ORIGINAL CLINICAL REPORT

OPEN

Feasibility of Setting the Tidal Volume Based on End-Expiratory Lung Volume: A Pilot Clinical Study

Alice Grassi, MD[1]
Maddalena Teggia-Droghi, MD[2]
Asia Borgo, MD[3]
Konstanty Szudrinsky, MD, PhD[4]
Giacomo Bellani, MD, PhD[5,6]

OBJECTIVES: To assess the feasibility of setting the tidal volume (TV) as 25% of the actual aerated lung volume (rather than on ideal body weight) in patients with Acute Respiratory Distress Syndrome (ARDS).

DESIGN: Physiologic prospective single-center pilot study.

SETTING: Medical ICU specialized in the care of patients with ARDS.

PATIENTS: Patients with moderate-severe ARDS deeply sedated or paralyzed, undergoing controlled mechanical ventilation with a ventilator able to measure the end-expiratory lung volume (EELV) with a washin, washout technique.

INTERVENTIONS: Three-phase study (baseline, strain-selected TV setting, ventilation with strain-selected TV for 24 hr). The TV was calculated as 25% of the measured EELV minus the static strain due to the applied positive end-expiratory pressure.

MEASUREMENTS AND MAIN RESULTS: Gas exchanges and respiratory mechanics were measured and compared in each phase. In addition, during the TV setting phase, driving pressure (DP) and lung strain (TV/EELV) were measured at different TVs to assess the correlation between the two measurements. The maintenance of the set strain-selected TV for 24 hours was safe and feasible in 76% of the patients enrolled. Three patients dropped out from the study because of the need to set a respiratory rate higher than 35 breaths per minute to avoid respiratory acidosis. The DP of the respiratory system was a satisfactory surrogate for strain in this population.

CONCLUSIONS: In our population of 17 patients with moderate to severe ARDS, setting TV based on the actual lung size was feasible. DP was a reliable surrogate of strain in these patients, and DP less than or equal to 8 cm H_2O corresponded to a strain less than 0.25.

KEYWORDS: acute respiratory distress syndrome; driving pressure; end-expiratory lung volume; lung strain; tidal volume

The low-respiratory system compliance (C_{RS}) observed in acute respiratory distress syndrome (ARDS) is proportional to the loss of aerated lung volume (1). Lung strain, the deformation of lung parenchyma due to positive pressure ventilation (2), is associated with alveolar inflammation and ventilation-induced lung injury (3, 4). Strain is proportional to the ratio between tidal volume (TV) and its resting volume (functional residual capacity, FRC), which is reduced to a variable extent in patients with ARDS. In this context, although guidelines recommend to target a protective ventilation strategy titrating TV on ideal body weight(5), ideally, a more protective ventilation should scale TV on actual ventilated lung size, hence avoiding an excessive strain. It is unknown if lung injury varies linearly with strain, or if a “safety threshold” exists, but some reports suggest an increased lung inflammation

DOI: 10.1097/CCE.0000000000001031

KEY POINTS

Questions: Is setting tidal volume (TV) based on the actual lung size (as estimated by end-expiratory lung volume) safe and feasible in acute respiratory distress syndrome patients? Is driving pressure (DP) a clinically valid surrogate of lung strain?

Findings: Setting TV based on the actual size of the baby lung is safe and feasible in the majority of patients enrolled. In this population, DP was a reliable surrogate of lung strain.

Meaning: Limiting lung strain is the objective of lung protective ventilation. Scaling the TV on actual lung size or targeting a low DP are clinically feasible ways of achieving this goal.

when the strain, also when calculated as the ratio TV/end-expiratory lung volume (EELV) exceeded a value around 0.25 (3, 4). Of note, this is also the "physiologic ratio" between a TV of 500 mL and an FRC of 2 L of a healthy person. This concept also gained popularity in recent years with the widespread use of driving pressure (DP) (6), which, given the proportionality between EELV and compliance, might represent a clinical surrogate of this term. In this respect, the role of positive end-expiratory pressure (PEEP) is twofold: on the one hand, PEEP may decrease strain (by promoting alveolar recruitment). On the other, even in the absence of recruitment, PEEP increases the resting volume of all alveolar units, thereby increasing "static strain."

We aim to verify if setting mechanical ventilation by targeting a lung strain lower than 0.25 is feasible in patients with ARDS. Second, we aim to assess if the DP of the respiratory system correlates with lung strain and could be potentially used as a surrogate for it.

MATERIALS AND METHODS

Patients admitted to the ICU, intubated, mechanically ventilated and diagnosed with ARDS since less than 96 hours according to the Berlin definition (7) were included. The exclusion criteria were age under 18 years, presence of spontaneous breathing, active air leaks, history of chronic obstructive pulmonary disease requiring home ventilation or oxygen therapy, emphysema, pulmonary fibrosis, impossibility to tolerate a 20% change in F_{IO_2}, presence or impending risk of extracorporeal membrane oxygenation. The study was approved by the research ethical board of Azienda Socio Sanitaria Territoriale of Monza with approval number 577 on March 27, 2018 with the title: "Tidal Volume Setting Based on End Expiratory Lung Volume: a safety and feasibility study". Informed consent was obtained from all participants. Study procedure followed the ethical standards of the institutional committee on human experimentation and the Helsinki Declaration of 1975. Anonymously collected data included age, sex, body mass index, arterial blood gas results, hemodynamic parameters, and ventilator settings. The study protocol included three sequential phases: baseline, TV setting phase, and strain-selected TV phase.

Baseline

Patients were connected to a CARESCAPE R860 ventilator, manufactured by General Electrics Healthcare (Waukesha, WI) with ability to measure EELV. The ventilation settings, maintained for at least 6 hours, were as follows: clinically set PEEP, TV of 6 mL/kg predicted body weight (PBW), respiratory rate (RR) to target a pH between 7.35 and 7.45. Hemodynamic and ventilatory parameters were recorded. Plateau pressure (Pplat) and intrinsic PEEP were measured; DP (Pplat-PEEP) and C_{RS} (TV/DP) were calculated. In the center where the study was conducted, PEEP is typically set by the clinicians based on physiologic considerations (a combination of best respiratory system compliance and oxygenation) (8).

Tidal Volume Setting Phase

EELV was measured at clinical PEEP, with an automatic, double measure (washin and washout) process performed by the ventilator, using a 20% F_{IO_2} change. This method, defined "oxygen washin, washout" was extensively described (9–11) and previously validated against classical techniques, such as helium dilution and the measurement of aerated lung volume on the CT scan (12), showing good correlation. In brief, the measurement estimates the dilution volume of a gas (which corresponds to the ventilated lung volume), by measuring the change in concentration of the inhaled and exhaled gas (nitrogen in this case).

EELV measured by washin, washout cannot be used directly in the calculation of strain, since PEEP will always increase EELV and hence, spuriously, decrease the strain. To take this effect into account, at the end of the measurement, the PEEP was decreased to zero and the ventilation mode was switched to pressure control with inspiratory peak pressure equal to the clinical PEEP value, RR 8, 3 s inspiratory time, 5 s expiratory time. The TV achieved in this phase (calculated as an average of three breaths) allowed to estimate the lung expansion due to PEEP ("static strain").

PEEP was then set back to the clinical level, and the TV was set as:

Strain-selected TV = (EELV – Static strain) × 0.25, up to a maximum of 8 mL/kg PBW.

Lastly, RR was adjusted to match the $Paco_2$ (± 5%) of the baseline phase.

Before moving on to the next study phase, DP was measured at increasing TV (and hence strain) of 4, 6, 8, 10, and 12 mL/kg, to assess the correlation between the two measurements.

Strain-Selected TV Phase

The strain-selected TV was maintained for 24 hr, when feasible. If required, RR was adjusted to maintain a pH between 7.35 and 7.45.

The study phases timeline is summarized in **Figure 1**.

"Feasibility" was defined as the possibility to maintain the strain-selected TV without the occurrence of any of the following: need to increase RR to greater than 35 breaths/min, hypoxemia requiring a greater than 20% Fio_2 change, the development of a Pplat greater than 30 cm H_2O, the need for paralytic agents' administration if not already administered at the time of enrollment.

STATISTICAL ANALYSIS

For this feasibility study, the sample size could not be inferred from previously published papers; therefore, we planned to enroll all patients who matched eligibility criteria during a 1-year period.

The statistical software SPSS 29.0 by IBM (Armonk, NY) was used for the analysis. Continuous data are

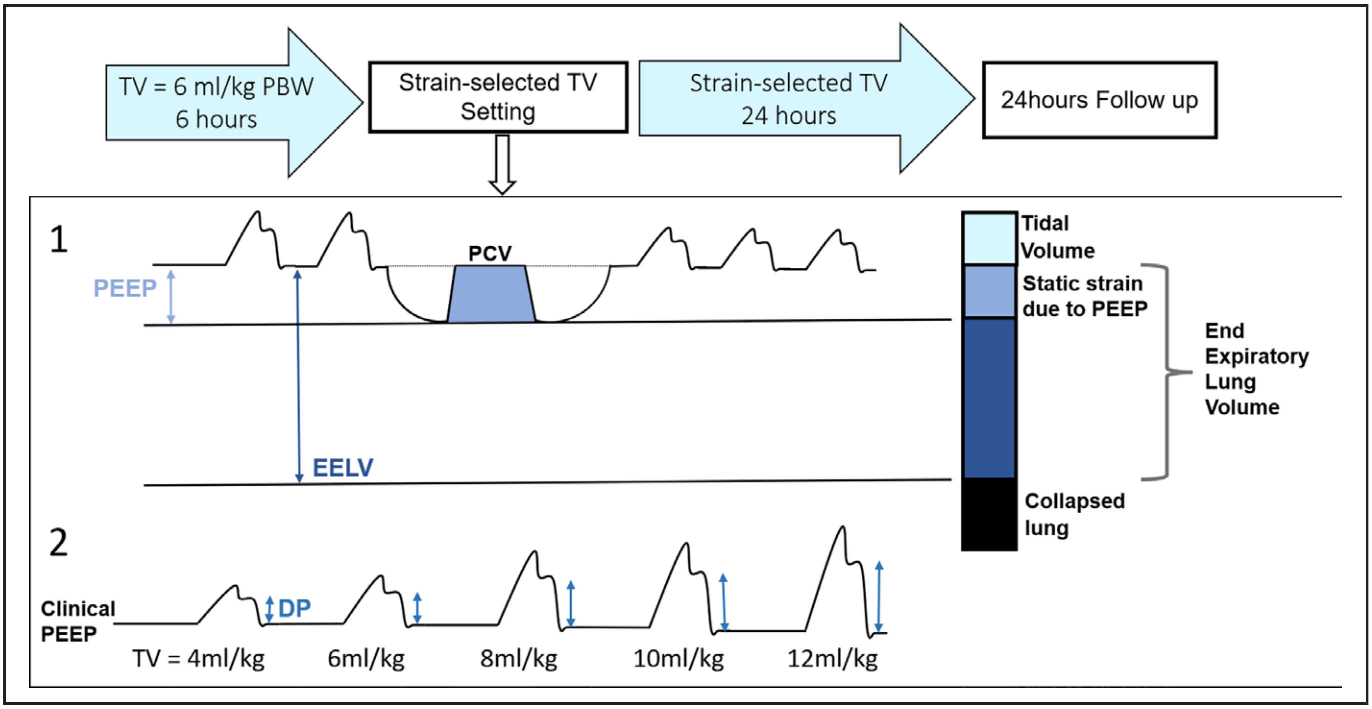

Figure 1. Methods. The time line at the top of the figure illustrates the three phases of the study. During the tidal volume (TV) setting, two different procedures were performed. Number 1 is the actual TV setting phase, were strain-selected TV is calculated as: 0.25 × (end-expiratory lung volume [EELV] – static strain due to positive end-expiratory pressure [PEEP]). The static strain due to PEEP was measured as the TV during a brief phase of pressure controlled ventilation (PCV) where the inspiratory pressure equals the clinical PEEP. The bar on the right *side* represents the lung volumes seen in overlap. Number 2 is the measurement of driving pressure (DP) at different TV (therefore at different strains). During procedure number 2, some breaths with the set TV were allowed to happen before measuring DP. PBW = predicted body weight.

expressed as mean ± SD, categorical data as number (%). Ventilation and gas exchange parameters were compared between the baseline, the start and the end of strain-selected TV phase. The normal distribution of data was assessed by Shapiro-Wilk test. Data were compared by paired *T*-test, one-way analysis of variance or Mann-Whitney *U* test, as appropriate. A *p* value of less than 0.05 was considered as statistically significant. A Pearson's linear correlation was drawn between DP and lung strain.

RESULTS

We enrolled 17 patients over the 1-year study period. Forty-seven percent (eight patients) were female, mean age was 62 ± 16 years, and mean time of invasive ventilation before inclusion was 0.9 ± 0.7 days.

Maintaining the strain-selected TV for 24 hours was feasible in 13 of 17 patients (76%). The reason for patients drop out was the need to set an RR higher than 35 breaths/min (three patients). In one patient the strain-selected TV was greater than 8 mL/kg, which was a criterion for discontinuing the study.

The clinical PEEP in the 17 patients enrolled was 12.4 ± 2.7 cm H_2O and this was left unchanged throughout the study.

The individual changes in TV, DP, strain, RR, and PaO_2/FIO_2 ratio between baseline and strain-selected TV setting phase are shown in **Fig. 2*A–E***. DP (Fig. 2*B*) significantly decreased from baseline to strain-selected TV phase (from 9 ± 1.7 cm H_2O to 7.6 ± 1.5 cm H_2O).

In the patients who reached the 24 hours time point, DP, RR, and the PaO_2/FIO_2 ratio remain unchanged (from strain-selected TV to 24 hours follow-up: DP 7.6 ± 1.5 cm H_2O to 8.6 ± 1.4 cm H_2O, $p = 0.26$; RR from 26.0 ± 5.2 to 25.3 ± 5.2 beats/min, $p = 0.29$; PaO_2/FIO_2 ratio 181.3 ± 52.1 to 190.6 ± 54.9, $p = 0.92$).

The correlation between DP of the respiratory system and measured lung strain was strong (**Fig. 3*A***), and it was even more accurate when the enrolled patients were classified into two groups. The first group (black dots) included the patients in whom continuation of strain-selected TV was feasible, the second one (orange dots) included those who dropped out because they required a RR increase to 35 breaths/min (**Fig. 3*B***).

DISCUSSION

The main result of this study is that setting TV based on the patient lung size, as estimated by EELV

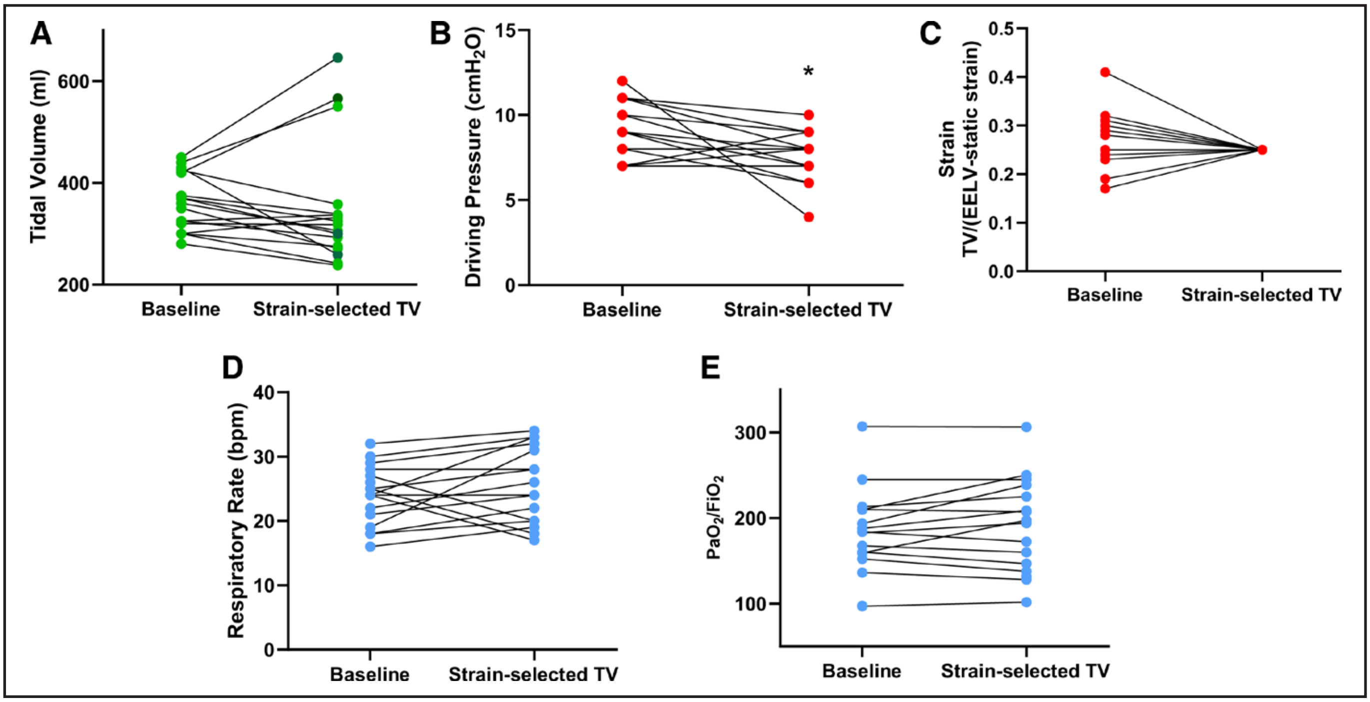

Figure 2. Changes in tidal volume (TV) (**A**), driving pressure (DP) (**B**), strain (TV/[end-expiratory lung volume-static strain] (**C**), respiratory rate (RR) (**D**), and PaO_2/FIO_2 (**E**) between the baseline phase (TV set at 6 mL/kg) and the strain-selected TV phase (TV set as 0.25 × [EELV − static strain]). In **A**, (TV) the *darker points* indicate the patients who dropped out. *$p < 0.05$.

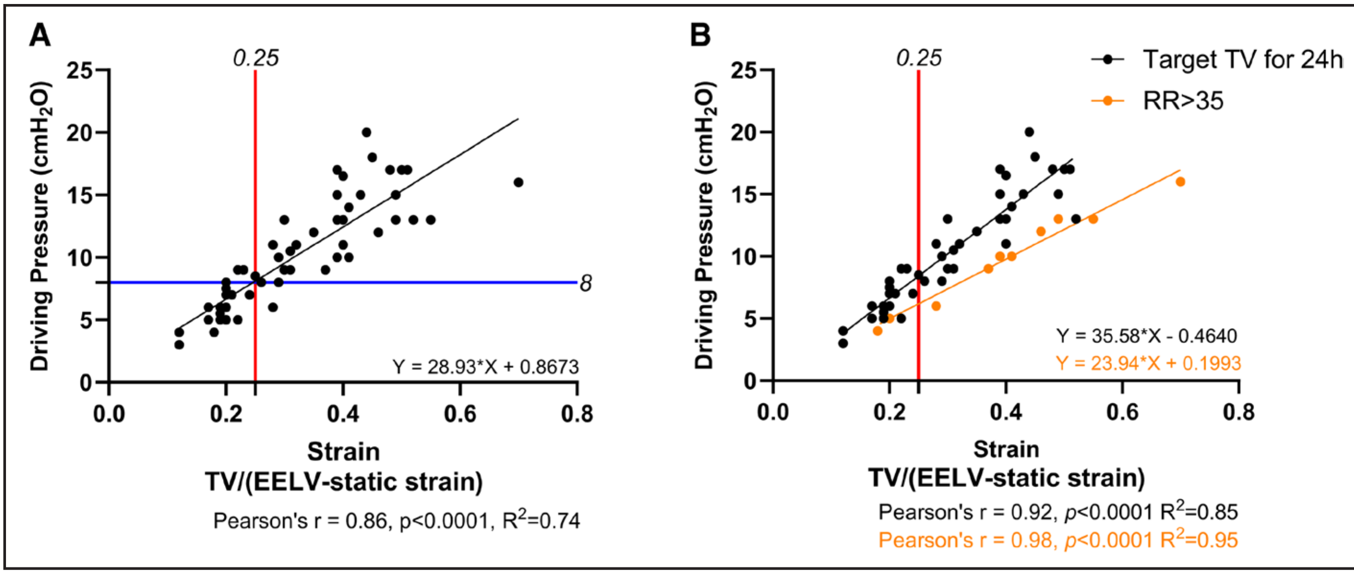

Figure 3. Correlation between driving pressure (DP) and lung strain. DP was measured in each patient after setting increasing tidal volume (TV) (4, 6, 8, 10, 12 mL/kg). **A** shows all the measurements performed (five dots per patient). **B** differentiates between the patients in whom the strain-selected TV was maintained for 24 hours and the ones who dropped out because of the need to increase the respiratory rate (RR).

measurement, was feasible in 76% of the patients enrolled. This led to an average decrease in DP of 1.3 cm H_2O with the strain-selected TV versus the 6 mL/kg TV, with no significant changes in RR and oxygenation in the patients who completed the study. At the 24 hours follow-up, the DP had returned to 8.6 ± 1.4, similar to the baseline value (TV of 6 mL/kg) of 9 ± 1.7 cm H_2O.

Additionally, the DP of the respiratory system provided a good estimate of the lung strain in this small population. Specifically, a DP lower than 8 cm H_2O was in all, but one case, associated with a strain less than 0.25.

The fact that the survival benefit conferred by lowering TV in ARDS depends on lung compliance has become clearer over the years. Starting from the ARDS network trial itself (13), there was an evidence that higher TV would increase mortality in patients with lower but not with higher C_{RS}. This is physiologically consistent with the baby lung concept (1), and indicates that lung strain, leading to inflammation, is a contributor to mortality. A more recent reanalysis of published studies, corroborates the dependence between the effect of TV on mortality and lung elastance (14).

Therefore, in the era of lung protective ventilation and individualized medicine, the attempt to measure the actual lung size and determine the most appropriate TV for the specific patient is imperative.

Despite setting TV based on the size of the aerated lung could seem clinically sound, this is rarely feasible at the bedside, because it requires a ventilator or a system (11) capable to measure of EELV from the exhaled gases. Given that this equipment is not always available, the correlation shown between measured strain and DP suggests that this could be a surrogate to allow a strain-based TV setting.

Indeed, the concept of DP is the one that constitutes a unifying point between lung compliance, TV and strain, as already shown (15). Our study brings further evidence on the linear relationship between DP and lung strain highlighting that an ultra protective ventilation strategy should target a DP lower than 8 cm H_2O. Not all the patients though behave in the same way and the same DP does not correspond to the same level of strain. Differently from Chiumello et al (2), we did not correlate lung strain with the transpulmonary DP, which reflects the strain to the lung and not to the respiratory system in its whole. It is possible that when noticing a different correlation between DP and strain in different patients, we are underlying a difference in chest wall compliance.

The fact that at 24 hours the DP had returned almost to the baseline value, could indicate slight alveolar derecruitment, possibly related to the lower strain-selected TV used in most of the patients. This suggests that the mechanical ventilation parameters, specifically the ones influencing strain (PEEP and TV) must be continuously reassessed to remain protective in a dynamic clinical context.

This study has several limitations. This is a single-center physiologic study, conducted on a small population treated with a uniform clinical approach, particularly concerning the setting of mechanical ventilation. Specifically, the study was conducted with the level of PEEP set by the clinician. PEEP influences EELV and it is a determinant of "static strain." In the center where the study was conducted, PEEP is usually set in an individualized and physiologically guided manner, looking for a balance between best compliance and oxygenation (8). Although knowing that no approach appears superiors to others in finding the "best PEEP," it is though possible that the results of this study were influenced by the "favorable" position on the pressure–volume curve of the respiratory system. This is also supported by the fact that in the baseline phase, the ventilation set by the clinician (selected PEEP and TV of 6 mL/kg) was already very protective, as testified by a baseline DP less than 10 cm H_2O. This, for different reasons, could not be the case for all the patients with moderate-severe ARDS ventilated in the ICU. Therefore, the results shown in this article can be considered a physiologic proof of concept and likely cannot be generalized.

CONCLUSIONS

In this population of 17 patients with moderate to severe ARDS, setting the TV based on lung size was feasible in a majority of cases. Given the small sample size, the results cannot be generalized but can set the ground for future research focused on targeting a TV scaled on the actual lung size or DP.

1 Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto General Hospital, University Health Network, Toronto, ON, Canada.

2 Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy.

3 School of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy.

4 Department of Anaesthesiology and Intensive Care, National Institute of Medicine of the Ministry of Interior and Administration in Warsaw, Warszawa, Poland.

5 Department of Anesthesia and Intensive Care, Santa Chiara Hospital, APSS Trento, Trento, Italy.

6 Centre for Medical Sciences CISMed, University of Trento, Trento, Italy.

General Electric kindly provided the CARESCAPE R860 ventilator. No other funds were obtained.

Dr. Bellani received lecturing or consultancy fees from Draeger Medical, Getinge, Siare Engineering International Group s.r.l., and Flowmeter SPA. The remaining authors have disclosed that they do not have any potential conflict of interest.

Dr. Grassi contributed to investigation, formal analysis of the data, writing (original draft and subsequent review and edits) and visualization; Drs. Teggia-Droghi and Borgo contributed to investigation, formal analysis and writing (review and editing); Dr. Szudrinsky contributed to investigation, supervision and writing (review and editing); Dr. Bellani contributed to conceptualization, methodology, supervision and writing (review and editing).

For information regarding this article, E-mail: alice.grassi@uhn.ca

REFERENCES

1. Gattinoni L, Pesenti A: The concept of "baby lung". *Intensive Care Med* 2005; 31:776–784
2. Chiumello D, Carlesso E, Cadringher P, et al: Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2008; 178:346–355
3. Bellani G, Guerra L, Musch G, et al: Lung regional metabolic activity and gas volume changes induced by tidal ventilation in patients with acute lung injury. *Am J Respir Crit Care Med* 2011; 183:1193–1199
4. González-López A, García-Prieto E, Batalla-Solís E, et al: Lung strain and biological response in mechanically ventilated patients. *Intensive Care Med* 2012; 38:240–247
5. Grasselli G, Calfee CS, Camporota L, et al: European Society of Intensive Care Medicine Taskforce on ARDS. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Intensive Care Med* 2023; 49:727–759
6. Amato MBP, Meade MO, Slutsky AS, et al: Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; 372:747–755
7. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin definition. *JAMA* 2012; 307:2526–2533
8. Rezoagli E, Bellani G: How I set up positive end-expiratory pressure: Evidence-and physiology-based! *Crit Care* 2019; 23:23–25
9. Mitchell RR, Wilson RM, Holzapfel L, et al: Oxygen wash-in method for monitoring functional residual capacity. *Crit Care Med* 1982; 10:529–533
10. Olegård C, Söndergaard S, Houltz E, et al: 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; 101:206–212, table of contents
11. Maisch S, Boehm SH, Weismann D, et al: Determination of functional residual capacity by oxygen washin-washout: A validation study. *Intensive Care Med* 2007; 33:912–916
12. Chiumello D, Cressoni M, Chierichetti M, et al: Nitrogen washout/washin, helium dilution and computed tomography in

the assessment of end expiratory lung volume. *Crit Care* 2008; 12:R150–R159

13. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *NEJM* 2001; 342:1301–1308
14. Goligher EC, Costa ELV, Yarnell CJ, et al: Effect of lowering vt on mortality in acute respiratory distress syndrome varies with respiratory system elastance. *Am J Respir Crit Care Med* 2021; 203:1378–1385
15. Xie J, Jin F, Pan C, et al: The effects of low tidal ventilation on lung strain correlate with respiratory system compliance. *Crit Care* 2017; 21:1–9