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Comparison of two different recruitment maneuver patterns in ARDS patients

Davide Chiumello^{1,2,3*} , Marialaura Montante^{1,2}, Pedro Wendel Garcia⁴, Tapesh Bansal⁵, Tommaso Pozzi^{1,2} and Silvia Coppola^{1,2}

Abstract

Background The differential effects of the two most commonly investigated recruitment maneuvers (RMs), i.e., sigh recruitment and sustained inflation, have not been fully investigated yet. This study aimed to compare the effects of these two RMs on respiratory mechanics, gas exchange, and electrical impedance tomography (EIT)-derived lung volumes on mechanically ventilated ARDS patients.

Results This is a two-period two-sequence randomized crossover study. Two RMs were tested in randomized sequence: a sigh recruitment (one minute with a PEEP of 5 cmH₂O, a driving pressure of 40 cmH₂O at a respiratory rate of 10 bpm) and a sustained inflation maneuver (constant airway pressure of 40 cmH₂O for 30 s). Following the application of the first RM, respiratory mechanics, hemodynamics and EIT-derived lung volumes were measured every 5 min for the following 30 min, while gas exchange was monitored every 15 min. After a 30-min washout period, intended to allow the lung to return to pre-recruitment steady-state conditions, the second RM was applied, and the same measurements were obtained. Twenty-three ARDS patients were enrolled; 13 patients underwent sigh recruitment as first RM and sustained inflation as the second RM, 10 patients underwent the opposite sequence. Patients who underwent both sigh recruitment or sustained inflation as first maneuver showed similar respiratory mechanics, hemodynamics, gas exchange and EIT-derived lung volumes before the RMs compared to patients who underwent sigh recruitment or sustained inflation as the second maneuver after the 30-min washout period. Independently from the order, after the application of each RMs, respiratory system, lung and chest wall mechanics, arterial oxygenation and EIT-derived lung volumes remained similar to baseline at all measurement timepoints from 5 to 30 min. Nine and 13% of patients increased PaO₂/FiO₂ over 20% from baseline 5 min after sigh recruitment and sustained inflation, respectively; a similar percentage was found after 30 min.

Conclusion Neither a sigh recruitment nor a sustained inflation maneuvers had clinically significant effect on respiratory mechanics, gas exchange, hemodynamics or EIT-derived lung volume distribution within the first 30 min after their application.

Keywords ARDS, Recruitment maneuver, Respiratory mechanics, Gas exchange, Electrical impedance tomography

*Correspondence:

Davide Chiumello
davide.chiumello@unimi.it

Full list of author information is available at the end of the article

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Introduction

Acute respiratory distress syndrome (ARDS) is a heterogeneous disease, with different degrees of lung collapse or consolidation and alveolar shunting, depending on the etiology, time of onset, fluid balance, amount of lung edema and lung and chest wall elastances [1, 2]. As a consequence, invasive mechanical ventilation is typically used to ensure adequate gas exchange and minimize ventilator-induced lung injury [3–5]. Nowadays, it is widely recommended that low tidal volumes and driving pressures be applied to limit lung stress and strain [6]. However, patients with ARDS can develop progressive alveolar collapse and hypoxemia related to the degree of hypoventilation [7, 8]. Quantitative lung CT scan analysis has shown that the amount of potentially recruitable lung (i.e., the amount of collapsed lung that can be re-expanded) can range from 5 to 60% of total lung weight [1, 7]. In order to reopen collapsed and atelectatic lung regions (i.e., to recruit these areas) it is necessary to increase airway pressure during inspiration in order to overcome the opening pressure [7, 9].

Recruitment maneuvers (RMs) are used to provide sufficient airway pressure for a sufficient period of time to reopen collapsed and atelectatic lung regions [10–12]. RMs can be used to improve gas exchange and respiratory mechanics (i.e., to ameliorate lung elastance) as part of a ventilator strategy or at the physician's discretion in case of lung derecruitment [10]. The main side effect of RMs is hemodynamic impairment, characterized by a decrease in cardiac output of up to 60%, which is usually reversible within a few minutes of resuming mechanical ventilation [10, 12–14]. The latest European guidelines on ARDS management recommended against the use of prolonged high-pressure RMs to reduce mortality in ARDS patients (moderate level of evidence against) [6]. Although the routine application of RMs does not affect the outcome, their use reduces the need for rescue therapy and they should be used on a case-by-case basis for hypoxemic patients as a life-saving procedure [6, 15]. The most commonly used RMs are the extended sigh, in which an intermittent increase in airway pressure is applied, or the sustained inflation, which is achieved by applying a constant airway pressure by combing different amount of PEEP and tidal volume for a continuous amount of time [10, 14, 16–18]. The response to RMs may differ according to the type of RM, the underlying etiology and the extent and distribution of the disease within the lung [19, 20]. In addition, the airway pressure applied to the respiratory system during the RM, as well as its duration (i.e., the inflation pressure–time product) can affect lung recruitment [21].

This study aimed to investigate the effects of two different RMs (an extended sigh and a sustained inflation

at similar airway pressures and durations) on respiratory mechanics, gas exchange, hemodynamics and electrical impedance tomography (EIT)-derived lung volumes in patients with ARDS.

Materials and methods

Study population

This two-period two-sequence randomized crossover study was performed from December 2022 to December 2024 at the ICU of the ASST Santi Paolo Carlo, San Paolo University Hospital, Milan, Italy. All patients with ARDS as defined by the Berlin definition criteria were considered eligible for the study. Exclusion criteria were: mechanical ventilation for more than 3 days and hemodynamic instability, defined as ongoing hyperlactatemia or the need for a norepinephrine infusion of more than 0.2mcg/kg/min.

The study was approved by the institutional review board of the ASST Santi Paolo e Carlo (protocol number 218/206) and informed consent was obtained in accordance with the Italian regulations.

Study protocol

Figure S1 summarizes the study protocol flow chart. Participants were randomized into treatment sequences (e.g., A-B or B-A) using a computer-generated permuted block algorithm with variable block sizes (2–4). This ensured balanced allocation and reduced predictability. The randomization list was prepared independently, and allocation concealment was implemented via a secure centralized system. Patients were ventilated according to a lung protective strategy with a tidal volume of 8 mL/kg of predicted body weight and a respiratory rate to maintain an arterial carbon dioxide between 40 and 60 mmHg. PEEP was set according to a decremental PEEP trial, as the best compromise between partitioned respiratory mechanics and gas exchange; this was chosen by the attending physician, who was not involved in the study. The inspired oxygen fraction (FiO₂) was adjusted to maintain arterial saturation between 90 and 95%. All enrolled patients were deeply sedated with propofol and remifentanyl and paralyzed with rocuronium to assure muscle relaxation. Before the randomization, an initial sigh recruitment maneuver (see below) was performed to remove the possible influence of possible confounders arising from routine clinical practice (e.g., daily nursing, airway suctioning, eventual disconnection, etc.), to homogenize lung aeration and mechanics and to achieve a uniform starting point for subsequent measurements of gas exchange and respiratory mechanics, before assessing the effects of the study interventions, as already performed in other clinical trials [1, 22, 23]. One hour later, the first recruitment maneuver was performed according

to the randomized sequence. Ventilatory settings were then resumed as previously described, after which the patients were monitored for 30 min, as we hypothesized to see the effects of the investigated RMs in this time-frame. After the end of the 30-min monitoring period following the application of the first RM of the randomized sequence, ventilatory settings were maintained unchanged for a further period of 30 min (*washout* period), to minimize the influence of the previous RM and to allow the lungs to return to their pre-recruitment steady-state conditions before applying the second RM in the randomized sequence [24, 25]. This was necessary to allow the comparison of RMs independently of their application order. After the application of the second RM, patients were monitored as after the first RM.

Recruitment maneuvers

The two recruitment maneuvers investigated were:

- a sigh recruitment maneuver, consisting of the application of 1 min of pressure-controlled ventilation with a PEEP of 5 cmH₂O and a driving pressure of 40 cmH₂O to reach a peak pressure of 45 cmH₂O with a respiratory rate of 10 bpm with an inspiratory-to-expiratory ratio of 1:1 [1];
- a sustained inflation maneuver, consisting in the application of a constant pressure of 40 cmH₂O for 30 s [16].

Data collection

Patients were equipped with an esophageal balloon (Nutrivent, Sidam, Modena, Italy), which was inserted to the lower third of the esophagus, as previously described [26], to obtain esophageal pressure measurements. After placement, an end-expiratory airway occlusion test was used to ensure the correct positioning the catheter [27]. A dedicated 16-electrode EIT belt was placed around the patient's thorax at the level of the fifth–sixth intercostal space, to obtain dynamic lung volume distribution data (PulmoVista® 500, Dräger, Lübeck, Germany).

After each recruitment maneuver, the following variables were obtained every 5 min for a period of 30 min:

- *Partitioned respiratory mechanics.* Airway plateau pressure (P_{plat}) and esophageal plateau pressure (P_{es,insp}) after a five-second long inspiratory hold; total PEEP and end-expiratory esophageal pressure (P_{es,exp}) after a five-second expiratory hold;
- *Hemodynamics.* Systolic, diastolic and mean blood pressures, central venous pressure and heart rate;
- *Dynamic lung imaging data.* End-expiratory lung impedance were collected for the whole lung and for

four dimensionally equal ventral-to-dorsal regions of interests (ROIs, from ROI1 the most ventral to ROI4 the most dorsal) in 2-min-long recordings by EIT at a frame rate of 50 Hz [28]. For each EIT-derived variable, the correct value was assumed as the average value from 5 consecutive breaths at the end of the tracing.

Moreover, every 15 min, gas exchange was assessed by an arterial blood gas analysis, to obtain arterial pH, carbon dioxide (PaCO₂) and oxygen (PaO₂) partial pressures, bicarbonate concentration and base excess.

Derived variables

See Supplementary Material for more details. Driving pressure, respiratory system elastance, chest wall and lung elastances, lung stress and mechanical power were calculated as previously described [20, 29].

Statistical analysis

Continuous data are reported as mean ± SD or median [IQR], as appropriate; categorical data are reported as number (%). Sample size was estimated for a two-period crossover design with a continuous endpoint (change in end-expiratory lung impedance, EELI). Based on previous literature [30], given the crossover design and assuming a high within-subject reproducibility of EIT measurements, to detect a minimum clinically relevant difference of 100 ΔZ in end-expiratory lung impedance between the interventions, a minimum of 23 patients was required to ensure the study a power of 0.80 with a significance level of 0.05. To assess differences between patients receiving sigh recruitment or sustained inflation as first or second RM, Student's t test or Wilcoxon–Mann–Whitney U test were used, as appropriate. One-way analysis of variance (ANOVA) for repeated measures or Friedman test were performed to assess differences within timepoints after each of the RM applied. A post hoc analysis with Bonferroni correction was performed for multiple comparisons. Fisher exact test was used to compare the proportions of patients considered as responders in terms of increase in PaO₂/FiO₂ ratio, using 20% increase from baseline as threshold to define responsiveness, 15 and 30 min after sigh recruitment or sustained inflation. To explore the temporal pattern of the responses after RM application, the time course of each variable was visually inspected; based on the observed trends, the appropriate modeling approach was selected. Specifically, changes over time and between groups were analyzed using mixed-effects models, with time and group (and their interaction) included as fixed effects and subject as a random effect. When the visual inspection

suggested an approximately linear evolution over time, a linear mixed-effects model was fitted; in cases where the response showed a nonlinear pattern, a nonlinear mixed-effects model was applied. Model assumptions were checked graphically, and model fit was compared using likelihood-based criteria (AIC) when relevant. A p value of <0.05 was considered as statistically significant. Statistical analyses and figures were performed using R Studio (RStudio. Integrated Development for R. RStudio, PBC, Boston, USA).

Results

Twenty-three ARDS patients were enrolled after 1 [1-2] days of mechanical ventilation. At enrollment a mean tidal volume of 470 ± 50 mL and a PEEP level of 10 [8-10] cmH₂O were applied (Table 1). Patients presented a mean PaO₂/FiO₂ of 149 ± 48 with a ventilatory ratio of 1.4 ± 0.4 . The resulting mechanical power was

17.5 ± 5.7 J/min. Hemodynamic data at enrollment are presented in Table S1.

Before the beginning of the study protocol

Thirteen patients underwent sigh recruitment as first RM and sustained inflation as the second RM, while 10 patients underwent the opposite sequence. Before the first RM (T0), patients who underwent sigh recruitment and sustained inflation as first RM had a mean tidal volume of 490 ± 50 and 450 ± 50 mL with a PEEP of 10 [10–12] and 10 [8–10] cmH₂O, respectively (Table S2). Regarding respiratory mechanics, driving pressure, partitioned respiratory mechanics (respiratory system, lung and chest wall elastance) and mechanical power were similar (Table S2). The PaO₂/FiO₂ was not different, while the PaCO₂ was significantly higher in the sustained inflation group (54 ± 8 vs 45 ± 7 mmHg, $p=0.023$) due a higher ventilatory ratio (Table S2).

Table 1 Baseline characteristics of the study population according to the first recruitment maneuver (RM) administered (sigh recruitment vs sustained inflation) in the randomized study protocol

	Sigh recruitment n = 13	Sustained inflation n = 10	<i>p</i>
Age, years	68 [49 – 77]	68 [57 – 73]	0.687
Male sex, % (n)	69 (9)	6 (60)	0.685
Weight, kg	83 ± 12	68 ± 14	0.016
Body mass index, kg/m ²	28 ± 5	25 ± 4	0.070
Tidal volume, mL	490 ± 50	450 ± 50	0.063
Respiratory rate, bpm	16 ± 2	18 ± 3	0.027
PEEP, cmH ₂ O	10 [10–12]	10 [8–10]	0.221
Plateau airway pressure, cmH ₂ O	23 ± 4	21 ± 3	0.306
Driving pressure, cmH ₂ O	12 ± 3	12 ± 3	0.863
Respiratory system elastance, cmH ₂ O/L	25 ± 7	25 ± 6	0.891
Chest wall elastance, cmH ₂ O/L	7 ± 2	8 ± 5	0.634
Lung elastance, cmH ₂ O/L	18 ± 8	18 ± 4	0.849
Lung stress, cmH ₂ O	16 ± 5	15 ± 4	0.602
Mechanical power, J/min	18.1 ± 6.3	16.7 ± 5.1	0.612
Arterial pH	7.39 ± 0.06	7.36 ± 0.05	0.233
PaCO ₂ , mmHg	47 [8, 16, 40–50]	50 [46 – 58]	0.222
Ventilatory ratio	1.2 ± 0.3	1.7 ± 0.3	0.001
PaO ₂ , mmHg	82 ± 20	83 ± 12	0.939
PaO ₂ /FiO ₂	152 ± 56	144 ± 39	0.672
[HCO ₃ ⁻], mMol/L	27.2 ± 3.5	29.9 ± 3.2	0.068
Base excess, mMol/L	2.3 ± 4.1	4.5 ± 3.2	0.155
Systolic arterial pressure, mmHg	123 ± 21	123 ± 22	0.224
Diastolic arterial pressure, mmHg	58 ± 9	57 ± 12	0.765
Mean arterial pressure, mmHg	80 ± 11	79 ± 13	0.498
Heart rate, bpm	79 ± 19	79 ± 19	0.945
Central venous pressure, mmHg	11 ± 3	11 ± 3	0.771

PEEP positive end-expiratory pressure, PaCO₂ arterial carbon dioxide partial pressure, PaO₂ arterial oxygen partial pressure, [HCO₃⁻] bicarbonate concentration

Adequacy of 30-min washout period

Patients who underwent sigh recruitment as first maneuver showed the same respiratory mechanics, hemodynamics, gas exchange and EIT-derived lung volumes at T0 than patients underwent sigh recruitment as second maneuver after the 30-min *washout* period. The same occurred to patients who received sustained inflation as first maneuver compared with patients who received sustained inflation as second maneuver.

Moreover, respiratory mechanics, hemodynamics, gas exchange and EIT-derived lung volumes showed the same time-course in patients who received sigh recruitment as first RM compared with patients who received sigh recruitment as second RM. The same occurred for sustained inflation (Table S3).

Effects of RMs independently from the order

Driving pressure, as well respiratory system, lung and chest wall elastances were not modified by the application of RMs, remaining unchanged over measurement timepoints. Thus, also mechanical power was not affected by RMs (Table 2 and Fig. 1). Hemodynamics did not change after both RMs and remained stable throughout the study.

Arterial oxygenation was not affected either by sustained inflation or sigh recruitment at each timepoints, while arterial carbon dioxide significantly increased after 15 and 30 from the application of both RMs without any differences between RMs (Table 3 and Fig. 1). Considering an increase in 20% in PaO₂/FiO₂ with respect to baseline as criterion to assess oxygen responsiveness to RMs, 9% and 13% of patients were considered responders after 15 min from the application of sigh recruitment and sustained inflation, respectively ($p=0.946$); after 30 min, responders were 13% and 10% for sigh recruitment and sustained inflation maneuvers, respectively ($p=0.981$).

The global end-expiratory lung impedance remained stable throughout the study (Table 4, Fig. 1). In addition, no redistribution of end-expiratory lung volume seems to be occurred from 5 to 30 min after each RM, as demonstrated by absence of interaction between the effect of time and each ROI (sigh recruitment: $p=0.941$; sustained inflation: $p=0.392$).

Discussion

The main finding of this study was that the application of two types of RMs (*i.e.*, a sigh recruitment or a sustained inflation) did not affect respiratory mechanics, gas exchange, hemodynamics and EIT-derived lung volumes either immediately after the maneuver or in terms

Table 2 Respiratory mechanics time-course according to recruitment maneuver (sigh recruitment or sustained inflation)

	Sigh recruitment n = 23	Sustained inflation n = 23	P_{RM}	P_{TIME}	P_{INT}
Driving pressure, cmH_2O					
T ₀	11 [10–14]	11 [9–12]	0.145	0.083	0.259
T ₅	11 [10–14]	11 [9–12]			
T ₁₀	11 [10–13]	11 [9–12]			
T ₁₅	11 [10–14]	11 [10–13]			
T ₂₀	11 [10–14]	12 [10–14]			
T ₂₅	11 [10–13]	11 [10–13]			
T ₃₀	11 [10–13]	11 [9–12]			
Respiratory system elastance, cmH_2O/L					
T ₀	26 ± 7	23 ± 6	0.138	0.084	0.258
T ₅	26 ± 7	25 ± 7			
T ₁₀	26 ± 7	24 ± 6			
T ₁₅	25 ± 6	25 ± 7			
T ₂₀	26 ± 7	26 ± 7			
T ₂₅	25 ± 6	25 ± 7			
T ₃₀	26 ± 6	24 ± 6			
Chest wall elastance, cmH_2O/L					
T ₀	5 [5–8]	6 [5–8]	0.758	0.063	0.307
T ₅	6 [3–8]	5 [2–7]			
T ₁₀	5 [3–8]	6 [4–7]			
T ₁₅	4 [3–7]	6 [5–7]			
T ₂₀	5 [3–7]	6 [5–7]			
T ₂₅	5 [3–7]	6 [5–8]			
T ₃₀	5 [3–7]	6 [5–7]			
Lung elastance, cmH_2O/L					
T ₀	18 [1, 16–22]	17 [13–18]	0.098	0.939	0.936
T ₅	18 [16–22]	18 [16–22]			
T ₁₀	19 [1, 16–22]	17 [14–21]			
T ₁₅	18 [1, 15–22]	18 [15–22]			
T ₂₀	18 [1, 16–22]	19 [1, 17–24]			
T ₂₅	18 [1, 15–22]	18 [15–22]			
T ₃₀	19 [15–22]	18 [15–22]			
Lung stress, cmH_2O					
T ₀	17 ± 4	15 ± 4	0.174	0.624	0.463
T ₅	17 ± 4	16 ± 5			
T ₁₀	17 ± 4	16 ± 4			
T ₁₅	17 ± 4	16 ± 4			
T ₂₀	17 ± 4	16 ± 4			
T ₂₅	17 ± 4	16 ± 4			
T ₃₀	17 ± 4	16 ± 4			
Mechanical power, J/min					
T ₀	17.6 ± 5.6	16.9 ± 5.7	0.958	0.093	0.076
T ₅	17.1 ± 5.8	16.9 ± 5.5			
T ₁₀	17.6 ± 5.5	17.0 ± 5.4			
T ₁₅	17.8 ± 5.3	17.1 ± 5.2			
T ₂₀	17.6 ± 5.3	16.6 ± 5.3			
T ₂₅	17.6 ± 5.7	17.0 ± 5.3			
T ₃₀	17.7 ± 5.6	16.6 ± 5.2			

p_{RM} between groups factor (sigh recruitment vs sustained inflation), p_{TIME} within group factor, p_{INT} interaction

of temporal patterns within 5 and 30 min afterwards in mild-moderate ARDS patients. However, considering a threshold for oxygen responsiveness as of 20% of increase

in PaO_2/FiO_2 , only a small proportion of patients were considered responders after 15 and 30 min from both RMs.

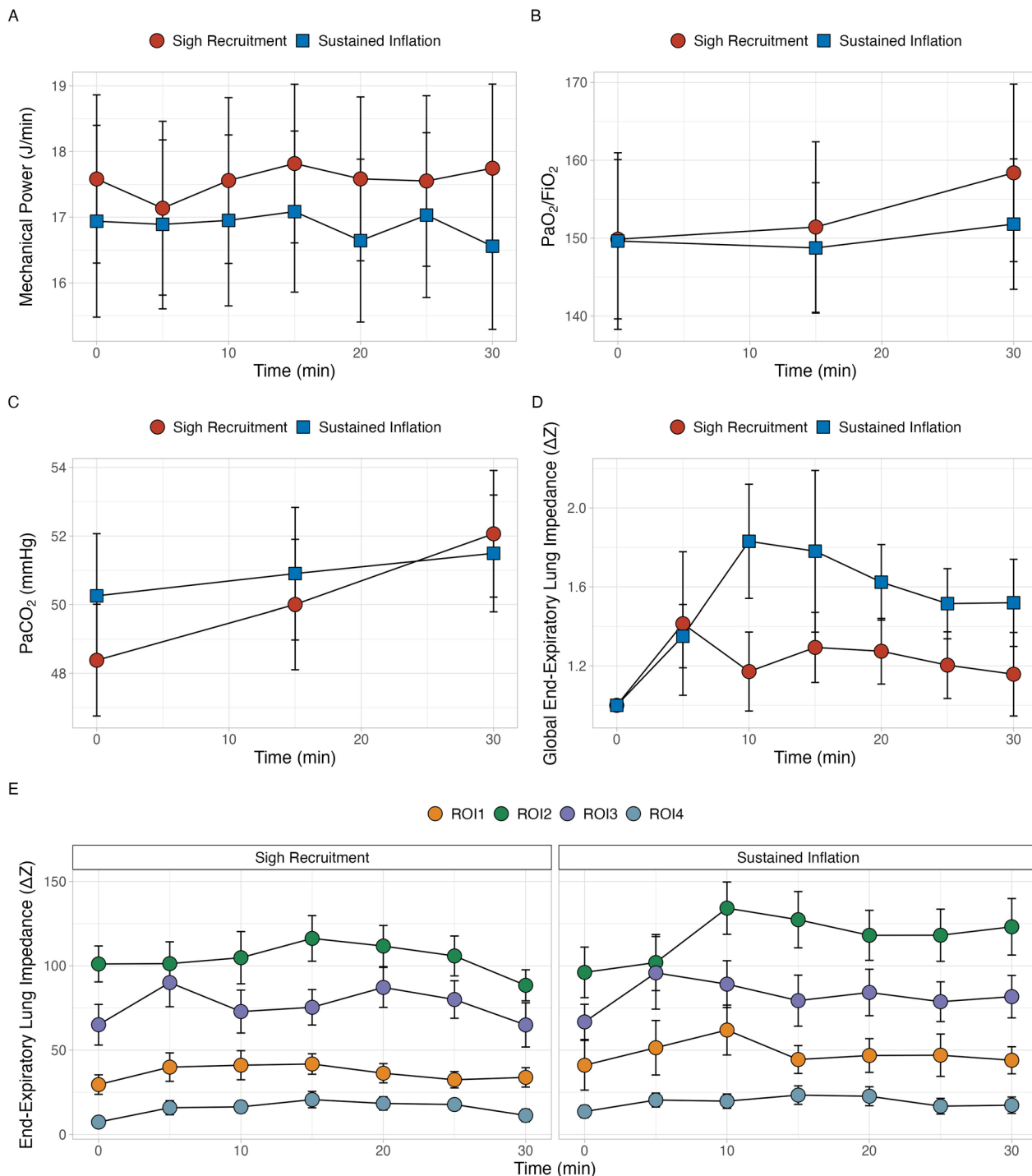


Fig. 1 Time course of mechanical power (A), PaO_2/FiO_2 ratio (B), arterial carbon dioxide partial pressure ($PaCO_2$ —C), global end-expiratory lung impedance (EELI—D) and regional EELI (E) across regions of interest (ROIs) according to the recruitment maneuver (RM) applied within measurement timepoints (every 5 min to 30 min after the application of the RM for respiratory mechanics and EIT-derived lung volumes, and every 15 min after the application of the RM for gas exchange)

Table 3 Respiratory mechanics time-course according to recruitment maneuver (sigh recruitment or sustained inflation)

	Sigh Recruitment n = 23	Sustained inflation n = 23	P_{RM}	P_{TIME}	P_{INT}
<i>PaCO₂</i> , mmHg					
T ₀	48 ± 8	50 ± 9	0.058	< 0.0001	0.106
T ₁₅	50 ± 9	51 ± 9			
T ₃₀	52 ± 9	52 ± 8			
Ventilatory ratio					
T ₀	1.4 ± 0.4	1.4 ± 0.4	0.634	< 0.001	0.118
T ₁₅	1.4 ± 0.4	1.4 ± 0.4			
T ₃₀	1.5 ± 0.4	1.5 ± 0.4			
<i>PaO₂/FiO₂</i>					
T ₀	150 ± 48	150 ± 53	0.972	0.134	0.574
T ₁₅	151 ± 51	149 ± 38			
T ₃₀	158 ± 54	152 ± 39			

PaCO₂: arterial carbon dioxide partial pressure; *PaO₂*: arterial oxygen partial pressure. P_{RM} : between groups factor (sigh recruitment vs sustained inflation); P_{TIME} : within group factor; P_{INT} : interaction

ARDS patients are characterized by the presence of collapsed lung regions, which can be caused by lung edema and the consequent superimposed pressure, by hypoventilation and by the administration of high oxygen fraction, resulting in reabsorption atelectasis [19]. Furthermore, the use of low tidal volumes in the context of a lung protective strategy can further worsen lung collapse and promote atelectasis [31, 32]. These factors result in a reduction in lung gas volume, contributing to the development of ventilator-induced lung injury [33]. Ideally, recruitment maneuvers (i.e., the transient increase in airway pressure) should not only increase the end-expiratory lung gas volume, but also recruit the lung by decreasing lung inhomogeneity. This should improve gas exchange by reducing shunt and avoid lung stress-strain [11, 34–37]. These theoretical advantages have led to the application of RMs since the 60' to reverse the lung collapse, increase oxygenation and improve compliance during general anesthesia [38]. However, previous studies showed an heterogeneous response to RMs reaching an airway pressure between 45 and 60 cmH₂O in terms of radiological recruitment and gas exchange [1, 7], depending on lung recruitability, which has been demonstrated to range from 5% up to 35–40% of the total lung weight, evaluated by CT scan [1]. Indeed, in poorly recruitable lungs, RMs might hyperinflate already ventilated regions, increasing the risk of barotrauma and promoting a decrease in cardiac output [39–41]. The RMs can induce hemodynamic impairment by increasing the intrathoracic

Table 4 Respiratory mechanics time-course according to recruitment maneuver (sigh recruitment or sustained inflation)

	Sigh Recruitment n = 23	Sustained inflation n = 23	P_{RM}	P_{TIME}	P_{INT}
Global EELI, ΔZ					
T ₀	197 [139 – 281]	165 [108 – 297]	0.845	0.175	0.164
T ₅	240 [124 – 367]	183 [116 – 414]			
T ₁₀	221 [102 – 312]	274 [192 – 344]			
T ₁₅	238 [173 – 318]	211 [176 – 310]			
T ₂₀	240 [181 – 293]	204 [180 – 374]			
T ₂₅	237 [176 – 304]	218 [173 – 344]			
T ₃₀	203 [106 – 261]	251 [155 – 363]			
EELI ROI 1, ΔZ					
T ₀	28 [1, 8–39]	16 [1, 7–38]	0.636	0.724	0.924
T ₅	32 [1, 8, 13–48]	18 [13 – 57]			
T ₁₀	29 [1, 8, 13–52]	36 [23 – 80]			
T ₁₅	40 [8, 16, 23–52]	24 [16 – 74]			
T ₂₀	29 [1, 8, 16, 18–51]	30 [17 – 68]			
T ₂₅	32 [1, 8, 13–45]	29 [11 – 59]			
T ₃₀	27 [1, 8, 15–49]	35 [22 – 59]			
EELI ROI 2, ΔZ					
T ₀	100 [56 – 140]	77 [41 – 144]	0.902	0.679	0.158
T ₅	103 [41 – 146]	72 [46 – 146]			
T ₁₀	92 [58 – 148]	130 [89 – 161]			
T ₁₅	103 [68 – 144]	120 [67 – 155]			
T ₂₀	114 [67 – 133]	104 [76 – 178]			
T ₂₅	95 [70 – 148]	101 [66 – 165]			
T ₃₀	81 [67 – 113]	112 [84 – 166]			
EELI ROI 3, ΔZ					
T ₀	62 [31 – 107]	61 [28 – 93]	0.659	0.643	0.915
T ₅	71 [42 – 118]	74 [36 – 126]			
T ₁₀	79 [15 – 120]	83 [56 – 103]			
T ₁₅	59 [42 – 105]	76 [29 – 115]			
T ₂₀	79 [47 – 119]	89 [42 – 124]			
T ₂₅	89 [44 – 117]	82 [53 – 110]			
T ₃₀	58 [21 – 91]	90 [33 – 106]			
EELI ROI 4, ΔZ					
T ₀	5 [1–15]	11 [4–21]	0.179	0.400	0.759
T ₅	12 [4–21]	17 [1, 7–28]			
T ₁₀	9 [1, 5–27]	15 [1, 5–26]			
T ₁₅	15 [1, 5–27]	16 [1, 4–34]			
T ₂₀	11 [6–21]	19 [1, 7–33]			
T ₂₅	17 [1, 8–26]	14 [1, 4–23]			
T ₃₀	12 [4–19]	11 [1, 3–29]			

EELI end-expiratory lung impedance, ROI region of interest. P_{RM} between groups factor (sigh recruitment vs sustained inflation), P_{TIME} within group factor; P_{INT} : interaction

pressure; thus, to minimize these effect, an airway pressure between 35 and 40 cmH₂O for a period of 30–40 s have been suggested [42, 43].

A seminal study in ARDS patients showed that applying 3 sighs per minute for one hour, reaching an airway pressure of 45 cmH₂O with high tidal volumes maintaining the same PEEP level significantly improved arterial oxygenation and respiratory mechanics [9]. However, oxygenation and elastance, which significantly improved during the application of the sighs, returned to their baseline values within 20 min after sigh interruption and remained stable at 60 min [9].

According to the available data from three randomized controlled trials (RCTs) in which high pressure (*i.e.*, higher than 35 cmH₂O) RMs were applied, no difference was found in terms of mortality and in barotrauma [8, 44, 45] as compared to ventilatory strategies without RMs. Indeed, the latest ESICM guidelines recommended against the use of high-pressure RMs to reduce mortality in patients with ARDS. In addition, it was also suggested against the routine use of brief high-pressure RMs to reduce mortality in ARDS patients (high level of evidence of no effect) [6]. The application of RMs should only be considered to reverse hypoxemia in the presence of derecruitment, for example after ventilator disconnection, suctioning, intubation or placement in the prone position [6]. The possible variables that could influence the response of RMs are the level of airway pressure, the application time, the ARDS etiology and the ventilatory settings (tidal volume and PEEP) after RMs [10, 21, 39, 46, 47].

The optimal level of airway pressure to be applied in ARDS patients depends also on the ratio between lung and chest wall elastances, which directly affects transpulmonary pressure, which is the pressure threshold for alveoli to be opened. For a similar airway pressure, the transpulmonary pressure can differ significantly [4]. Grasso et al. found that non-responders to RM presented a significantly higher chest wall elastance, resulting in a lower transpulmonary pressure. Additionally, non-responders exhibited a greater reduction in cardiac output due to a significant decrease in the pressure gradient for venous return [47].

Several studies have shown that RMs improve oxygenation and lung mechanics, particularly in patients in whom PEEP was increased after RM. These beneficial effects were not present when PEEP did not change as compared to the pre-recruitment ventilatory setting [12, 16, 46].

There are a variety of methods for performing RMs. The most common and straightforward approach is to set the ventilator in CPAP mode and increase PEEP to 30–40 cmH₂O for 30–40 s [25, 35, 48]. Other methods proposed the increase in airway pressure by intermittently applying a high tidal volume (*i.e.*, sighs) or by

simultaneously increasing PEEP and decreasing tidal volume to obtain a constant airway pressure [16–18].

A small randomized study found that, compared to sustained inflation at a similar airway pressure, a RM performed as sighs in pressure-controlled ventilation at 45 cmH₂O significantly improved oxygenation with lower arterial carbon dioxide and hemodynamic impairment.

It has been suggested that the level of airway pressure applied by the ventilator, as well as the duration (*i.e.*, an adequate pressure–time product), affects lung recruitment. When a sustained inflation of up to 40 cmH₂O was applied, the majority of the recruited lung volume was achieved within the first 10 s [49].

The present study evaluated two different RMs: sustained inflation and pressure-controlled ventilation, which both reached a similar peak airway pressure and inflation. Possible changes in lung volumes were assessed using electrical impedance tomography [50].

Thirty minutes after the application of both recruitment maneuvers, no differences in lung gas volume, arterial oxygenation or respiratory mechanics were found. The absence of any response could be explained by various factors, such as a low amount of lung recruitability (*i.e.*, a low amount of edema) or the presence of adequate PEEP levels, which already kept the lung “open”, the shorter duration of RMs and the evaluation timeframe (*i.e.*, during the RM/immediately after *vs* in the first hour after the RM). Furthermore, the application of RMs in ARDS patients with a focal rather than a diffuse morphology showed significantly lower lung recruitment and higher oxygenation [51]. A small increase in arterial carbon dioxide partial pressure was observed after the application of both sustained inflation and sigh recruitment; this minimal effect could be related to changes in lung perfusion induced by the increase in alveolar pressure during RMs.

Concerning the choice to apply a standardized recruitment maneuver before randomization, it could have been useful to homogenize lung aeration and mechanics before assessing the effects of different ventilatory strategies and to achieve a uniform starting point for subsequent measurements of gas exchange and respiratory mechanics, although it might also have decreased the potential positive effect of study interventions.

In conclusion, in patients with mild–moderate ARDS ventilated with moderate PEEP levels, the application of a RM, either as sigh recruitment or as sustained inflation, provided neither beneficial effects, in terms of improving oxygenation, respiratory mechanics and lung volumes, nor detrimental effects, in terms of hemodynamic impairment after 5 to 30 min.

Abbreviations

ARDS Acute respiratory distress syndrome

CT	Computed tomography
CPAP	Continuous positive airway pressure
PEEP	Positive end-expiratory pressure
ICU	Intensive care unit
EIT	Electrical impedance tomography
Pplat	Airway plateau pressure
Pes, insp	Esophageal plateau pressure
Pes, exp	End-expiratory esophageal pressure
PaCO ₂	Arterial carbon dioxide partial pressure
PaO ₂	Arterial oxygen partial pressure
FiO ₂	Inspired oxygen fraction

Supplementary Information

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Supplementary material 1.

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Author contributions

Study concept and design: D.C. and S.C.; measurements and data curation: M.M. and T.P.; data analysis: P.W.G., T.P. and S.C.; writing—first draft: D.C.; editing and revising—final draft: M.M., P.W.G., T.B., T.P. and S.C.

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Data availability

The dataset used in this study is available upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of the ASST Santi Paolo e Carlo (protocol number 218/206); informed consent was obtained according to the Italian regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests in performing this study.

Author details

¹Department of Health Sciences, University of Milan, Milan, Italy. ²Department of Anesthesia and Intensive Care, ASST Santi Paolo E Carlo, San Paolo University Hospital, Milan, Italy. ³Coordinated Research Center on Respiratory Failure, University of Milan, Milan, Italy. ⁴Institute of Intensive Care Medicine, University Hospital Zurich, Zurich, Switzerland. ⁵Department of Critical Care Medicine, Paras Hospital, Gurgaon, India.

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