PRESSure supPoRT vEntilation + Sigh in aCuTe hypoxemIc respiratOry failure patieNts (PROTECTION): a pilot randomized controlled trial

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Background and significance

Mortality of intubated acute hypoxemic respiratory failure (AHRF) and acute respiratory distress syndrome (ARDS) patients remains considerably high (around 40%) (1). Clinical severity of lung injury at presentation and early appropriate treatment are main determinants of patients’ outcome (2). However, while the lungs recover, additional injury by mechanical ventilation (i.e., ventilator-induced lung injury [VILI]) might significantly impact survival (3). VILI is associated with: delayed lung healing that prolongs ventilator dependency (4); systemic release of inflammatory mediators that increases the risk of distal organs dysfunction (5); use of muscle relaxants and additional sedation that might aggravate muscles’ weakness (6). Recent studies testing strategies that enhance lung protection (e.g., early referral to an extracorporeal membrane oxygenation [ECMO] center (7); use of muscle relaxants during the first 48 hours after intubation (8); early use of extended sessions of prone positioning (9)) proved to significantly decrease mortality. However, such trials enrolled only the most severe patients on controlled ventilation. A recent large observational trial (1), instead, showed that most ventilated patients admitted to the intensive care unit (ICU) have mild to moderate AHRF or ARDS that anyway leads to considerably high mortality
Moreover, the same study reported that around 30% of invasively ventilated AHRF and ARDS patients are on some form of spontaneous breathing since day 1 from intubation, independently from their severity (1), and this proportion likely increases to most intubated patients within one week. Thus, early implementation of a specific mechanical ventilation mode that enhances lung protection in patients with mild to moderate AHRF and ARDS on spontaneous breathing may have a tremendous impact on clinical practice.

Among others, key determinants of VILI in intubated AHRF and ARDS patients include: elevated ventilation pressures and inspired fraction of O₂ (FiO₂) (10); heterogeneous distribution of alveolar collapse that increases the regional tidal volume/end expiratory lung volume (Vt/EELV) ratio (i.e., the regional lung strain) (11); strenuous inspiratory effort and low regional compliances that determines elevated regional transpulmonary pressure (i.e., the regional lung stress) (12). To this end, previous studies showed that the addition of cyclic short recruitment maneuvers (Sigh) to assisted mechanical ventilation: improves oxygenation without increasing ventilation pressures and FiO₂; decreases the tidal volumes by decreasing the patient’s inspiratory drive; increases the EELV by regional alveolar recruitment; decreases regional heterogeneity of lung parenchyma; decreases patients' inspiratory efforts limiting transpulmonary pressure; improves regional compliances (13-19). Thus, physiologic studies generated the hypothesis that addition of Sigh to pressure support ventilation (PSV, the most common assisted mechanical ventilation mode) might decrease ventilation pressures and FiO₂, and limit regional lung strain and stress through various synergic mechanisms potentially yielding decreased risk of VILI, faster weaning and improved clinical outcomes.

Given the relevant clinical implications and sound physiologic background, we designed a study protocol for a large randomized controlled trial (RCT) to test the impact of early application of PSV+Sigh on long-term clinical outcomes of mild to moderate AHRF and ARDS patients undergoing spontaneous breathing, as compared to protective PSV alone. However,
prospective clinical trials including long-term use of PSV+Sigh lack. Thus, we first conceived a pilot RCT to verify clinical feasibility of the addition of Sigh to PSV in comparison to standard PSV. Then, if positive, the same study protocol will be adopted in a larger RCT aimed at verifying the impact of PSV+Sigh on a composite endpoint including 28-day survival and ventilator-free days. Moreover, to explore the possibility of implementing predictive enrichment in the larger future RCT (20), we also planned a pre-randomization test to assess prevalence of AHRF and ARDS patients who improve oxygenation after introduction of Sigh.

**Specific aims**

This pilot RCT will serve to test the hypothesis that application of PSV+Sigh in spontaneously breathing intubated patients with mild to moderate AHRF and ARDS is feasible and to collect preliminary data on the safety of such an approach.

**Research design and methods**

**Study design.** We will conduct a pilot RCT on intubated spontaneously breathing patients with mild to moderate AHRF and ARDS admitted to the ICU.

**Ethics approval.** We will seek approval from the institutional review boards of each participating center prior to start of enrollment and consent/information will be obtained from each patient or next of kin following local regulations.

**Inclusion criteria.** We will enroll patients intubated since >24 hours and ≤7 days, undergoing PSV since >4 and ≤24 hours, with PaO₂/FiO₂ ratio ≤300 mmHg (measured at clinical positive end-expiratory pressure [PEEP] and FiO₂ values) while on clinical PEEP ≥5 cmH₂O, and with stable Richmond Agitation-Sedation Scale (RASS) value of -2 to 0 (21).

**Exclusion criteria.** We will exclude: patients with PEEP ≥15 cmH₂O; PaCO₂ >60 mmHg; arterial pH <7.30; age <18 year-old; PaO₂/FiO₂ ratio ≤100 mmHg (measured at clinical PEEP and FiO₂
values); central nervous system or neuromuscular disorders; history of severe chronic obstructive pulmonary disease or fibrosis; AHRF fully explained by cardiac failure or fluid overload (e.g., left ventricle ejection fraction ≤40% with no other risk factor); impossibility to titrate sedation to desired RASS value of -2 to 0; evidence of active air leak from the lung (e.g., pneumothorax); cardiovascular instability (e.g., systolic blood pressure [SBP] <90 mmHg despite vasopressors); clinical suspect of elevated intracranial pressure; extracorporeal support; moribund status; refusal by the attending physician.

**Prevalence of Sigh responders.** After enrollment, FiO₂ will be titrated to obtain SpO₂ of 90-96% and then each patient will first undergo a clinical test of PSV vs. PSV+Sigh to assess the prevalence of Sigh responders vs. non-responders in respect to improved oxygenation. To this end, we will record the SpO₂/FiO₂ during clinically set PSV. Then, Sigh will be added as cyclic pressure control phase set at 30 cmH₂O for 3 seconds once per minute (16). Briefly, ventilators will be switched to biphasic positive airway pressure mode (e.g., BiPAP on Drager ventilators, SIMV-PC on Maquet and GE, SIMV-PC on Hamilton, etc.) with the lower pressure level set at clinical PEEP and the higher-pressure level of the Sigh set at 30 cmH₂O with a 3-second inspiratory time and then a 57-second expiratory time, while leaving clinically set PSV level and FiO₂. After 30 minutes of clinical PSV+Sigh, SpO₂/FiO₂ ratio will be collected again to quantify the number of patients in whom it increased (i.e., “Sigh responders”) (22). Based on previous physiologic study (16), the expected prevalence of Sigh responders should be 50%.

**Randomization.** After this test, patients will be randomized through an online automatic centralized and computerized system to the following study groups (1:1 ratio):

- **PSV group:** will be treated by protective PSV settings until day 28 or death or performance of spontaneous breathing trial (SBT);
- **PSV+Sigh group:** will be treated by protective PSV settings with the addition of Sigh until day 28 or death or performance of spontaneous breathing trial (SBT).
**PSV group settings.** Initially, clinicians will set PSV to meet the following targets: tidal volume (Vt) of 6-8 mL/Kg of predicted body weight (PBW), with respiratory rate (RR) 20-35 bpm. In presence of Vt >8 ml/kg PBW and/or RR <20 bpm, PSV zero (CPAP) will be selected. FiO₂ will be left as selected before the pre-randomization Sigh test, while PEEP will be left as clinically set.

**PSV+Sigh group settings.** Similarly, PSV in this group will be set with the same protective targets of the PSV group (see above) and cyclic pressure control phase at 30 cmH₂O for 3 seconds delivered once per minute (i.e., Sigh) (16) will be added. PSV+Sigh is an easy to implement ventilation mode and, for the present study, we will use high performance ICU ventilators already available in each clinical unit. Briefly, ventilators will be switched to biphasic positive airway pressure mode (e.g., BiPAP on Drager ventilators, SIMV-PC on Maquet and GE, DuoPAP on Hamilton) with the lower pressure level set at clinical PEEP and the higher pressure level set at 30 cmH₂O with a 3-second inspiratory time and then a 57-second expiratory time. This Sigh rate of one per minute can be obtained by virtually all the already available high performance ICU ventilators, thus, even though a lower Sigh rate might be regarded as more physiological (17), we choose the 1/min rate for feasibility and costs related to the future large RCT. FiO₂ will be left as selected before the pre-randomization Sigh test.

**Adjusting ventilation settings.** In both groups, PSV will be adjusted at least every 8 hours in the following way:

- PSV support will be decreased by 2 cmH₂O step if Vt >8 ml/kg PBW and/or RR <20;
- PSV support will be increased by 2 cmH₂O step if Vt <6 ml/kg PBW and/or RR >35 and or signs of respiratory distress (e.g., marked use of the accessory muscles);
- PEEP and then FiO₂ will be increased by 2 cmH₂O and 0.1 steps if SpO₂ is <90%;
- FiO₂ and then PEEP will be decreased by 0.1 and 2 cmH₂O steps if SpO₂ is >96%;
Sigh settings instead will be left unchanged until day 28, death or SBT.

**Switch to controlled mechanical ventilation.** In both groups, switch to protective controlled ventilation will be allowed if patient will develop at least one of the following conditions:

- PSV support >20 cmH₂O;
- PEEP ≥15 cmH₂O;
- unstable hemodynamic status (SBP <90 mmHg with vasoactive drug);
- active cardiac ischemia (dynamic ST changes on cardiac monitor or electrocardiogram);
- unstable arrhythmias (heart rate >140 or <40);
- uncontrolled hypertension (SBP>180 mmHg);
- abrupt decrease in the level of consciousness (RASS <-3);
- dangerous agitation (RASS >+2);
- pH <7.3;
- PaO₂/FiO₂ ratio ≤100 mmHg;
- necessity to perform diagnostic test (e.g., CT scan or bronchoscopy).

Controlled ventilation will be set on volume mode with Vt 6-8 ml/kg PBW, RR to control pH, unchanged PEEP and FiO₂. Controlled ventilation will be thereafter adjusted according to clinical evolution. Patients switched to controlled ventilation will be reassessed at least every 8 hours and they will be switched back to PSV or PSV+Sigh (to maintain study group assignment) targeting the abovementioned settings and adjustments as soon as all the following conditions will be met:

- Patient is able to trigger ventilator breaths;
- PaO₂/FiO₂ >100 mmHg;
- PEEP <15 cmH₂O;
- pH ≥7.3;
• Stable hemodynamic status with stable or decreasing doses of vasopressors for ≥6 hours.

Rescue therapy. In case of desaturation (SpO₂ ≤90%) of a patient it will be crucial to exclude hemodynamic impairment as a possible cause. Also, airway obstruction and ventilator malfunction must be ruled out as possible causes. Provided those factors are excluded, a rescue step-up strategy is allowed as follows: institution of protective controlled mechanical ventilation (see above for settings) and performance of recruitment maneuvers at 40-50 cmH₂O, PEEP ≥15 cmH₂O, prone positioning, inhaled nitric oxide, extracorporeal membrane oxygenation. Patients undergoing rescue treatments will be reassessed at least every 8 hours and switched back to PSV or PSV+Sigh (to maintain study group assignment) with the abovementioned settings and adjustments as soon as all the following conditions will be met:

• Patient can trigger ventilator breaths;
• PaO₂/FiO₂ >100 mmHg;
• PEEP <15 cmH₂O;
• pH ≥7.3;
• Stable hemodynamic status with stable or decreasing doses of vasopressors for ≥6 hours.

Spontaneous breathing trial (SBT).
Patients with SpO₂ ≥90% on FiO₂ ≤0.4 and PEEP ≤5 cmH₂O, no agitation, hemodynamically stable with norepinephrine ≤0.1 ug/kg/min or equivalent and at a stable or decreasing dose ≥6 hours (23) and without any of the abovementioned criteria for switch to controlled ventilation will undergo a SBT:

• For patients in the PSV group, the attending physician will perform the SBT directly.
• For patients in the PSV+Sigh group, the attending physician will first withdraw Sigh, wait 60 min and confirm criteria: if confirmed, SBT will be performed; if not, Sigh will
be reintroduced and clinical criteria will be checked again to repeat the procedure after at least 8 hours.

SBT will last at least 60 minutes with a combination of PEEP 0-5 cm H$_2$O and PSV 0-5 cm H$_2$O. At the end of the 60 minutes, patient will fail the SBT if any of the following will be present:

- criteria to start the SBT will not be confirmed;
- sustained (>5 min) respiratory rate >35 bpm;
- HR >140 bpm;
- SBP >180 or <80 mmHg;
- marked complaint of dyspnea;
- increased somnolence with elevated pCO$_2$ and/or pH<7.3
- a cough will not be strong enough to clear secretions
- active cardiac ischemia (dynamic ST changes on cardiac monitor or electrocardiogram)
- abrupt decrease in the level of consciousness with RASS <-3.

Patients who will fail the SBT will be switched back to PSV or PSV+Sigh (to maintain study group assignment) and clinical criteria will be checked again to repeat the procedure after at least 6 hours.

Patients who will pass the SBT will be extubated or, in the presence of tracheostomy, mechanical ventilation will be discontinued. If a patient will be re-intubated or mechanically ventilated through a tracheostomy again within 48 hours, PSV or PSV+Sigh (to maintain study group assignment) will be restored. If a patient will remain extubated or separated from the ventilator for >48 hours data collection only will continue.
Reasons for re-intubation.

After extubation, re-intubation should be promptly performed if at least one of the following criteria is present:

- cardiac arrest;
- respiratory arrest (respiratory pauses with loss of consciousness or gasping for air);
- respiratory failure with SpO₂ <90% and/or RR >35 bpm despite NIV;
- decreased level of consciousness impinging ability to protect airway;
- hemoptysis or hematemesis impinging ability to protect airway;
- abundant secretions that cannot be effectively cleared or are associated with lobar collapse, acidosis, hypoxemia, or change in mental status;
- surgical/invasive procedure requiring sedation/anaesthesia +/- neuromuscular blockade such that patient will no longer be able to sustain unassisted breathing;
- hemodynamic instability with SBP <80 mmHg despite vasoactive drugs.

Standard of care. In all patients, standard of care for intubated hypoxemic acute respiratory failure patients (e.g., restrictive fluid strategy, early appropriate antibiotics, prophylaxis of gastric stress ulcer and deep veins thrombosis, semi-recumbent positioning, respiratory physiotherapy, adequate nutrition, monitoring of sedation, pain and delirium, tracheostomy, non-invasive ventilation for post-extubation respiratory failure) will be granted throughout the whole ICU stay in accordance to local protocols.

Data collection

At enrolment

Before the Sigh test, we will anonymously collect patients’ demographic information (e.g., age, sex, height, weight), past (e.g., hypertension, chronic medications) and recent (e.g., etiology of the acute respiratory failure, days since intubation) medical history, severity of lung injury
(e.g., ventilation setting, arterial blood gases, respiratory system compliance, diagnosis of ARDS) and of systemic diseases (e.g., presence of shock, number of organs failure), ventilation settings (e.g., PEEP, FiO\textsubscript{2}, PSV level).

**After the Sigh test**

Then, we will collect SatO\textsubscript{2}/FiO\textsubscript{2} change in response to the pre-randomization Sigh test.

**First 24 hours from randomization**

In both groups for the first 24 hours we will assess every 4 hours the SpO\textsubscript{2}/FiO\textsubscript{2} ratio, RR and tidal volume delivered both during protective PSV and during Sigh to further characterize physiologic response to Sigh over time.

**Daily**

From day 1 (i.e., within 24 hours from enrollment) to day 28 or death or discharge from the ICU, the following data will be collected every day between 6:00 and 10:00 in the morning: switch from the allocated treatment to the other study arm for ≥24 hours, reason for switch from the allocated treatment, adverse events (i.e., hemodynamic instability with hypotension with SBP <90 mmHg despite vasoactive drugs; arrhythmias with heart rate <40 or >140 bpm; radiographic evidence of barotrauma with pneumothorax, pneumomediastinum, pneumatocele, or subcutaneous emphysema), arterial SpO\textsubscript{2}, arterial and central venous blood gas analyses, numbers of quadrants involved on standard chest X-ray, ventilation settings and pattern (i.e., Sigh pressure level, Sigh tidal volume, PSV level, PSV tidal volume, respiratory rate, PEEP, FiO\textsubscript{2}, minute ventilation, P0.1, mean airway pressure), switch to controlled ventilation for ≥24 hours, reason for switch to controlled ventilation, use of rescue treatments (i.e., use of PEEP ≥15 cmH\textsubscript{2}O, prone positioning, inhaled nitric oxide, extracorporeal membrane oxygenation), dosage of sedative agents, RASS value, tracheostomy, patient’s comfort through visual analog scale, heart rate, arterial blood pressure, central venous pressure, dosage of vaso-active drugs, cumulative fluid balance, SOFA score, SBT
failure in the previous 24 hours, reason for SBT failure, time since extubation or separation from mechanical ventilation, time since re-intubation, reason for re-intubation.

Day 28
At day 28, for all enrolled patients, mortality and ventilator-free days will be collected. Ventilator-free days will be calculated as 28 minus the number of days between intubation and successful extubation or separation from mechanical ventilation for tracheostomized patients (i.e., for ≥48 hours).

Study endpoints and sample size

Primary endpoint. The primary endpoint of the pilot trial will be to verify feasibility of PSV+Sigh vs. PSV. To this end, feasibility will be assessed by measuring the number of patients in each group experiencing at least one of the following failure criteria (24):

- switch to controlled ventilation following presence of one of the abovementioned reasons for ≥24 hours consecutively;
- use of PEEP ≥15 cmH₂O, prone positioning, inhaled nitric oxide, extracorporeal membrane oxygenation;
- re-intubation within 48 hours from extubation following one of the abovementioned reasons.

Patients with failure criteria will exit the protocol and treated as per clinical decision but data collection will continue.

Based on previous data (24), the expected rate of failure in patients undergoing PSV will be 22% and we hypothesize a rate of 15% for patients in the PSV+Sigh group. Furthermore, we assume a non-inferiority of the treatment with PSV+Sigh, with a tolerance of 5%. Thus, a sample size of 258 patients (with 129 patients per study arm) will be sufficient to assess feasibility of the PSV+Sigh strategy in this pilot phase with power of 0.8 and alpha 0.05.
Secondary endpoints.

- Preliminary evaluation of the safety of PSV+Sigh will compare incidence of the following adverse events in the two study groups:
  
  - hemodynamic instability with hypotension (i.e., SBP <90 mmHg) despite vasoactive drugs;
  - arrhythmias with heart rate <40 or >140 bpm;
  - radiographic evidence of barotrauma (i.e., pneumothorax, pneumomediastinum, pneumatocele, or subcutaneous emphysema);
  - new chest tube placement.

- Quantification of the prevalence of short- (i.e., within 30 minutes) and long-term (i.e., within 24 hours in the PSV+Sigh group) Sigh responders in respect to improved oxygenation.

- Then, all the following analyses will be performed comparing the 2 study groups: 28-day mortality; ventilator-free days; PSV level, PEEP value and oxygenation index on day 1-3; number of days on assisted ventilation until day 28; use of rescue treatments; number of quadrants involved at chest X-ray on day 1-5; ICU and hospital length of stay; patients’ comfort by visual analog scale; tracheostomies.

- We will also perform the abovementioned analysis of clinical outcomes comparing the study groups only among Sigh responder patients. We expect that prevalence of Sigh responder patients will be 50% (16) in both groups.

Ethical implications

The present study will be conducted in adherence the World Medical Association's Declaration of Helsinki. Ethics approval will be sought from each participating institution before starting enrollment and consent will be obtained for each patient following local regulations. Nonetheless, we believe that, based on our clinical experience and results of
physiologic studies, the additional risks for patients enrolled in the PSV+Sigh arm will be minimal in comparison to standard of care while benefits could be relevant. Finally, each patient enrolled in this study will be covered by dedicated specific insurance for any complication that might derive from study treatments.

**Design of the future large RCT**

If the present pilot RCT will be successfully completed and its primary endpoint verified, we will design a larger RCT to test the effects of the same study protocol on a composite endpoint of mortality and ventilator-free days.
Figure 1. Study flow chart
References


