A Novel Noninvasive Tool to Assess Recruitability During Assisted Ventilation

The Sigh to Tidal Respiratory System Compliance Ratio

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BACKGROUND: Lung recruitability refers to the capacity of lung parenchyma to regain aeration and functional units in response to increased airway pressure. Assessing lung recruitability is clinically relevant because it may guide ventilator settings, particularly the selection of positive end-expiratory pressure (PEEP). No validated method exists to assess recruitability in pressure support ventilation (PSV) because the active respiratory drive of the patient interferes with the methods available for controlled mechanical ventilation. The application of a mandatory sigh (a breath 2-3 times greater in volume than tidal breath) during PSV is proven to be safe and physiologically beneficial.

RESEARCH QUESTION: Because a mandatory sigh transiently generates airway pressures higher than those of a conventional tidal breath, is it possible to detect lung recruitment potential during PSV by comparing the respiratory system compliance (C_{rs}) of a sigh breath ($C_{rs\ sigh}$) with that of a tidal breath ($C_{rs\ tidal}$)?

STUDY DESIGN AND METHODS: This bicentric prospective study comprised 2 steps lasting 15 minutes each: clinical PEEP and clinical PEEP plus 3 cm H_2O. Patients were in PSV mode with a periodic sigh set by the attending clinician. The level of pressure support was set by the attending clinician. The sigh was set as a sustained inflation of 30 cm H_2O lasting 3 s/min. For every patient, we calculated $C_{rs\ sigh}$, $C_{rs\ tidal}$, and—exclusively at clinical PEEP—sigh to tidal compliance ratio (S/T; or $C_{rs\ sigh}$ to $C_{rs\ tidal}$ ratio).

RESULTS: One hundred ten patients were enrolled. $C_{rs\ tidal}$ was feasible. S/T of > 1 (36% of patients) was associated significantly with a higher $C_{rs\ tidal}$ and better oxygenation when PEEP was increased by 3 cm H_2O as compared with baseline (median, 53 mL/cm H_2O [interquartile range (IQR), 44-63 mL/cm H_2O] vs 48 mL/cm H_2O [IQR, 41-59 mL/cm H_2O]; $P < .001$; and median Pa_{O_2} to F_{IO_2} ratio of 308 [IQR, 191-352] vs 269 [IQR, 164-299]; $P <$ .001; respectively). Conversely, S/T of ≤ 1 was associated with a significant reduction in both $C_{rs\ tidal}$ and Pa_{O_2} to F_{IO_2} ratio when PEEP was increased.

INTERPRETATION: Our results show that normalizing $C_{rs\ sigh}$ over $C_{rs\ tidal}$—leading to the S/T index—provides useful bedside information about the potential of lung recruitment in patients undergoing PSV.

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KEY WORDS: assisted mechanical ventilation; inspiratory effort; lung recruitment; PEEP; respiratory system compliance; sigh

Take-Home Points

Study Question: Can a mandatory sigh breath during assisted mechanical ventilation be used to infer lung recruitability and help to guide positive end-expiratory pressure (PEEP) optimization?

Results: A ratio between sigh and tidal respiratory system compliance (sigh to tidal compliance ratio [S/T]) of > 1 was correlated with improved respiratory mechanics and oxygenation after a 3-cm H_2O increase in PEEP.

Interpretation: Our results show that S/T is a simple, noninvasive bedside index that provides information about lung recruitability during assisted mechanical ventilation, particularly when S/T is > 1.

Evidence supports the transition from controlled to assisted ventilatory modes. A common assisted mode is pressure support ventilation (PSV), which requires lighter sedation. PSV has well-established benefits such as accelerating the weaning process and preventing ventilator-induced diaphragm dysfunction.[1-3] In contrast to controlled ventilation, titration of positive end-expiratory pressure (PEEP) during PSV remains challenging.[4] Optimal PEEP selection is linked closely to lung recruitability, which reflects the propensity of lung parenchyma to regain aeration of previously collapsed units when airway pressures increase.[5] Although we can obtain a reliable plateau pressure (P_{plat}) during PSV, and thus reliable static respiratory system compliance (C_{rs}),[6,7] many of the tools commonly used to assess lung recruitability during passive mechanical ventilation are not applicable in assisted modes because of the patient's respiratory drive interference.[8] The application of a sigh during PSV increases oxygenation by reducing alveolar collapse.[9,10] Recent evidence showed that it is safe in patients being treated for trauma.[11] In certain patient subgroups, it also may reduce mortality.[12] A sigh is a mandatory breath with an expirated volume that is 2 to 3 times the normal tidal volume (Vt).[13] This difference in volume (and pressure) inflating the lungs may elicit different static mechanical response from the respiratory system compared with a tidal breath, potentially providing bedside insight into lung recruitability.

We hypothesized that the ratio between the C_{rs} calculated during a sigh breath and the C_{rs} calculated over an assisted tidal breath in PSV may provide useful information about the respiratory system recruitability, and therefore may help to predict the response to an increase in PEEP. Because driving pressure seems to be an independent risk factor for mortality in patients receiving PSV,[13] improved assessment of lung recruitability may allow for more individualized PEEP titration and optimization of ventilator settings.

Study Design and Methods

We conducted a bicentric prospective ventilator treatment study in patients admitted to the General Intensive Care Unit of Maurizio Bufalini Hospital in Cesena and to the General Intensive Care Unit and Cardiac Intensive Care Unit of Fondazione IRCCS San Gerardo dei Tintori in Monza, Italy. The study was designed according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonization. It was approved by the institutional ethics committees (Comitato Etico della Romagna Identifiers: 3777, 3815/2024; and Comitato Etico Territoriale 3 Identifiers: 5681, C1.2024.0002222). Informed consent was obtained from each patient.

ABBREVIATIONS: C_{rs} = respiratory system compliance; C_{rs} overplat = sigh volume − Vt / P_{sigh} − P_{plat}; $C_{rs\ sigh}$ = respiratory system compliance of a sigh breath; $C_{rs\ tidal}$ = respiratory system compliance of a tidal breath; DAG = directed acyclic graph; DP_{dyn} = dynamic driving pressure; DP_{st} = static driving pressure; IQR = interquartile range; PEEP = positive end-expiratory pressure; P_{plat} = plateau pressure; Psigh = inspiratory pressure; PSV = pressure support ventilation; S/T = sigh to tidal compliance ratio (or $C_{rs\ sigh}$ to $C_{rs\ tidal}$ ratio); V_{rec} = sigh recruited volume; Vt = tidal volume

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The inclusion criteria were: age ≥ 18 years, admission to ICU, and assisted mechanical ventilation in pressure support mode with a periodic sigh set by the attending clinician as per Pressure Support Ventilation + Sigh in Acute Hypoxemic Respiratory Failure Patients (PROTECTION) study protocol.[14] The exclusion criteria were: any clinical contraindication to an increase of PEEP and hemodynamic instability defined as a Sequential Organ Failure Assessment cardiovascular score of ≥ 3.

Study Protocol

The protocol consisted of 2 15-minutes steps (e-Fig 1): (1) clinical PEEP and (2) clinical PEEP increased by 3 cm H_2O. Clinical PEEP was set at the discretion of the treating clinician (ie, without a formal titration algorithm). The magnitude of PEEP increase (3 cm H_2O) was selected to standardize PEEP augmentation across a heterogeneous patient population. Conversely, the sigh breath was standardized for every patient as follows: 1 mandatory (non-patient-triggered) sustained inflation lasting 3 seconds at a pressure of 30 cm H_2O/min.[15] To ensure that end-inspiratory alveolar pressure reached 30 cm H_2O, the sigh inspiratory time was prolonged beyond 3 seconds whenever end-inspiratory flow failed to reach 0 L/min.

Throughout both steps, the ventilatory setting was unchanged with the exception of PEEP. We used, as in routine clinical practice, the pressure controlled bilevel positive airway pressure ventilatory mode, which allows setting the respiratory rate of mandatory breaths (1/min), the inspiratory time, and high-pressure level (inspiratory pressure [Psigh]), in addition to trigger sensitivity and pressure support level.

Baseline demographic characteristics, comorbidities, and hemodynamic parameters were collected. An end-inspiratory and an end-expiratory hold were performed at the end of each step, allowing us to calculate mechanical ventilation parameters during a tidal assisted breath, as follows: P_{plat} (according to the literature, the P_{plat} was deemed reliable only when the pressure curve remained visually stable during an inspiratory hold manoeuvre),[16] static driving pressure (DP_{st}; $DP_{st} = P_{plat} - PEEP$), dynamic driving pressure (dynamic driving pressure = pressure support + $[\Delta P_{occ} \times 0.75]$, where ΔP_{occ} is the difference between total PEEP and the low level of airway pressure during an expiratory hold manoeuvre),[17] Vt, tidal respiratory system compliance ($C_{rs\ tidal}$; $C_{rs\ tidal} = Vt\ /\ DP_{st}$), sigh respiratory system compliance ($C_{rs\ sigh}$; $C_{rs\ sigh}$ = effective sigh volume / Psigh), occlusion pressure in the first 100 ms, occlusion pressure, pressure muscle index (pressure muscle index = P_{plat} − peak pressure), and ventilatory ratio.

C_{rs} also was calculated during the mandatory sigh before and after clinical PEEP increase. Volume and pressure for the sigh C_{rs} calculation were collected as soon as: (1) flow had reached 0 L/min during the sigh breath and (2) the airway pressure was deemed visually stable (Fig 1). Importantly, the sigh pressure did not change between steps.

Therefore, having the C_{rs} during a tidal-assisted breath ($C_{rs\ tidal}$) and the C_{rs} during the mandatory sigh ($C_{rs\ sigh}$), we calculated the sigh to tidal compliance ratio (S/T; or $C_{rs\ sigh}$ to $C_{rs\ tidal}$ ratio). Arterial blood gas analysis was collected at the end of each step.

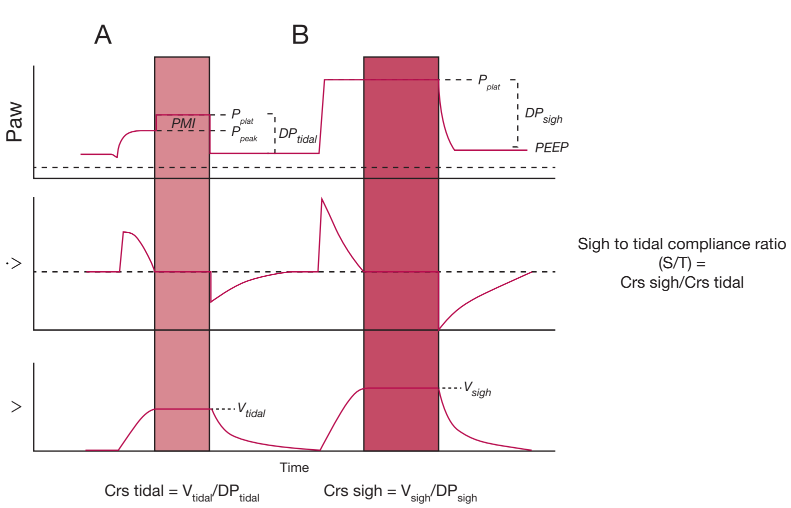

Figure 1 – *A, Graph showing P_{plat}, DP (DP = P_{plat} − PEEP), PMI (PMI = P_{plat} − P_{peak}), and tidal volume measured performing an inspiratory hold maneuver (light grey) during an assisted tidal breath. B, Graph showing the same parameters (except for PMI) obtained during the sigh as soon as the flow reaches 0 L/min (dark grey). Crs tidal = respiratory system compliance at the inflation of the tidal volume; Crs sigh = respiratory system compliance at the inflation of the sigh volume; DP = driving pressure; DP tidal = tidal volume related drigving pressure; DP sigh = sigh breath related driving pressure; PEEP = positive end-expiratory pressure; PMI = pressure muscle index; P_{peak} = peak pressure; P_{plat} = plateau pressure; V tidal = tidal volume; V sigh = sigh volume. P_{aw} = airway pressure; V = volume.*

Quantification of Estimated vs Effective Volume at Sigh Pressure

Based on $C_{rs\ tidal}$ baseline, we estimated the volume (expressed in milliliters) produced by a mandatory sigh, called volume expected (sigh volume expected = [sigh peak pressure – PEEP] × $C_{rs\ tidal}$ baseline). The effective sigh volume inflating the lungs was obtained directly from the ventilator at the end of each sigh breath (sigh volume effective). Sigh recruited volume (V_{rec}) was defined as follows: V_{rec} = sigh volume effective – sigh volume expected.

To explore respiratory system behavior above tidal pressures, we calculated $C_{rs\ overplat}$ as the difference between sigh volume and tidal volume divided by the difference between sigh pressure and plateau pressure [$C_{rs\ overplat}$ = (sigh volume – Vt) / (P_{sigh} – P_{plat})]. This measure reflects how compliance changes in a range between P_{plat} (Vt) and sigh pressure (sigh volume), providing a functional estimate of the lung's modification beyond the normal Vt, complementing other indices such as sigh to tidal compliance ratio (S/T).

Statistical Analysis

Data were expressed as mean (SD) or median (interquartile range [IQR]) according to data distribution assessed by Shapiro-Wilk test. Categorical data were expressed as count (proportion). According to data distribution, differences between continuous variables were tested using the unpaired *t* test or Mann-Whitney *U* test for independent measurements and the paired *t* test or Wilcoxon test for repeated measurements before and after clinical PEEP increase. Differences among multiple groups were determined using the analysis of variance or Kruskal-Wallis test, as appropriate. Correlations between S/T (S/T = $C_{rs\ sigh}$ / $C_{rs\ tidal}$) at baseline and the ratio of C_{rs} after vs before the clinical PEEP increase (C_{rs} PEEP baseline + 3 / C_{rs} PEEP baseline) and S/T and the ratio of Pa_{O_2} to Fi_{O_2} ratio after vs before the clinical PEEP increase (Pa_{O_2} to Fi_{O_2} ratio PEEP baseline + 3 / Pa_{O_2} to Fi_{O_2} ratio PEEP baseline) were examined by nonlinear regression, and the association was described by nonparametric Spearman correlation coefficient. The strength of association was expressed by the coefficient of determination (R^2). For descriptive and subgroup comparisons, S/T also was analyzed as a binary variable using a prespecified cutoff at unity (> 1 vs ≤ 1). This threshold was chosen for its physiologic interpretation: because S/T is a ratio, values of > 1 indicate higher compliance during the sigh than during tidal ventilation, consistent with recruitment (opening of additional lung units) during the maneuver, whereas values of ≤ 1 indicate no increase in compliance with the sigh, and therefore limited or absent recruitability.

Covariates included in the multivariable linear regression model were selected a priori based on prior and current scientific knowledge of the causal relationships between patient characteristics, ventilatory variables, and lung recruitability, in accordance with the framework proposed by Lederer et al.[18] Covariate selection aimed at controlling for confounding, rather than optimizing statistical significance. The final model included demographic variables (age, sex, and BMI), comorbidities (COPD), cause of admission (respiratory vs nonrespiratory), level of sedation (Richmond Agitation-Sedation Scale), ventilator settings (PEEP), respiratory mechanics (C_{rs}, S/T). The S/T ratio was specified as the primary explanatory variable reflecting lung recruitability (expressed as V_{rec}) as a diagnostic maneuver. Of note, although both S/T and V_{rec} are derived from respiratory mechanics measurements, they are conceptually and mathematically distinct. S/T is a dimensionless ratio of normalized variables and is constrained to positive values only reflecting the relationship between volume and pressure over different portions of the pressure-volume curve. V_{rec} is a purely volumetric estimate that does not incorporate the pressure required to achieve this volume; it may assume both positive and negative values and reflects deviation from linear behavior. Therefore, despite sharing underlying measurements, the 2 indices capture different physiologic constructs. A directed acyclic graph (DAG) was constructed to formalize the assumed causal structure and to justify the adjustment set. Adjusted regression coefficients (β) with 95% CIs from the fully adjusted model are presented in a forest plot. Collinearity was explored for all variables included in the multivariable model by the assessment of variance of inflation factors. We also performed an additional multivariable analysis treating S/T as a categorical variable (> 1 vs. ≤ 1). Adjusted associations were reported by ORs with 95% CIs. A 2-tailed *P* value of < 0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 10.3.1 software.

Sample Size

For the sample size calculation, we used a paired *t* test assuming a conservative expected difference of 4 mL/cm H_2O between $C_{rs\ sigh}$ and $C_{rs\ tidal}$. This value corresponds to an anticipated 10% change in respiratory system compliance, based on a low-compliance scenario of approximately 40 mL/cm H_2O. We assumed an SD of ± 12 mL/cm H_2O and an α level of 5%. With a statistical power of 0.8, the minimum required sample size was 73 patients. Because P_{plat} measurements derived from pressure-time curves during PSV may not always be fully reliable, we prospectively planned to enroll at least 100 patients (ie, ≥ 30% than the minimum estimated sample size) to ensure robustness of the analysis.

Results

Demographic and Ventilatory Characteristics at Baseline Stratified by S/T Ratio

A total of 110 patients were enrolled in the study. Ten patients (9%) were excluded because of P_{plat} instability during the inspiratory hold. The median time from the switch from controlled to assisted mechanical ventilation to enrollment was 1 day (IQR, 1-2 days) (Table 1). Among the 100 patients who fulfilled all criteria, 50 patients were from Bufalini Hospital, Cesena, and 50 patients were from IRCCS San Gerardo, Monza. Thirty-nine percent of patients were female, median age was 66 years (IQR, 54-75 years), and median BMI was 26 kg/m^2 (IQR, 23-31 kg/m^2). At baseline, median Vt was 488 mL (IQR, 409-578 mL), median pressure support was 8 cm H_2O (IQR, 6-10 cm H_2O), median PEEP was 6 cm H_2O (IQR, 5-8 cm H_2O), mean (SD) DP_{st} was 9 (2) cm H_2O, and median Pa_{O_2} to F_{IO_2} ratio was 265 mm Hg (IQR, 179-312 mm Hg). We provided a stratified analysis based on the level of S/T ratio: S/T ≤ 1 (64 of 100) and S/T > 1 (36 of 100).

TABLE 1] Study Population Characteristics at PEEP Baseline

Variable	Total	S/T ≤ 1	S/T > 1	*P* Value
Age, y	66 (54 to 75)	66 (58 to 75)	67 (50 to 75)	.48
Female sex, %	39	34	47	.29
BMI, kg/m^2	26 (23 to 31)	26 (23 to 28)	27 (24 to 33)	**.02**
RASS	−2 (−3 to −1)	−2 (−3 to −1)	−2 (−3 to −1)	.94
No. of days after transition from passive MV	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)	.41
Vt, mL	488 (409 to 578)	503 (430 to 586)	442 (387 to 540)	**.03**
DP, cm H_2O	9 (2)	9 (2.2)	9.6 (2.4)	.25
ΔP,dyn, cm H_2O	12 (10.7 to 14)	12 (10.7 to 14)	12.1 (10.1 to 14.1)	.72
PS, cm H_2O	8 (6 to 10)	8 (6 to 10)	10 (6 to 12)	.13
PEEP, cm H_2O	6 (5 to 8)	6 (5 to 8)	6 (5 to 8)	.81
PMI, cm H_2O	0 (−1 to 2.8)	0 (−1 to 3)	0 (−1 to 2.4)	.34
C_{rs}, mL/cm H_2O	57 (42 to 70)	61 (48 to 71)	48 (41 to 59)	**.006**
$V_{sigh}eff - V_{sigh}exp$, mL	− 83 (−204 to 64)	−155 (−331 to −74)	134 (68 to 247)	**< .0001**
$(V_{sigh}eff - V_{sigh}exp) / V_{sigh}exp$	−0.06 (−0.16 to 0.06)	−0.12 (−0.2 to −0.05)	0.13 (0.07 to 0.19)	**< .0001**
$P_{0.1}$, cm H_2O	0.9 (0.5 to 1.5)	1 (0.5 to 1.7)	1 (0.3 to 1.4)	.36
P_{occ}, cmH_2O	5.6 (2 to 8.9)	6 (3.9 to 8.5)	3.1 (1 to 9.8)	**.03**
Pa_{O_2} to F_{IO_2} ratio, mm Hg[a]	265 (179 to 312)	252 (191 to 326)	269 (164 to 299)	.49
VR[a]	1.3 (1.2 to 1.6)	1.3 (1.1 to 1.6)	1.3 (1.2 to 1.6)	.39
P_{CO_2}, mm Hg[a]	42 (38 to 46)	41 (38 to 47)	42 (37 to 44)	.54
RR, breaths/min[a]	15 (12 to 18)	14 (11 to 18)	18 (13 to 21)	**.008**

Data were expressed as mean ± SD or median [interquartile range] according to data distribution assessed by Shapiro-Wilk test. Categorical data were expressed as count (proportion). Bold values are statistically significant ($P < .05$).

C_{rs} = respiratory system compliance; ΔP,dyn = dynamic driving pressure; DP = driving pressure; MV = mechanical ventilation; PEEP = positive end-expiratory pressure; PMI = pressure muscle index; P_{occ} = occlusion pressure; PS = pressure support; $P_{0.1}$ = occlusion pressure in the first 100 ms; RASS = Richmond Agitation Sedation Scale; RR = respiratory rate; S/T = sigh to tidal respiratory system compliance ratio; VR = ventilatory ratio; $V_{sigh}eff$ = effective sigh volume; $V_{sigh}exp$ = expected sigh volume; Vt = tidal volume.

[a]76 patients.

TABLE 2] Changes in Respiratory Mechanics, Blood Oxygenation, and Cardiovascular Parameters After Baseline PEEP Increase of 3 cm H_2O

	S/T ≤ 1			S/T > 1		
Parameters	PEEP Baseline	+3 cm H_2O	*P* Value	PEEP Baseline	+3 cm H_2O	*P* Value
Vt, mL	503 (430 to 586)	474 (382 to 585)	**.01**	442 (387 to 540)	496 (414 to 574)	**.01**
DP, cm H_2O	9 (2.2)	8.8 (2)	.3	9.6 (2.4)	9.1 (2.4)	**.02**
ΔPl,dyn, cm H_2O	12 (10.7 to 14)	12 (10 to 14)	.07	12.1 (10.1 to 14.1)	11.9 (10.1 to 14.2)	.97
PMI, cm H_2O	0 (−1 to 3)	0.5 (−1 to 2.4)	.4	0 (−1 to 2.4)	−1 (−2 to 2)	**.02**
C_{rs}, mL/cm H_2O	61 (48 to 71)	57 (46 to 68)	**.03**	48 (41 to 59)	53 (44 to 63)	**< .0001**
V_{sigh}eff − V_{sigh}exp, mL	−151 (−331 to −74)	−132 (−223 to −44)	.1	134 (68 to 247)	−34 (−100 to 53)	**< .0001**
$P_{0.1}$, cm H_2O	1 (0.5 to 1.7)	1 (0.5 to 1.5)	.39	1 (0.3 to 1.4)	0.8 (0.3 to 1.5)	.29
P_{occ}, cm H_2O	6 (3.9 to 8.5)	5.8 (3 to 9)	.07	3.1 (1 to 9.8)	4 (1 to 8.4)	.91
Pa_{O_2} to F_{IO_2} ratio, mm Hg[a]	252 (191 to 326)	244 (200 to 337)	**.05**	269 (164 to 299)	308 (191 to 352)	**< .0001**
VR[a]	1.3 (1.1 to 1.6)	1.2 (1 to 1.5)	.05	1.3 (1.2 to 1.6)	1.4 (1.2 to 1.7)	.64
P_{CO_2}, mm Hg[a]	41 (38 to 47)	42 (38 to 48)	.31	42 (37 to 44)	41 (35 to 44)	.82
RR, breaths/min[a]	14 (11 to 18)	14 (10 to 18)	.33	18 (13 to 21)	17 (14 to 19)	.17
BP, mm Hg[a]						
Systolic	119 (107 to 134)	121 (103 to 131)	.19	124 (104 to 142)	128 (108 to 137)	.51
Diastolic	60 (49 to 72)	62 (48 to 71)	.59	67 (55 to 78)	67 (55 to 78)	.29
HR, beats/min	83 (16)	83 (15)	.39	82 (18)	78 ± 17	**< .0001**

Data were expressed as mean ± SD or median [interquartile range] according to data distribution assessed by Shapiro-Wilk test. Bold values are statistically significant ($P < .05$). C_{rs} = respiratory system compliance; ΔPl,dyn = dynamic driving pressure; DP = driving pressure; HR = heart rate; PEEP = positive end-expiratory pressure; PMI = pressure muscle index; P_{occ} = occlusion pressure; $P_{0.1}$ = occlusion pressure in the first 100 ms; RR = respiratory rate; S/T = sigh to tidal compliance ratio; VR = ventilatory ratio; V_{sigh}eff = effective sigh volume; V_{sigh}exp = expected sigh volume; Vt = tidal volume.
[a]76 patients.

Patients with an S/T of > 1 demonstrated a higher BMI, a significantly lower Vt (median, 442 mL [IQR, 387-540 mL] vs 503 mL [IQR, 430-586 mL]; $P = .03$), and a lower baseline $C_{rs\ tidal}$ (48 mL/cm H_2O [IQR, 41-59 mL/cm H_2O] vs 61 mL/cm H_2O (IQR, 48-71 mL/cm H_2O]; $P = .006$) as compared with patients with an S/T of ≤ 1. A comprehensive description of all baseline parameters was reported in Table 1 and e-Table 1.

Physiologic Response to PEEP Increase of 3 cm H_2O

Increasing PEEP in patients with an S/T of ≤ 1 (ie, $C_{rs\ sigh} \leq C_{rs\ tidal}$) led to a decrease of Vt and $C_{rs\ tidal}$ as compared with baseline (median, 474 mL [IQR, 382-585 mL] vs 503 mL [IQR, 430-586 mL; $P = .01$] and 57 mL/cm H_2O [IQR, 46-68 mL/cm H_2O] vs 61 mL/cm H_2O [IQR, 48-71 mL/cm H_2O; $P = .03$], respectively). Pa_{O_2} to F_{IO_2} ratio was slightly reduced (median, 244 mm Hg [IQR, 200-337 mm Hg] vs 252 mm Hg [IQR, 191-326 mm Hg; $P = .05$). The comprehensive description of the physiologic response to PEEP increase is reported in Table 2.

Conversely, the PEEP increase in patients with an S/T of > 1 led to a significant improvement of the $C_{rs\ tidal}$ (median, 53 mL/cm H_2O [IQR, 44-63 mL/cm H_2O] vs 48 mL/cm H_2O [IQR, 41-59 mL/cm H_2O]; $P < .0001$), leading to a reduction in DP_{st} (mean [SD], 9.1 [2.4] cm H_2O vs 9.6 [2.4] cm H_2O; $P = .02$) despite a higher Vt (median, 496 mL [IQR, 414-574 mL] vs 442 mL (IQR, 387-540 mL]; $P = .01$). No difference was observed in respiratory drive and efforts (ie, occlusion pressure in the first 100 ms and occlusion pressure), but pressure muscle index was significantly lower (median, 0 cm H_2O [IQR, −1 to 2.4 cm H_2O] vs −1 cm H_2O (IQR, −2 to 2 cm H_2O]; $P = .02$). Oxygenation significantly improved (Pa_{O_2} to F_{IO_2} ratio: median, 308 mm Hg [IQR, 191-352 mm Hg] vs 269 [IQR, 164-299 mm Hg]; $P < .0001$), whereas Pa_{CO_2} and ventilatory ratio remained unchanged. Finally, heart rate was reduced when PEEP was augmented (mean [SD], 78 [17] beats/min vs 82 [18] beats/min; $P < .0001$) without BP change (Table 2).

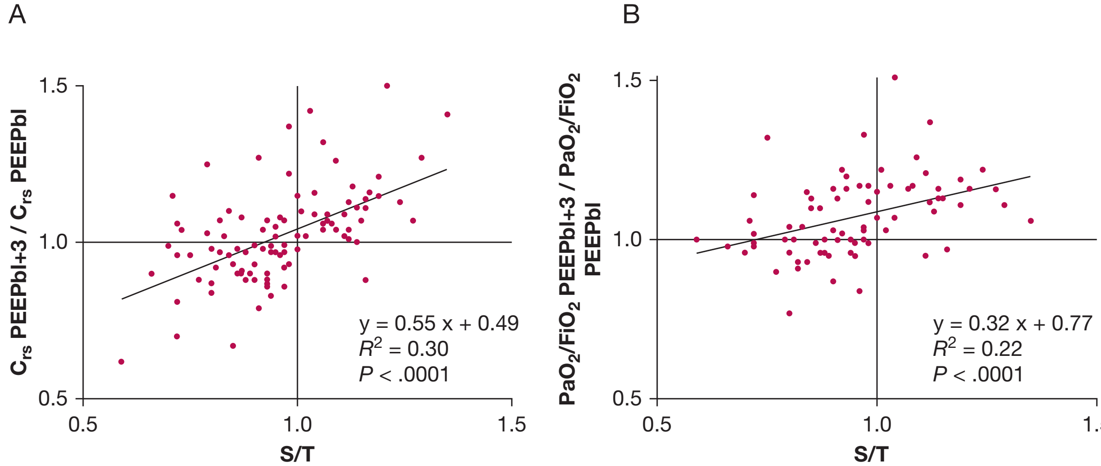

Figure 2 – *A, B, Graphs showing moderate correlation between S/T and the variation in $C_{rs\ tidal}$ (A) and in PaO_2 to FIO_2 ratio (B) after positive end-expiratory pressure increase compared with baseline. PEEPbl = positive end-expiratory pressure at baseline; S/T = sigh to tidal compliance ratio.*

The S/T correlated well with the change in $C_{rs\ tidal}$ (C_{rs}PEEP at baseline + 3 / C_{rs}PEEP at baseline) and in PaO_2 to FIO_2 ratio (PaO_2 to FIO_2 ratio PEEP at baseline + 3 / PaO_2 to FIO_2 ratio PEEP at baseline) after PEEP increase from baseline ($R^2 = 0.30$ [$P < .0001$] and $R^2 = 0.22$ [$P < .0001$], respectively) (Fig 2). In Figure 2A, it is possible to discriminate 2 subgroups of patients based on the S/T: S/T > 1 (34 of 100 patients [34%]) and S/T ≤ 1 (66 of 100 patients [66%]). Although patients belonging to the first subgroup experienced a univocal response in $C_{rs\ tidal}$ to the increase of PEEP, patients in the second group experienced an heterogeneous response. Twenty of 66 patients demonstrated a $C_{rs\ tidal}$ increase and 46 of 66 patients showed a decrease in $C_{rs\ tidal}$. The baseline characteristics of these populations having different behavior are listed in e-Figure 2. The $C_{rs\ sigh}$ before and after the increase in PEEP were not statistically different: median, 52.7 (IQR, 44.4-63.8 mL/cm H_2O) vs 52.0 mL/cm H_2O (IQR, 43.2-62.2 mL/cm H_2O (P = .2) (e-Fig 3).

Finally, we performed an analysis based on S/T tertiles: S/T > 1, S/T ≥ 0.9 and ≤ 1, and S/T < 0.9. Patients with an S/T between 0.9 and 1 did not show any significant change in respiratory mechanics variable from PEEP baseline to PEEP +3 cm H_2O. Conversely to

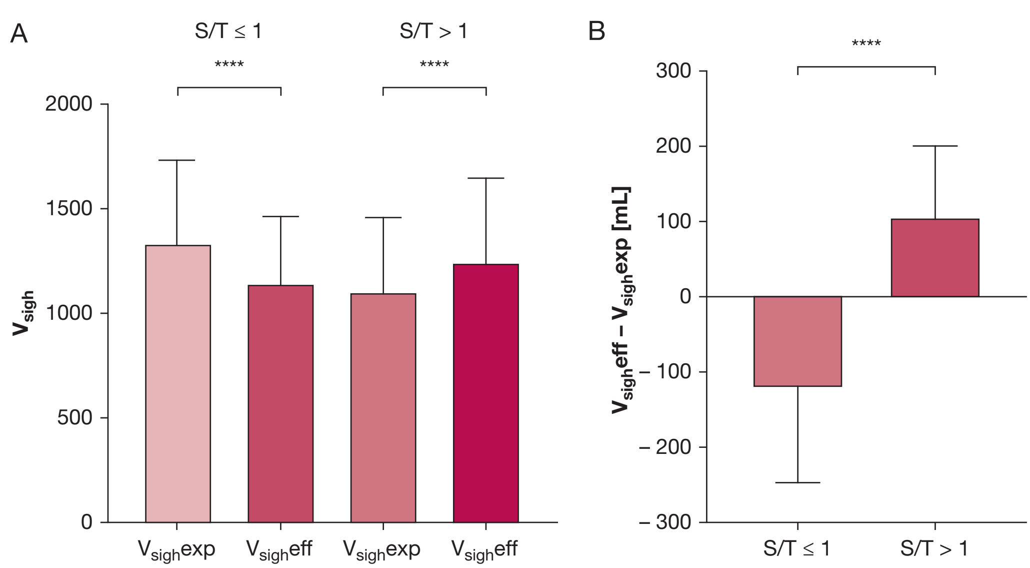

Figure 3 – *A, Graph showing V_{sigh}exp from baseline tidal respiratory system compliance and V_{sigh}eff in patients with an S/T of ≤ 1 and an S/T of > 1. B, Graph showing mean difference between the V_{sigh}eff and V_{sigh}exp (effective volume – expected volume) in the 2 subgroups of patients. S/T = sigh to tidal compliance ratio; V_{sigh} = sigh volume; V_{sigh}eff = sigh volume effective; V_{sigh}exp = sigh volume expected. ****P < .0001.*

the ST > 1 group, patients with an S/T of < 0.9 experienced a significant reduction in $C_{rs\ tidal}$ compared with baseline as soon as PEEP was raised (median, 55 mL/cm H_2O [IQR, 46-73 mL/cm H_2O] vs 62 mL/cm H_2O [IQR, 49-73 mL/cm H_2O]; $P = .02$) (e-Table 2).

Recruitability Based on S/T

In the S/T > 1 subgroup, the sigh expected volume was significantly lower than the sigh effective volume (median, 1,033 mL [IQR, 906-1,308 mL] vs 1,235 mL [IQR, 969-1,437 mL], a 13% increase; $P < .001$). In patients with an S/T of ≤ 1, the sigh volume expected was significantly higher than the volume (median, 1,306 mL [IQR, 1,017-1,596 mL] vs 1,165 mL [IQR, 868-1,374 mL], a 12% decrease; $P < .001$) (Figs 3A, 3B). $C_{rs\ overplat}$ was significantly higher in patients with an S/T of > 1 as compared with $C_{rs\ tidal}$ at baseline (median, 54 mL/cm H_2O [IQR, 45-68 mL/cm H_2O] vs 48 mL/cm H_2O [IQR, 41-59 mL/cm H_2O]; $P < .001$), whereas it was significantly lower in patients with an S/T of ≤ 1 (median, 46 mL/cm H_2O [IQR, 30-56 mL/cm H_2O] vs 61 mL/cm H_2O [IQR, 48-71 mL/cm H_2O]; $P < .001$) (e-Fig 4).

In multivariable analyses adjusted for all variables selected a priori based on the DAG (e-Fig 5), S/T emerged as the main explanatory variable associated with lung recruitment (V_{rec}). Conditional adjusted associations for all covariates are presented in e-Table 3 and are summarized in Figure 4. Notably, higher S/T values were strongly and positively associated with increased V_{rec}, whereas other covariates—including age, BMI, sex, comorbidities, cause of admission, sedation level, PEEP, and respiratory system compliance (C_{rs})—were included as part of the prespecified adjustment set to control for confounding, rather than selected for statistical significance. The variance of inflation factors was explored for all variables included in the multivariable model and excluded the presence of collinearity (e-Table 4). The additional multivariable analysis treating S/T as a categorical variable (> 1 vs ≤ 1) yielded consistent results (e-Table 5).

Difference Between Centers

Patients enrolled at the Cesena center showed lower $C_{rs\ tidal}$ (mean [SD], 52 [15] mL/cm H_2O vs 61 [18] mL/cm H_2O; $P = .02$) and DP_{st} (median, 10 cm H_2O [IQR, 9-11 cm H_2O] vs 8 cm H_2O [IQR, 7-10 cm H_2O]; $P = .002$) compared with patients enrolled at the Monza center, along with lower drive and effort (occlusion pressure in the first 100 ms: median, 0.8 cm H_2O [IQR, 0.3-1.2 cm H_2O] vs 1.3 cm H_2O [IQR, 0.5-1.9 cm H_2O]; $P = .02$; and occlusion pressure: median, 3.5 cm H_2O [IQR, 1-6.3 cm H_2O] vs 7.8 cm H_2O [IQR, 4.9-11 cm H_2O]; $P < .0001$). No difference was found in the

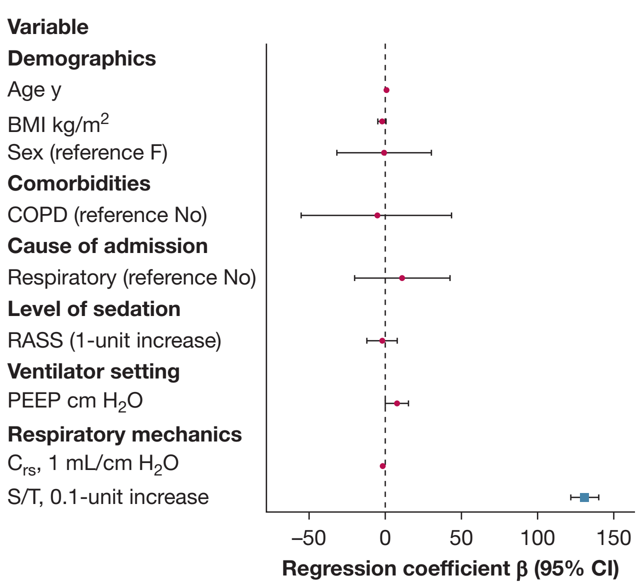

Figure 4 – *Forest plot showing adjusted associations between variables across prespecified domains and lung recruitment (V_{rec}). Points indicate multivariable linear regression coefficients (β) and horizontal lines represent 95% CIs from a model adjusted for all variables shown. Covariates were selected a priori using an explicit causal model (directed acyclic graph) to control for confounding, rather than statistical significance. The S/T (per 0.1-unit increase) is shown as the primary explanatory variable reflecting lung recruitability during the diagnostic maneuver. C_{rs} = respiratory system compliance; F = female; PEEP = positive end-expiratory pressure; RASS = Richmond Agitation Sedation Scale; S/T = sigh to tidal compliance ratio.*

correlation between S/T and the change in $C_{rs\ tidal}$ after PEEP increase by 3 cm H_2O ($R^2 = 0.3$; $P < .0001$) (e-Fig 6).

Discussion

We can summarize the main study findings as follows: (1) the ratio between the C_{rs} during sigh breath and the C_{rs} calculated over a tidal-assisted breath (S/T) identified 2 distinct subgroups of patients: those with S/T of > 1 and those with S/T of ≤ 1; (2) the S/T > 1 group showed a higher potential for recruitability as compared with the S/T ≤ 1 group during PSV, and this was demonstrated by a larger inflated volume during the sigh breath compared with the expected inflated volume calculated from the baseline $C_{rs\ tidal}$; (3) an S/T of > 1 suggests a favorable response to PEEP increase, reflected by improved C_{rs}, more protective ventilation, and enhanced oxygenation, with no adverse hemodynamic effects; and (4) in the DAG-informed multivariable model summarized in the forest plot, the conditional association between S/T and V_{rec} was preserved after adjustment for the prespecified confounding set, reinforcing S/T as the main explanatory marker of recruitability during the maneuver. This was confirmed further by exploring S/T as a categorical variable.

Although PSV is encouraged, determining the PEEP setting remains challenging.[19] Some authors advocate pragmatic approach to the PEEP setting based on the severity of respiratory illness.[20] Recent studies have explored PEEP titration during PSV using tools such as electrical impedance tomography[21] and esophageal pressure monitoring.[4,22] Although promising, these approaches are characterized by substantial interindividual variability and rely on specialized monitoring devices that are not available universally and require considerable technical expertise.

In this study, we examined whether S/T index could be an indicator of the potential for lung recruitment. By definition, in patients with S/T of > 1, $C_{rs\ sigh}$ exceeded $C_{rs\ tidal}$. Similarly, $C_{rs\ overplat}$ was higher than $C_{rs\ tidal}$. These data suggest that the inspiratory pressure beyond tidal ventilation (and thus beyond P_{plat} and up to 30 cm H_2O) acted on a steeper portion of the pressure-ventilation loop within a breath. This finding explains why the effective sigh volume exceeded the sigh volume expected based on baseline tidal compliance. Further supporting this interpretation, 97% of patients with an S/T of > 1 showed improved $C_{rs\ tidal}$ after PEEP augmentation. The PEEP change, in turn, led to more protective ventilation, significantly better oxygenation, and no hemodynamic compromise. Taken together, in the S/T > 1 subgroup, intrasigh recruitment is likely to occur. We were unable to assess the effects of intrasigh recruitment or intrasigh overdistension on ventilator-induced lung injury or mortality. Although existing literature supports the beneficial effects of periodic sighs,[9-12] those studies did not describe intrasigh respiratory mechanics.

From a gas exchange perspective, ventilatory ratio and Pa_{CO_2} did not change after 15 minutes of higher PEEP compared with baseline in any group. Besides the complex interplay behind the CO_2 washout in actively breathing patients, this finding may be explained by the longer equilibration time of Pa_{CO_2} after PEEP change. Conversely, modification in Pa_{O_2} is physiologically faster and increases progressively over time.[23] Therefore, we observed a rapid improvement in oxygenation in the S/T > 1 group. The concomitant improvement in $C_{rs\ tidal}$ and oxygenation and a significant reduction in heart rate after PEEP increase suggests that Pa_{O_2} values were driven mainly by a reduction in the right-to-left shunt fraction because of alveolar recruitment.[24]

It is worth mentioning that the present study was not designed to assess mortality or long-term outcomes. The significant improvement of $C_{rs\ tidal}$ and Pa_{O_2} after 15 minutes in the S/T > 1 group suggests that PEEP augmentation favorably affected respiratory system mechanics. However, no data are available to determine whether these physiologic improvements translate into major clinical benefits.

Although some preclinical studies reported a reduction in inspiratory effort as PEEP increases,[25] we did not find similar results. This discrepancy may be explained by several factors: (1) the magnitude of PEEP increase was moderate (+3 cm H_2O) compared with the one observed in a preclinical model (+8 cm H_2O),[25] (2) the baseline inspiratory effort in our sample was quite low, and (3) the patients did not experience severe hypoxemia.

Patients with an S/T of > 1 showed a lower $C_{rs\ tidal}$ (e-Fig 7) and a significant higher BMI compared with those with S/T of ≤ 1, possibly indicating inadequate PEEP setting in patients at higher risk of atelectasis.[12] Although baseline $C_{rs\ tidal}$ was related to V_{rec}, our findings suggest that S/T captures complementary information on recruitability during the diagnostic maneuver. Using a prespecified DAG, the conditional association between S/T and V_{rec} was preserved after adjustment for potential confounders.

The S/T $\leq$ 1 group manifested an ambivalent behavior in response to PEEP increase. Most patients experienced a reduction in $C_{rs\ tidal}$ and a significant decline in oxygenation. Tertile analysis showed that lower S/T values (< 0.9) were associated with the worst $C_{rs\ tidal}$ response after PEEP increase. In this case, the sigh probably produced an intrasigh overdistension, and it might be used as an incentive to decrease PEEP. Conversely, patients with an S/T between 0.9 and 1 showed similar mechanical variables across study steps. Because we did not assess individual pressure-ventilation loop, we can only speculate that patients with S/T of < 0.9 were—at PEEP baseline—near the upper inflection point.[24] Because of the limited size of these subgroups, we were unable to characterize fully their specific feature. Overall, S/T of ≤ 1 did not seem—based on the present findings—to be a reliable parameter for guiding further PEEP titration.

$C_{rs\ sigh}$ at baseline and after the increase in PEEP were almost identical (same peak pressure, but different DP during sigh), suggesting: (1) the stability of the $C_{rs\ sigh}$ data obtained at flow of 0 mL/s and without inspiratory hold and (2) that the PEEP augmentation did not alter the overall shape of the compliance curve of the respiratory system, but simply shifted the starting point of a breath along the curve.

The present study has some limitations. First, the magnitude of PEEP increase (3 cm H_2O) was chosen arbitrarily to avoid excessive PEEP in patients without significant hypoxemia. This modest increase may have limited our ability to detect significant changes, particularly in the S/T < 1 subgroup, Second, the enrolled patients were mildly hypoxemic, the baseline $C_{rs\ tidal}$ was only slightly impaired, and the respiratory effort was normal; therefore, our results cannot be translated fully into patients with ARDS. Third, cardiac output was not monitored continuously, although invasive hemodynamic monitoring ensured cardiovascular stability. Fourth, we did not use an esophageal pressure. Thus, we were unable to quantify the contribution of chest wall and lung to the increase (or decrease) in C_{rs} and we were unable to monitor inspiratory effort (if any) within the sigh breath. The sigh P_{plat} was deemed reliable exclusively based on visual inspection. Finally, CT imaging, wash-in and wash-out methods, and electrical impedance tomography were not used, limiting us to mechanical and gas exchange variables for estimating lung recruitment.

Interpretation

In critically ill patients undergoing pressure support ventilation, assessment of the C_{rs} during sigh breath is feasible. Normalizing C_{rs} during sigh to C_{rs} during tidal breath (ie, S/T) could provide useful, noninvasive information into lung recruitability at the bedside. Our data showed that when S/T was > 1, increasing PEEP improved respiratory system mechanics, promoted more protective ventilation, and improved oxygenation. Further studies focusing on patients with ARDS are warranted.

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Author contributions: L. B. conceived the study, conducted the study, analyzed and interpreted data, and wrote and revised the manuscript. R. G. conducted the study, analyzed the data, and revised the manuscript. L. A. conducted the study, analyzed the data, and revised the manuscript. E. Russo conducted the study and interpreted the data. T. M. interpreted data and revised the manuscript. G. F. interpreted data and revised the manuscript. V. A. interpreted data and revised the manuscript. E. Rezoagli conceived the study, conducted the study, analyzed and interpreted data, wrote and revised the manuscript, and was the supervisor of the project.

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Availability of data and materials: The data sets used or analyzed during the current study are available from the corresponding author on reasonable request.

Additional information: The e-Figures and e-Tables are available online under "Supplementary Data."

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