± 13.24	162.55 ± 100.61	98.47 ± 19.98
			2	5.06 ± 1.59	45.10 ± 14.08	114.58 ± 20.68	9.80 ± 3.24	88.55 ± 26.18	112.34 ± 21.17
			3	4.42 ± 0.77	34.44 ± 6.90	133.52 ± 27.92	6.50 ± 1.07	50.90 ± 10.48	133.88 ± 28.33
		4	4.57 ± 0.84	27.95 ± 4.40	170.75 ± 46.66	6.64 ± 1.03	38.17 ± 7.34	184.88 ± 48.11	
		5	7.24 ± 2.80	26.82 ± 5.27	288.82 ± 134.81	9.95 ± 3.11	29.07 ± 7.90	388.69 ± 153.55	

$V_T$ , tidal volume; mL/kg, milliliters per kilogram of body weight;  $R_{RS}$ , resistance of the respiratory system;  $E_{RS}$ , elastance of the respiratory system;  $\tau_E$ , time constant of expiration; Pre, before injury; Post, after injury. All data are presented as mean and 95% confidence intervals.

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