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Sigh in patients with acute hypoxemic respiratory failure and acute respiratory distress syndrome: the PROTECTION pilot randomized clinical trial.

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Sigh in patients with acute hypoxemic respiratory failure and acute respiratory distress syndrome: the PROTECTION pilot randomized clinical trial.

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Short title: Sigh in acute hypoxemic respiratory failure and ARDS

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ABBREVIATION LIST

AHRF: Acute Hypoxemic Respiratory Failure

ARDS: Acute Respiratory Distress Syndrome

BMI: Body Mass Index

ESICM: European Society of Intensive Care Medicine

FiO_2: Fraction of Inspired Oxygen

GEE: Generalize Estimate Equation

ICU: Intensive Care Unit

MV: Mechanical Ventilation

PaO_2/FiO_2 ratio: Arterial Partial Pressure of O_2/ Fraction of Inspired Oxygen

$PaCO_2$: Arterial Partial Pressure of CO_2

PBW: Predicted Body Weight

PEEP: Positive End Expiratory Pressure

P-SILI: Patient - Self Inflicted Lung Injury

PSV: Pressure Support Ventilation

RCT: Randomized Control Trial

RASS: Richmond Agitation- Sedation Scale

RR: Respiratory Rate

SAPS II: Simplified Acute Physiology Score II

SBT: Spontaneous Breathing Trial

SOFA: Sequence Organ Failure Assessment

SpO_2: Peripheral Oxygen Saturation

SpO_2/FiO_2 ratio: Peripheral Oxygen Saturation/ Fraction of Inspired Oxygen

TRALI: Transfusion-Related Acute Lung Injury

VFDs: Ventilator- free days

Vt: Tidal Volume

ABSTRACT

Background. Sigh is a cyclic brief recruitment manoeuvre: previous physiological studies showed that its use could be an interesting addition to pressure support ventilation to improve lung elastance, decrease regional heterogeneity and increase release of surfactant.

Research Question. Is the clinical application of sigh during pressure support ventilation (PSV) feasible?

Study Design and Methods. We conducted a multi-center non-inferiority randomized clinical trial on adult intubated patients with acute hypoxemic respiratory failure or acute respiratory distress syndrome undergoing PSV. Patients were randomized to the No Sigh group and treated by PSV alone, or to the Sigh group, treated by PSV plus sigh (increase of airway pressure to 30 $cmH_2O$for 3 seconds once per minute) until day 28 or death or successful spontaneous breathing trial. The primary endpoint of the study was feasibility, assessed as non-inferiority (5% tolerance) in the proportion of patients failing assisted ventilation. Secondary outcomes included safety, physiological parameters in the first week from randomization, 28-day mortality and ventilator-free days.

Results. Two-hundred fifty-eight patients (31% women; median age 65 [54-75] years) were enrolled. In the Sigh group, 23% of patients failed to remain on assisted ventilation vs. 30% in the No Sigh group (absolute difference -7%, 95%CI -18% to 4%; p=0.015 for non-inferiority). Adverse events occurred in 12% vs. 13% in Sigh vs. No Sigh (p=0.852). Oxygenation was improved while tidal volume, respiratory rate and corrected minute ventilation were lower over the first 7 days from randomization in Sigh vs. No Sigh. There was no significant difference in terms of mortality (16% vs. 21%, p=0.342) and ventilator-free days (22 [7-26] vs. 22 [3-25] days, p=0.300) for Sigh vs. No Sigh.

Interpretation. Among hypoxemic intubated ICU patients, application of sigh was feasible and without increased risk.

Clinical Trial registration. ClinicalTrials.gov Identifier: NCT0320126328 June 2017

BACKGROUND

Mechanical ventilation is a vital support for intubated patients with acute hypoxemic respiratory failure (AHRF) and acute respiratory distress syndrome (ARDS)[1,2]. Early switch to assisted ventilation modes carries significant benefits, including reduced sedation and improved hemodynamics[2]. Around 30% of invasively ventilated patients breathe spontaneously at day 1 from intubation and, at day 7, pressure support ventilation (PSV) is the most widely used mode of ventilation world-wide[3].

Multiple physiological studies showed that use of sighs could be an interesting addition to pressure support ventilation. Sigh may improve lung function through improved lung elastance [4], decreased regional heterogeneity[5],increased release of active surfactant [6]and decreased effort [5], the latter being protective also for the diaphragm. Moreover, sigh has been shown to allow a reduction in tidal volume and respiratory rate, reducing the ventilation load applied to the lungs [4,5,7]. These studies generated the hypothesis that addition of sigh to PSV might improve clinical outcomes of patients with AHRF and ARDS. However, no randomized clinical trial (RCT) on sigh addition to PSV has ever been performed, and, before conducting a larger trial aimed at verifying improved survival, we first conceived a pilot RCT to verify the clinical feasibility of sigh in comparison to standard PSV [8] and to have preliminary estimates of adverse events, lost to follow-up, outcomes and its variabilities. A non-inferiority approach was chosen to demonstrate that application of sigh in the clinical setting is as feasible as standard PSV, which is the most widely adopted assisted ventilation mode.

In the present trial, sigh was applied early after switching to PSV in intubated AHRF or ARDS patients and maintained until successful weaning, death or day 28. The study aimed attesting the non-inferiority of sigh, as compared to standard PSV without sigh, in terms of failure of assisted ventilation. Failure was defined as the occurrence of any of these conditions: switch back to controlled ventilation; use of rescue therapies for refractory hypoxemia; re-intubation. Secondary outcomes included comparison between the two study arms in the incidence of adverse events, physiological parameters, survival and ventilator-free days.

METHODS

Study design and population. The present study was a pilot RCT conducted between December 2017 and May 2019 at the ICUs of 20 hospitals from 8 countries: Italy, Spain, United Kingdom,

Germany, Slovenia, Greece, China, Brazil. Centres were recruited through a call to members of the PLUG working group of the European Society of Intensive Care Medicine (ESICM) and through publication of the protocol on the ESICM website. ESICM also endorsed and funded, in part, the study. The study design and statistical analysis plan have been published[8]. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (international leading coordination center, date 6-6-2017, No. 318). The institutional review boards of all centres approved the trial. The study was registered on ClinicalTrials.gov (Identifier: NCT03201263 28 June 2017). Informed consent was obtained for all individual participants included in the study, following local regulations. The trial enrolled patients admitted to each participating ICU receiving invasive ventilation since >24 hours and ≤7 days, undergoing PSV since ≥4 and ≤24 hours, with PaO_2/FiO_2 ratio ≤300 mmHg and clinical positive end-expiratory pressure (PEEP) ≥5 cmH_2O. Richmond Agitation-Sedation Scale (RASS)[9] value at enrolment had to be between -2 and 0. Exclusion criteria can be found in the Online Supplement 1 (Page 2).

Sigh test, randomization and interventions. After enrollment, all patients underwent a 30-minute test of addition of Sigh to clinical PSV to assess the prevalence of sigh responders vs. non-responders as defined by improved oxygenation. Briefly, the ventilator inspired oxygen fraction (FiO_2) was titrated to obtain a peripheral oxygen saturation (SpO_2) of 90-96%, while keeping the same clinical PEEP and PSV levels. Then, sigh was added as a pressure control phase set at total end-inspiratory pressure of 30 cmH_2O for 3 seconds insufflation time, once per minute. At the beginning and after 30 minutes, the SpO_2/FiO_2 ratio was collected. Based on previous physiological study, the expected prevalence of sigh responders (i.e., patients improving SpO_2/FiO_2 by >1%) was estimated to be 50%[5].

After completion of the sigh test, patients were randomized by a 1:1 ratio to a strategy of PSV titrated following a predefined protocol with addition of sigh (Sigh group) or to a strategy of PSV titrated following the same protocol but without Sigh (no Sigh group). The local investigators randomized patients using a central, dedicated, password-protected, web-based, automated randomization system. The randomization sequence was generated using a permuted blocks randomization scheme (block size of 6).

After randomization, in the Sigh group, PSV was targeted to a tidal volume (Vt) of 6-8 mL/Kg of predicted body weight (PBW), with respiratory rate (RR) 20-35 breaths/min (bpm) and clinical PEEP. FiO_2 was left as selected during the pre-randomization sigh test. Sigh was promptly added as

a pressure control breath at total end-inspiratory pressure of 30 cmH_2O for 3 seconds delivered once per minute. Ventilators were switched to biphasic synchronized positive airway pressure mode (also known as synchronized intermittent mandatory ventilation combining pressure control and PSV) with the lower pressure level set at clinical PEEP and the higher-pressure level set at 30 cmH_2O with a 3-second inspiratory time. Sigh settings were left unchanged until switch to controlled ventilation, day 28, death or performance of a successful spontaneous breathing trial (SBT, see below). In the No Sigh group, after randomization, PSV was set to obtain the same targets as above with clinical PEEP and the FiO_2 selected during the pre-randomization sigh test. Then, in both groups at least every 8 hours, the PSV level was adjusted to maintain Vt of 6-8 ml/kg PBW and RR of 20-35 bpm, while PEEP and FiO_2 were managed to keep SpO_2 of 90-96%.

In both groups, switch to protective controlled ventilation was indicated when patients developed specific pre-defined criteria[8]. Patients switched to controlled ventilation were reassessed at least every 8 hours and switched back to Sigh or No Sigh group as soon as pre-defined criteria for improvement were met[8].

Patients with SpO_2 ≥90% on FiO_2 ≤0.4 and PEEP ≤5 cmH_2O, no agitation and hemodynamically stable underwent a SBT. For patients in the Sigh group, the attending physician withdrew sigh, waited 60 min, confirmed the abovementioned criteria and performed the SBT; if criteria weren't anymore met, sigh was re-introduced and this procedure was repeated after at least 8 hours. SBT lasted at least 60 minutes with a combination of PEEP 0-5 cmH_2O and PSV level of 0-5 cmH_2O. Criteria for success vs. failure of the SBT were pre-defined by study protocol[8]. Subjects successfully completing the SBT were promptly extubated or, in the presence of tracheostomy, mechanical ventilation was discontinued. Patients who failed the SBT were switched back to Sigh or No Sigh and criteria for SBT were checked again after at least 6 hours. After extubation, re-intubation was performed if at least one of the criteria pre-defined by the study protocol was present[8].

Outcomes. The primary endpoint of this trial[8] was to assess non-inferiority of Sigh feasibility vs. No Sigh by comparing the number of patients in each group experiencing at least one of the following criteria for failure of assisted ventilation: switch to controlled ventilation for ≥24 consecutive hours; use of rescue therapy; re-intubation within 48 hours.

Secondary outcomes included: comparison of selected physiological variables during the first 7 days from randomization in the two study groups; evaluation of the clinical safety of Sigh vs. No Sigh by comparing incidence of pre-defined adverse events; quantification of responders and non-

responders to the pre-randomization Sigh test; 28-day mortality and ventilator-free days in the two study groups and in responders and non-responders.

Statistical analysis. Based on previous data [10], we computed that a sample size of 258 patients (with 129 patients per study arm) was sufficient to assess feasibility of the Sigh strategy (primary outcome) using a non-inferiority test with a tolerance of 5%, power of 0.8, alpha 0.05, 22% and 15% as the expected rate of failure of assisted ventilation in patients undergoing No Sigh and Sigh treatment, respectively. Failure of assisted ventilation in patients treated with Sigh was compared to patients with No Sigh using a one-tailed non-inferiority test for proportions with a 5% tolerance. In details, non-inferiority of Sigh was established when failure in the Sigh group was lower than failure of No Sigh plus 5%. This is the standard alternative hypothesis for non-inferiority tests[11]. Thus, in this study, p-value lower than 0.05 (type I error) for the non-inferiority test would reject inferiority of the new treatment (Sigh) compared to No Sigh. Survival at 28th day was analysed using Kaplan Meier curves and Log-Rank test was used to test differences between curves. Continuous variables are described by mean and standard deviation when normally distributed or as median and interquartile range otherwise. Categorical variables are reported as number and proportion (%). Statistical significance of differences between the two study groups (Sigh vs. No Sigh) was tested using Chi-squared or Fisher's Exact Test for categorical variables, T-test for continuous normally distributed variables and Wilcoxon Signed Rank Test for non-normally distributed continuous variables.

To test differences in time-trends of physiological and clinical parameters between the two study groups we used Generalized Estimating Equation (GEE) models to account for repeated measures.

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RESULTS

Patients. One-thousand-sixty-four intubated ICU patients undergoing PSV were screened. A total of 806 were not enrolled, of whom 726 (90%) met at least one of the exclusion criteria and 80 (10%) were eligible but could not be enrolled for various reasons (Figure 1). Two-hundred-fifty-eight patients completed the Sigh test and were subsequently randomized, 129 to the Sigh group and 129 to the No Sigh group. None of the patients with drew consent after randomization. Sigh was applied for 4 [2-9] days in the Sigh group. Follow-up until day 28 was complete for all patients.

Data for 258 subjects (129 in each group) were considered for the primary intention to treat analysis (Figure 1).

Three patients in the Sigh group and two patients in the PSV group were not included in the per-protocol analysis because of switch to the other study arm due to adverse event, discomfort and hypoxemia; 126 patients in the Sigh group and 127 in the No Sigh group were kept for the per-protocol analysis.

Baseline characteristics were well balanced between the two study groups (Table 1). Males were 67% (87 patients) and 71% (92 patients) in Sigh group and in No Sigh group, respectively. Mean age of patients was 63±15 years, with no significant difference between groups. Prevalence of comorbidities and general severity at admission were comparable (Table 1). Prevalence of the diagnosis of ARDS was 46% in the Sigh and 53% in the No Sigh group, with non-significant difference (Table 1).

Outcomes. Twenty-eight days after randomization, 30 patients (23%) in the Sigh group vs. 39 (30%) in the No Sigh group (Table 2) experienced at least one criterion for failure of assisted ventilation were. Sigh treatment group was therefore non-inferior to No Sigh treatment group in terms of failure of assisted ventilation (absolute difference -7%; 95%CI -18% to 4%, p=0.015 for non-inferiority test) (Figure 2)**.** Specific reasons for failure of assisted ventilation and type of rescue treatment are shown in Table 2. Per-protocol analysis showed similar results with 29 (23%) patients failing to remain on assisted ventilation in the Sigh group vs. 37 (29%) in the No Sigh group (absolute difference -6%; 95%CI -17% to 5%, p=0.022 for non-inferiority test).

Adverse events (i.e. hemodynamic instability, arrhythmias and barotrauma) did not differ between the 2 study groups (16 (12%) patients in the Sigh group vs. 17 (13%) patients in the No Sigh group, p=0.852). Type of adverse events are described in Table 2.

Twenty-one patients (16%) died by day 28 in the Sigh group vs. 27 patients (21%) in No Sigh group (p=0.337) (Table 2)**.** Survival was analyzed by Kaplan-Meier curves (Figure 3) (p=0.342 by Log-Rank test)**.** Ventilator-free days at day 28 were 22 (7-26) days in the Sigh group and 22 (3-25) in the No Sigh group (p=0.300) (Table 2). The number of patients failing an SBT was 23 (18%) in the Sigh group and 21 (16%) in the No Sigh group (p=0.741). The number of SBT failed was 1 [1-2] per patient for both groups, with no significant difference.

Outcomes in responders and non-responders. Sigh responders, defined as patients in whom the SpO_2/FiO_2 increased by >1% during the Sigh pre-randomization test, were 156 (60%), 73 (47%) in the Sigh group and 83 (53%) in the No Sigh group. Thus, non-responders were 102, 56 (55%) in the

Sigh group and 46 (45%) in the No Sigh group. Baseline demographics and clinical characteristics did not differ between the study groups both for responders and non-responders (eTable 1 and eTable 2 in the Online Supplement 1). In responders, mortality was 16% (n=12) in the Sigh group vs. 13% (n=11) in the No Sigh group (p=0.575). In non-responders, mortality was 16% (n=9) in the Sigh group vs. 35% (n=16) in the No Sigh group (p=0.029). Ventilator-free days did not differ in responders enrolled in the Sigh vs. No Sigh group (21 (5-26) vs. 23 (15-25) days, p=0.380). Ventilator-free days were significantly higher in non-responders treated with Sigh vs. No Sigh (23 (9-26) vs. 10 (0-24) days, p=0.006).

Physiology. Over the first seven days from randomization, the PEEP level and set FiO_2 did not differ between groups. PaO_2/FiO_2ratio was significantly higher while respiratory rate, tidal volume and corrected minute ventilation (i.e., the minute ventilation multiplied by actual $PaCO_2$ divided by 40 mmHg, with lower values indicating higher efficiency to clear CO_2 by the respiratory system) were all significantly lower in the Sigh group (eTable 3 and eFigure 1 in the Online Supplement 1). The tidal volume delivered by Sigh in the first seven days from randomization remained stable and around 15 ml/kg PBW (eFigure 2 in the Online Supplement 1). $PaCO_2$ and pH, RASS score and SOFA score were similar (eTable 3 and eFigure 1 in the Online Supplement 1).

DISCUSSION

This randomized clinical trial showed the feasibility of adding sigh to PSV: the rate of failure of assisted ventilation was non-inferior to conventional PSV. Secondary outcomes indicated safety of sigh with a similar rate of adverse events, a comparable mortality and number of ventilator-free days. Moreover, improved physiology was confirmed in the first week from randomization by addition of sigh.

Sigh is commonly performed during quiet breathing by healthy subjects, mainly acting as negative feedback on respiratory drive with positive functional and psychological consequences [12]. Many studies performed both in hypoxemic patients[13,14] and in animal models of lung injury[15] showed that sigh is associated with improved physiology. Sigh induces recruitment of the collapsed lungs, restores surfactant production, decreases ventilation heterogeneity, improves regional mechanics, increases oxygenation and modulates the inspiratory effort [5,16]. On the other hand, sigh cyclically delivers large inspiratory volumes in patients in whom current guidelines recommend mandatory reduction of tidal volume [1,17]. Since no study existed on the feasibility and safety of long-term

application of sigh to hypoxemic patients, it seemed important to conceive a large non-inferiority randomized controlled trial aimed at assessing the clinical feasibility and the safety of sigh.

The present trial indicates that addition of sigh to PSV leads to a rate of patients with acute hypoxemic respiratory failure or ARDS experiencing failure of assisted ventilation similar to traditional PSV. Moreover, number of adverse events were similar and low, with only 2 patients per group experiencing barotrauma; in only two patients sigh was stopped to continue with traditional PSV; mortality and ventilator-free days did not differ. Taken together, these results suggest that sigh could be added to PSV without causing any additional risk and yielding similar clinical outcomes in acute hypoxemic respiratory failure and ARDS patients. Possible explanations for these findings could be that sigh was not able to produce any clinical benefits in comparison to PSV alone; or that the non-significant difference in mortality showed in this trial might become significant in a study performed with the same protocol but with larger sample size.

Reduction of mortality with sigh in the subgroup of patients not responding in terms of oxygenation during a 30-minute sigh test performed before randomization is an additional intriguing finding that will require confirmation.

Assisted ventilation carries the intrinsic risk of additional patient self-inflicted lung injury (P-SILI)[18] and respiratory muscles myotrauma[19], making lung and diaphragm protection a key clinical goal[20]. Limiting the inspiratory volume and transpulmonary pressure is the recommended strategy for hypoxemic patients on PSV to minimize the risk of P-SILI [21,22]. We confirmed that sigh improves oxygenation and decreases respiratory rate, tidal volume and minute ventilation during the first week, potentially decreasing the risk of additional P-SILI. As un-physiological high inspiratory pressure and volume leading to P-SILI increase the risk of prolonged ventilation and worse outcome [23], the physiological analyses from this study might help generating a more solid hypothesis on the clinical effects of sigh.

Our results suggest that sigh is easy to implement and could be already seen as alternative ventilation mode for ICU physicians, even in resource-limited settings[24].

Sigh can be delivered for longer time period (e.g., from intubation), at more physiological lower rate (e.g., once every other minute) and at different inspiratory pressure (e.g., personalized based on transpulmonary pressure) than in our study. Sigh isn't a general concept but rather a mechanical ventilation strategy with specific settings and variability in the delivery of Sigh may alter the results presented herein.

The present study has limitations. First, at enrolment, the patients were on mechanical ventilation since 3 [2-5] days and sigh was applied only for approximately half the total number of days spent on mechanical ventilation. We can't answer as to whether application of sigh earlier and for longer time period might lead to increased benefits (from improved physiology) or harm (from higher risks of cyclic over-distension and atelectrauma). However, application of sigh during controlled ventilation requires specific machines and we reasoned that sigh has specific advantages in patients on assisted ventilation (e.g., modulation of effort). Second, we delivered sigh at the same total inspiratory pressure in all patients, which, based on predictable differences in respiratory mechanics, could have determined variable levels of transpulmonary pressure. Response to the pre-randomization Sigh test might have been influenced by this, too, with non-responders receiving insufficient volume. Personalized sigh settings based on specific patients' characteristics could lead to higher number of responders and improved outcomes. Third, the rate of sigh in this study was one per minute, while physiological studies suggested that lower rate may be more effective[5]. Once again, to our knowledge, only few ventilators can deliver sigh during PSV once every two minutes. Fourth, because of the nature of the intervention, physicians and nurses attending patients enrolled in the study could not be blinded. However, we provided detailed protocols for changes in PSV settings, performance of rescue therapies, spontaneous breathing trials, extubation and re-intubation [8],which should have limited biases in primary outcomes. Fifth, we defined sigh responders based on improvement of the SpO_2/FiO_2 by >1% during the pre-randomization sigh test. This threshold could be seen as too low for being clinically meaningful, however, the analysis was exploratory and higher threshold would have yielded large imbalances in groups numerosity.

INTERPRETATION

Addition of sigh to PSV in patients with acute hypoxemic respiratory failure or ARDS is as feasible as traditional PSV in terms of failure of assisted ventilation, and yields comparable adverse events, mortality and ventilator-free days. Results from the present trial could inform planning and design of larger clinical trials aimed at verifying reduced mortality by application of sigh.

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Dr Mauri and Prof Pesenti had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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TAKE HOME POINT

Study Question. The aim of this Randomized Clinical Trial was to determine the feasibility of the application of sigh during pressure support ventilation (PSV).

Results. The study showed that in mechanically ventilated patients with acute hypoxemic respiratory failure or acute respiratory distress syndrome addition of Sigh in comparison to No Sigh during PSV was feasible and safe: no increase in patients failing to remain on assisted ventilation (23% vs. 30%, respectively) and similar proportion of adverse events (12% vs. 13%, respectively).

Interpretation. Addition of sigh to PSV is feasible and safe in intubated ICU patients with acute hypoxemic respiratory failure or acute respiratory distress syndrome.

FIGURE LEGENDS

Figure 1. Flow of patients in the trial

Figure 2. Treatment difference for failure of assisted ventilation between study groups. Dot and error bars indicate absolute value and 2-sided 95% CIs. 5% was the maximum tolerance accepted in this non-inferiority RCT (light blue dotted line)

Figure 3. 28-day mortality in the study groups

TABLES

Table 1. Baseline characteristics

	Sigh (N=129)	No Sigh (N=129)	P Value[a]
Demographics			
Male, No.(%)	87 (67)	92 (71)	0.499
Age, mean (SD),years	63 (17)	63 (14)	0.676
Height, median (Q1, Q3), cm	170 (165, 178)	170 (160, 176)	0.298
Predicted Body Weight, median (Q1, Q3), Kg	80 (67, 90)	78 (65, 86)	0.432
BMI, median (Q1, Q3), Kg/m^2	26.1(23.4, 31.0)	26.2 (23.5, 29.7)	0.967
Comorbidities, No.(%)			
Chronic cardiovascular disease	66 (51)	79 (61)	0.103
Chronic pulmonary disease	19 (15)	27 (21)	0.193
Diabetes	26 (20)	28 (22)	0.735
Chronic renal disease	14 (11)	24 (19)	0.079
Cancer	13 (10)	18 (14)	0.338
Number of comorbidities, No.(%)			
0	40 (34)	32 (25)	0.199
1	48 (37)	44 (35)	
2	23 (18)	31 (24)	
≥3	14 (11)	21 (16)	
Recent medical history			
In-hospital days, median (Q1, Q3)	5 (3,8)	5 (3, 8)	0.785
ICU days, median (Q1, Q3)	3 (2,5)	3 (2, 5)	0.513
Intubation days, median (Q1, Q3)	3 (2, 5)	3 (2, 4)	0.358
SAPS II, median (Q1, Q3)	42 (32, 55)	42 (32, 56)	0.796
SOFA, median (Q1, Q3)	7 (5, 10)	7.5 (5, 9)	0.857
RASS, No. (%)			
-2	64(50)	72(56)	0.588
-1	27(21)	25(19)	
0	38(29)	32(25)	
Diagnosis of sepsis, No. (%)			
Sepsis	43 (33)	39 (30)	0.144
Septic Shock	20 (15)	35 (27)	
No sepsis	60 (47)	51 (40)	
Not Specified	6 (5)	4 (3)	
Etiology			
Pneumonia, No. (%)	79 (61)	75 (58)	0.612
Aspiration of gastric content, No. (%)	15 (12)	11 (9)	0.408
Vasculitis, No. (%)	1 (1)	1 (1)	1.000

Non-pulmonary sepsis, No. (%)	20 (16)	24 (19)	0.508
Trauma, No. (%)	8 (6)	6 (5)	0.583
Pancreatitis, No. (%)	4 (3)	4 (3)	1.000
Burns, No. (%)	1 (1)	1 (1)	1.000
TRALI, No. (%)	3 (2)	4 (3)	0.702
Others, No. (%)	15 (12)	16 (12)	0.848
Pulmonary infiltrates, No. (%)			
None	28 (22)	22 (17)	0.427
Unilateral	42 (33)	38 (30)	
Bilateral (ARDS diagnosis)	59 (46)	69 (53)	
PEEP, median (Q1, Q3), cmH_2O	10 (8,12)	10 (8,11)	0.487
PSV, median (Q1, Q3), cmH_2O	10 (8,12)	10 (8,12)	0.967
RR, median (Q1, Q3), bpm	18 (10,30)	18 (15,23)	0.445
pH, mean (SD)	7.43 (0.05)	7.43 (0.06)	0.510
PaO_2/FiO_2, median (Q1, Q3), mmHg	222 (192, 252)	228 (187, 251)	0.991
$PaCO_2$, median (Q1, Q3), mmHg	44 (38, 49)	43 (39, 47)	0.695

Continuous data are reported as median (Q_1, Q_3) or mean (SD). Categorical data are report as No. (%).

Abbreviations: BMI= Body Mass Index, ICU= Intensive Care Unit, SASPS=Simplified Acute Physiology Score, SOFA=Sequential Organ Failure Assessment, RASS= Richmond Agitation Sedation Score, TRALI= transfusion-related acute lung injury, PEEP=Positive end-expiratory pressure, PSV=Pressure Support Ventilation, RR= Respiratory Rate, PAO_2= partial pressure of oxygen, FiO_2= inspired oxygen fraction; $PaCO_2$=Partial pressure of carbon dioxide in the arterial blood, bpm=breaths/min

[a] Tests for differences between PSV+Sigh vs. PSV: t-test or Wilcoxon, chi-square or Fisher, as appropriate.

Table 2. Study outcomes

	Sigh (N=129)	No Sigh (N=129)	P Value[a]
Failure of assisted ventilation, No. (%) - Non-inferiority test	30 (23)	39 (30)	0.015
Reasons for failure			
Switch to controlled MV ≥24 hours, No. (%)	15 (12)	26 (20)	0.061
Rescue treatment for hypoxemia, No. (%)	14 (11)	19 (15)	0.351
Reintubation within 48 hours, No. (%)	13 (9)	12 (9)	0.833
Type of rescue treatment, No. (%)			
Recruitment maneuver	9 (7)	14 (11)	0.735
PEEP ≥15 cmH_2O	3(2)	2 (2)	
Prone position	2(2)	3 (2)	
Reasons for switch to MV, No. (%)			
Support >20 cmH_2O or arterial pH <7.3	4 (3)	8 (6)	0.262
PEEP ≥15 cmH_20 or PaO_2/FiO_2 ≤100 mmHg	8 (6)	8 (6)	
Hypotension or hypertension	0 (0)	1 (1)	
Active cardiac ischemia or unstable arrhythmias	0 (0)	1 (1)	
RASS<-3 or RASS>2	3 (2)	5 (4)	
Necessity to perform diagnostic test	0 (0)	3 (2)	
Adverse events, No. (%)	16 (12)	17 (13)	0.852
Type of Adverse Event, No. (%)			
Hemodynamic instability	5 (4)	6 (5)	1.00
Arrhythmias	2 (2)	2 (2)	
Barotrauma	9 (7)	9 (7)	
Sigh Responders[b], No. (%)	73 (56)	83 (64)	0.609
Tracheostomy, No. (%)	22 (17)	19 (15)	0.441
Deaths at 28 days , No. (%)	21 (16)	27 (21)	0.337
VFDs, median (Q1, Q3)	22 (7, 26)	22 (3, 25)	0.300
Length of ICU stay, median (Q1, Q3),days	7 (3, 13)	7 (5, 11)	0.695

Continuous data are reported as median (Q_1-Q_3) or mean ± std. Categorical data are reported as No. (%).

Abbreviations: MV= mechanical ventilation, PEEP=Positive end-expiratory pressure, PSV= Pressure Support Ventilation, PaO_2= partial pressure of oxygen, FiO_2= inspired oxygen fraction, RASS= Richmond Agitation Sedation Score, VFDs= Ventilator-Free Days, ICU= intensive care unit

[a] Tests for differences between Sigh vs. No Sigh: non-inferiority for "Failure of assisted ventilation"; chi-square or Fisher for other variables

[b] SpO_2/FiO_2 increase >1% during the pre-randomization Sigh test