HElmet NonInvasive Ventilation versus high-flow Oxygen Therapy in acute hypoxemic respiratory failure

A pilot, open-label, multicentre randomized trial

The HENIVOTpilot study

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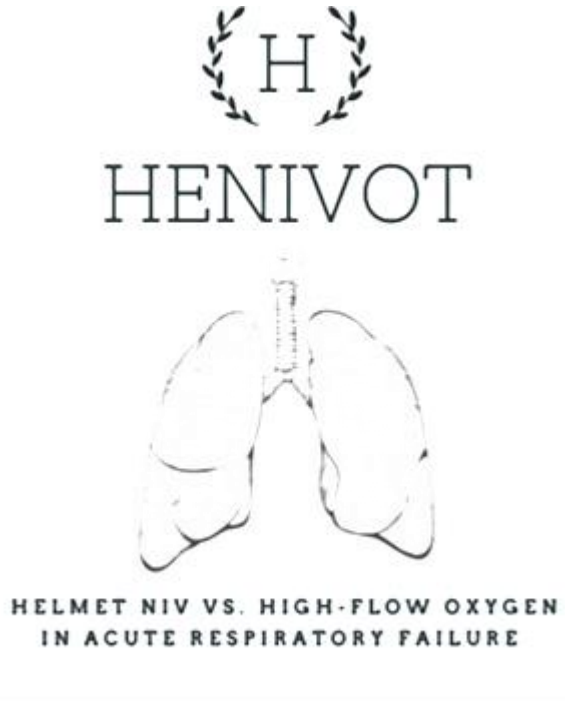

https://clinicaltrials.gov/ct2/show/NCT04502576

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IN ACUTE RESPIRATORY FAILURE

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Background

Non-invasive positive pressure ventilation (NIV) has been convincingly shown to be safe and effective as first line treatment in patients with acute hypercapnic respiratory failure and acute cardiogenic pulmonary oedema [1–4]. Despite some data suggest NIV may also avoid intubation in heterogeneous categories of patients with acute hypoxemic respiratory failure (AHRF)[5–11], its safety and efficacy in such a context is still debated, given the high failure rate and the possible detrimental effect on the clinical outcome [12–16].

Nasal high flow oxygen (NHF) is a new and promising tool for oxygen therapy in critically ill patients: NHF allows accurate delivery of the set FiO_2, anatomical dead space clearance due to a washout effect in the upper airways and provides a small, variable amount of positive end end-expiratory pressure[12,17–21]. Different studies have investigated its safety and efficacy in several clinical settings[20,22,23] and a multicentre randomized controlled trial showed that NHF, as compared to NIV sessions delivered via a face mask, may reduce the intubation rate and improve clinical outcome in severely hypoxemic patients with *de novo* AHRF[24].

As patients' comfort is crucial for NIV success, over the last years a great effort has been made to optimize NIV tolerability. Different interfaces are available for non-invasive ventilation[25]: in spite of face masks being more commonly used, helmet has been shown to improve patients' comfort, allowing patients' interaction, speech, feeding and not limiting cough. Nonetheless, skin necrosis, gastric distension, or eye irritation are seldom observed during helmet NIV, while may be consequences of long-term treatments with face masks[26,27].

Moreover, differently from face masks, helmets permit longer-term treatments and allow the setting of higher levels of PEEP without causing air leaks; this aspect may be crucial

when treating severely hypoxemic patients with acute respiratory failure and the acute respiratory distress syndrome (ARDS)[28]. Interestingly, higher PEEP during fully controlled mechanical ventilation in the early phase of the disease improves mortality in ARDS patients and raising evidence indicates that it may exert beneficial effects also if spontaneous breathing is maintained [28–30]. In this sense, a recent randomized controlled trial comparing continuous NIV delivered with helmet or face-mask in patients with ARDS showed a lower intubation rate and a lower 90-day mortality in patients in the helmet group who, accordingly, underwent treatments with higher PEEP and lower FiO_2[31].

We previously showed that helmet NIV may provide physiological benefits over NHF [32], but whether first-line treatment with helmet NIV as compared to NHF may improve clinical outcome in acute hypoxemic respiratory failure remains uncertain.

The uncertainaity about the initial management of acute hypoxemic respiratory failure has been emphasized by the recent COVID-19 pandemic. SARS-COV-2 is a novel coronavirus with an outbreak of unusual viral pneumonia in Wuhan, China, and that progressively became pandemic. In some patients (5-15%), it can cause acute hypoxemic respiratory failure and Acute Respiratory Distress Syndrome (ARDS) needing ventilatory support and admission to the intensive care unit (ICU).

We designed an open-label, multicentre randomized trial to assess first-line treatment with helmet NIV as compared to NHF may increase the amount of 28-day ventilatory support-free days of patients admitted to the intensive care unit due to acute hypoxemic respiratory failure.

Methods

Design

Open-label multicentre randomized trial.

Objectives

To demonstrate a clinical benefit by the early application of Helmet NIV in patients with acute hypoxemic respiratory failure, as compared to NHF.

Setting

This is a multi-centre study. Eligible patients will be screened in the ICUs at the "Fondazione Policlinico Universitario A. Gemelli IRCCS" (Rome, Italy), and the "Policlinico SS. Annunziata" (Chieti, Italy). Further centres in Italy will be eventually involved according to availability of resources, materials and investigators, that are limited for ICU personnel due to the COVID-19 pandemic. All recruiting centres will be run by personnel with experience in the use of non-invasive ventilation.

Patients

All consecutive adult patients suffering from *de novo* acute hypoxemic respiratory failure will be assessed for the enrolment.

Acute hypoxemic respiratory failure will be defined as:

- Symptoms onset within 14 days before the assessment for enrolment in the study;
- Oxygenation impairment (SpO2 < 90% in ambient air, or requirement for oxygen supplementation according to the decision of the attending physician).

Eligibility inclusion criteria will be assessed within the first 72 hours from ICU admission and preferentially while patients receive standard oxygen therapy (VenturiMask). In case this is not available, patients will be evaluated during oxyged while are receiving oxygen therapy through a non-rebreather reservoir bag mask, with FiO_2 estimated as 0.21+ oxygen flow rate in L/min×3 [33].

Patients will be considered eligible, whether all the following inclusion criteria are met:

1. PaO_2/FiO_2 ratio ≤ 200;
2. $PaCO_2$≤45mmHg;
3. Absence of history of chronic respiratory failure or moderate to severe cardiac insufficiency (NYHA>2 or left ventricular ejection fraction<50%);
4. The informed consent form needs to be signed and dated by the patient or a relative/legal guardian before of any procedure related to the study; if the patient is initially unable to sign the informed consent form, but later regains the ability to sign it, a new informed consent form will be given to the patient and must be signed and dated.

Exclusion criteria:

- Pregnancy;
- Body mass index>40;
- Exacerbation of asthma or chronic obstructive pulmonary disease;

- Known hypercapnia ($PaCO_2$>45 mmHg) with or without respiratory acidosis;
- More than 2 organ failures, including the lung.
- Documented pneumothorax;
- Clinical diagnosis of Cardiogenic pulmonary oedema;
- Haemodynamic instability (Systolic blood pressure<90 mmHg or mean arterial pressure<65mmHg) and/or lactic acidosis (lactate>5 mmol/L) and/or clinically diagnosed Shock requiring administration of vasoactive agents (norepinephrine>0.1 mcg/Kg/min);
- Metabolic Acidosis (ph <7.30 with normal- or hypo-carbia);
- Chronic kidney failure requiring dialysis before ICU admission;
- Chronic hypoxemic respiratory failure requiring long-term oxygen therapy;
- Altered neurological status that requires immediate intubation and/or making the patient uncooperative;
- Urgent need for endotracheal intubation, according to the decision of the attending physician;
- Do not intubate order;
- Decision of withdrawal of life-sustaining therapy;
- Thoracic or abdominal surgery in the previous 7 days;
- Any condition that makes the patient very likely to require endotracheal intubation due to a reason different from respiratory failure;
- Recent head surgery or anatomy that prevent the application of helmet or Optiflow to patient's face.

Patients that have already received NIV continuously for more than 12 hours before the screening visit will be excluded.

Protocol

Assessment of the oxygenation criteria

Nonhypercapnic patients with a $PaO_2/FiO_2 \leq 200$ mmHg will be enrolled.

In the absence of exclusion criteria, and if all others inclusion criteria are met, patients showing $PaO_2/FiO_2 \leq 300$ and >200 mmHg will be treated according to the clinical practice of each institution and eventually reassessed for the presence of oxygenation criterion up to 72 hours from ICU admission.

Randomization

Enrolled patients will be randomized in a 1:1 ratio to receive helmet PSV or NHF as first-line treatment for AHRF. A computer-generated permuted block randomization scheme with varying block sizes ranging from 3 to 9 managed by a centralized web-based system will be used to allocate patients to each group.

Randomization will be stratified according to the presence of SARS-CoV-2 infection (diagnosed with a positive polymerase chain reaction (PCR) testing of the nasopharyngeal or tracheal sample)

Patients will have to undergo the allocated treatment within 1 hour from the moment of enrolment criteria validation.

Study treatments

In both arms, the treatment according to the assigned protocol will be continued until the patient requires endotracheal intubation or (in case of no intubation) up to ICU discharge. Patients will have to undergo the allocated treatment within 1 hour from the moment of oxygen criteria validation.

<u>High-flow oxygen therapy</u>

Nasal high flow oxygen therapy will be delivered with the Optiflow system.

Initial set flow will be ≥ 50 /min, and flows will be decreased in case of intolerance and/or according to patients' requirements: flows≥30 L/min will be mandatory in all enrolled patients. Humidification chamber (MR860, Fisher and Paykel healthcare, New Zealand) will be set at 37 °C or 34 °C according to patient's comfort[34]. FiO_2 will be titrated to obtain an SpO_2≥92% and ≤98%.

Weaning the patient from NHF will be considered only after 48 hours from enrolment.

Weaning from NHF within the first 2 days of the study will be allowed only whether the patient is considered for ICU discharge, according to the decision of the attending physician.

All enrolled patients will be discharged from the ICU while undergoing low-flow oxygen, according to the prescription of the attending physician and the clinical practice of each participating institution (VenturiMask, nasal prongs, non-rebreathing oxygen mask). As suggested by Maggiore (NCT02107183), weaning from NHF will be allowed when FiO_2<40% and respiratory rate<25/min. Oxygen flow will be lowered to 10 L/min, keeping FiO_2 unchanged. Weaning from NHF will be considered successful if the SpO_2 remains between 92% and 98% and the respiratory rate ≤ 25/min with an oxygen flow of

10 L/min. In this case, the NHF device will be replaced by the low-flow oxygen and oxygen flow or FiO_2 will be set to obtain the same SpO_2 target.

NHF treatment can be resumed any time if the patient is experiencing respiratory distress and hypoxemia, according to the prescription of the attending physician.

Helmet PSV

Patients in PSV group will receive continuous helmet pressure support ventilation for at least 16 hours/day the first 2 calendar days. Continuous NIV without interruptions will be strongly encouraged in the first 24 hours of treatment. When NIV is interrupted, patients will receive low flow oxygen therapy or nasal high flow oxygen therapy, according to physician's decision. Dedicated helmets for NIV (Dimar, Italia, or Intersurgical, UK) and size will be chosen according to neck circumference, as suggested by Antonelli et al. [26], or according to manufacturer recommendations, if present (Appendix, table 1).

Each patient will be connected to an ICU compressed gas based ventilator through a bitube circuit with no humidification

The ventilator will be set in PSV (the choice to use NIV modes will be left to the decision of the physician in charge of the patient), with the following suggested settings [35–39]:

1. initial pressure support≥8-10 cmH_2O and adequate to permit of a peak in the inspiratory flow of 100 l/min;
2. positive end-expiratory pressure ≥10 cmH_2O and increased to achieve the oxygenation target according to the choice of the attending physician.
3. FiO_2 will be titrated to obtain an SpO_2≥92% and ≤98%.
4. Inspiratory flow trigger = 1 l/min or according to the practice of each institution;
5. fastest pressurization time;
6. expiratory trigger: 10-50% of the maximum inspiratory flow;
7. maximum inspiratory time 1.2 second.

The use of earplugs to mitigate noise-related discomfort will be allowed according to the decision of the attending physician and will be encouraged especially overnight.

Any modification in the ventilator settings and in the interface set-up to optimize comfort and patient-ventilator interaction will be allowed at the discretion of the attending physicians. However, maintenance of PEEP ≥10 during the treatment is mandatory.

Weaning from PSV will be discouraged within the first 48 hours from enrolment. Weaning from PSV at any time will be attempted only whether $FiO_2 \leq 40\%$, respiratory rate≤25%: to assess the readiness for interrupting PSV, PEEP will be lowered to 8 cmH_2O with pressure support=8 cmH2O, keeping FiO_2 unchanged. If the patient maintains $SpO_2 \geq 92\%$ and respiratory rate≤25 during the following 30 minutes with these settings, PSV weaning will be considered successful. After weaning from PSV and between two NIV sessions, patients will undergo low-flow, VenturiMask or NHF, according to the choice of the attending physician: oxygen flow or FiO_2 will be set to obtain the same SpO_2 target.

PSV will be resumed at any time if the respiratory rate is more than 25 breaths per minute and SpO_2 is less than 92% with and/or anytime deemed necessary by the attending physician.

Standard Management

In both arms, standard care (diagnostic tests, antibiotics administration, fluid therapy, haemodynamic management) will be applied according to the clinical practice of each institution.

Mild sedation will be allowed during the treatment in both groups to achieve a RASS=0 and according to the physician's preference, but the contemporary use of sedative and analgesic drugs will be not allowed [40].

In NHF group, a NIV trial with face mask before endotracheal intubation will be only allowed in case of hypercapnia and respiratory acidosis (i.e. $PaCO_2$>45 mmHg with pH<7.35). Similarly, in helmet group, a NIV trial with oro-nasal or full face mask will be permitted in case of hypercapnia with acidosis (i.e. $PaCO_2$>45 mmHg with pH<7.35).

Allocated treatment will be resumed as soon as hypercapnia is deemed resolved by the attending physician.

Hemodynamic management

Fluid overload will be discouraged. If appropriate fluid challenge fails to restore adequate blood pressure and organ perfusion and if the patient is deemed not to be fluid-responsive, therapy with vasopressor agents will be started.

Severe haemodynamic instability, cardiac arrest, pneumothorax or any other adverse event possibly related or worsened by the assigned treatments will be recorded in the CRF.

Norepinephrine will be the first-choice vasopressor agent to correct hypotension in septic shock.

Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressors.

In patients developing documented cardiac failure, dobutamine, if not contraindicated, will be the first line agent to increase cardiac output. If used in the presence of low blood pressure, it should be combined with vasopressor therapy.

Nutrition/Glucose Control

All enrolled patients will be allowed and encouraged to drink and early enteral feeding through a nasogastric tube will be initiated within the first 48 hours of ICU stay and/or as soon as it is deemed safe by the treating physicians. Exogenous insulin will be provided with the goal a blood glucose level below 180-200 mg/dl.

Rescue therapies

Extracorporeal CO_2 removal ($ECCO_2$-R) or extracorporeal membrane oxygenation (ECMO) before intubation will not be permitted in any enrolled patient. The use of ECMO and $ECCO_2$-R after intubation, will be allowed in both groups as rescue therapies and according to the decision of attending physicians: any of these procedures will be accurately recorded on the CRF.

Treatment failure

In the entire cohort, the final decision to intubate the patient will be left to the attending physician.

However, in order to avoid any delay in intubation, and to standardize the treatment in both groups, coherently with previous studies with similar design, the decision to intubated will be based on predefined criteria [5,24,31].

Patients will be intubated in case of persisting or worsening respiratory failure, defined by at least two of the following:

1. worsening or unchanged unbearable dyspnea
2. lack of improvement in oxygenation
3. lack of improvement of signs of respiratory-muscle fatigue
4. development of unmanageable tracheal secretions
5. respiratory acidosis with a pH below 7.30 despite NIV with face mask
6. SpO_2 below 90% for more than 5 min without technical dysfunction
7. intolerance to the used device

Patients will also be intubated in case of hemodynamic instability (SBP below 90 mmHg, MBP below 65 mmHg and/or requirement for high-dosage vasopressors and/or hyperlactatemia) or deterioration of neurologic status with a Glasgow coma scale below 12 points.

Since the final decision on intubation will be left to the physician in charge that cannot be blinded to the study group, an Adjudication Committee will verify whether the decision to intubate was unbiased and in compliance with the required criteria, as already suggested by Maggiore et al**.** (NCT02107183). Three physicians, with expertise in the field, not directly involved in the study and blinded to patients' allocation, will review *a*

posteriori the records of all intubated patients and verify the presence of intubation criteria.

After intubation, patients will be managed according to the clinical practice of each institution: however, tidal volume exceeding 8 ml/Kg IBW will be avoided in all patients as a standard of care and tidal volume of 6 ml/kg IBW will be strongly encouraged in ARDS patient during the acute phase of the disease. Forty-eight hours of paralysis and prone position are suggested in ARDS patients with PaO_2/FiO_2<150 mmHg after intubation and/or anytime during the ICU stay.

A daily assessment for readiness for undergoing a spontaneous breathing trial will be done (Appendix).

Patients in both groups will receive NHF after extubation[23]. Pre-emptive NIV (any interface allowed) after extubation will be allowed in prolonged to wean patients (i.e. more than 3 SBT failure or more than 7 days from the first SBT to being extubated)[16,41,42]. In case of respiratory failure during oxygen therapy via high flow nasal cannula after extubation, a rescue NIV (any interface allowed) trial will be allowed before reintubation in all enrolled patients at the discretion of the attending physician.

Decision to perform tracheostomy to enhance the weaning process will be left to the attending physicians.

Measurements

Patient's demographics will be collected at study entry:

- initials, age, sex, height, weight, BMI;
- cause of hospital and ICU admission;
- SAPS II;
- SOFA score;
- timing of respiratory symptoms onset;
- date and time of hospital admission;
- Time of stay in medical or surgical ward before randomization;
- Time of ICU stay before randomization;
- Date and time of enrolment;
- Main comorbidities;
- NYHA category before respiratory failure;
- Body temperature;
- Presence of bilateral or monolateral infiltrates at the chest x-ray (jpeg images) or chest CT scan (whether available);
- Baseline clinical parameters: arterial pressure, heart rate, respiratory rate, SpO_2 and blood gases (PaO_2, $PaCO_2$, pH and PaO_2/FiO_2, serum lactate),;
- IL-6, C Reactive Protein, ferritin and D-Dimer will be measured according to the practice of each institution;
- Time from oxygen criteria validation and beginning of assigned treatment.

Following data will be recorded 1-6-12-24-48 hours from randomization and then on a daily basis (72-96-120…etc.) up to 28 days or ICU discharge.

- Ventilatory management
  - ✓ **NHF group**: NHF settings (flows, humidification chamber temperature, FiO_2) or VenturiMask settings (FiO_2)
  - ✓ **Helmet PSV group**: NIV settings (pressure support, FiO_2, PEEP, cycling off criteria, maximum inspiratory time, peak inspiratory flow) or, if, receiving low-flow oxygen, oxygen therapy settings (device, flow, flow-FiO_2).
  - ✓ **Intubated patients, after treatment failure**: type of ventilation, FiO_2, tidal volume, mean airway pressure, PEEP, Pplat if available, minute ventilation, respiratory rate, proportion of spontaneous ventilation on minute ventilation
- Respiratory rate, SpO_2, pH, PCO_2, PaO_2, SaO_2, PaO_2/FiO_2;
- Heart Rate, arterial blood pressure;
- If patient is not intubated, dyspnoea, as defined by a visual analogic scale (Appendix, Figure 1) (VAS), discomfort related to the device, as defined by a visual analogic scale (VAS) adapted to rate the procedural pain of ICU patients (Appendix, Figure 2)[43];
- Richmond agitation and sedation scale (RASS) (Appendix, Figure 3) and sedative drugs administered, if any;
- IL-6, C Reactive Protein, ferritin and D-Dimer will be measured (only on a daily basis).

Simplified organ failure assessment score (SOFA) (Appendix, Table 1), modified clinical pulmonary infection score (CPIS) (Appendix, Table 2) will be calculated daily.

The hours spent by the patient on NIV, NHF, low-flow oxygen or invasive mechanical ventilation will be also recorded daily.

The total hours during the ICU stay spent by the patient in the prone positioning will be recorded.

At ICU discharge, in-ICU mortality will be recorded. Tracheostomized patients discharged while receiving mechanical ventilation will be recorded as well.

At hospital discharge, 90-day and in-hospital mortality and the days without invasive ventilation on a 28,60 and 90-day basis will be recorded.

The daily cumulative doses of vasopressors (norepinephrine, adrenaline, dobutamine), sedative and analgesic agents (sufentanil, propofol, midazolam, dexmedetomidine), the total amount of administered crystalloids and colloids, the use of diuretics, diuresis and net fluid balances will be calculated for each patient and recorded.

To assess quality-adjusted life year (QUALY), patients discharged alive from the hospital will be contacted 6 and 12 months from hospital discharge and will ask to undergo a telephone interview to answer the Short-form 36 (SF-36) questionnaire.

Outcome measures

Primary endpoint

The primary outcome will be the number of ventilatory support-free days at day 28 day from enrolment. Ventilatory support will include: invasive positive pressure ventilation (through endotracheal tube or tracheostomy), noninvasive ventilation and NHF.

Secondary endpoints

Main secondary endpoints will be:

1. the proportion of patients who require endotracheal intubation within 28 days from study enrolment
2. 28-day, 60-day mortality, 90-day mortality
3. 'In-hospital' mortality
4. Days of ICU stay after randomization
5. Days of hospital stay after randomization
6. 6- and 12-month quality of life

The main safety endpoints will be:

1. In patients meeting the primary endpoint, time (hours) from randomization to intubation.

2. Among patients meeting the primary endpoint, proportion of patients requiring 'emergency intubation', defined according to the judgement of the attending physician.

3. Among patients meeting the primary endpoint, the cause of non-invasive treatment failure (as defined by the intubation criteria).

Other explored endpoints will be:

- PaO_2/FiO_2 ratio at 1-6-12-24-48-72 hours after randomization

- $PaCO_2$ 1-6-12-24-48-72 hours after randomization
- Respiratory rate 1-6-12-24-48-72 hours after randomization
- Discomfort related to the device 1-6-12-24-48-72 hours after randomization
- Dyspnoea 1-6-12-24-48-72 hours after randomization at the different timepoints.
- Daily measured SOFA
- Rate of hospital acquired pneumonia
- Catecholamine-free days/days of ICU stay

Power analysis

Systematic data about the total duration of respiratory support in patients affected by hypoxemic respiratory failure with PaO2/FiO2 lower than 200 mmHg and treated solely with high-flow nasal oxygen are lacking. Data from a single-center exploratory report indicate that the mean 28-day respiratory support-free days of patients receiving first line treatment with high-flow nasal oxygen is 11.6±5 days [24]. We hypothesized that this parameter would be 25% higher in patients receiving helmet noninvasive ventilation (14.5 days). Assuming a normal distribution of the primary endpoint, we calculated that the enrolment of 50 patients per group would provide 80% power to detect a 25%-increase in the number of ventilatory-support free days on a 28-day basis in the helmet group, with an alpha level of 0.05. The attrition rate was expected to be smaller than 10% and likely due to protocol violations, absence of objective criteria to define the need for endotracheal intubation, cross-over and drop-outs. We planned to enrol a total of 110 patients.

Statistical analysis

Results will be expressed as mean ± SD or median [interquartile rage] or number of events [%]. All data collected will be tabulated descriptively by study group and analysed on an intention-to-treat basis. In addition, a *per protocol* analysis will be conducted on the patients who successfully underwent the allocated treatments for the time defined by the study protocol.

Comparisons between groups regarding qualitative variables will be performed with the Chi-Squared test or the Fisher's exact test, as appropriate. Ordinal qualitative variables or non-normal quantitative variables will be compared Mann-Whytney test. Quantitative normal variables will be compared with the Anova test. Kaplan-Meier curves will be displayed for significant results concerning intubation rate and mortality.

Inter-group differences in quantitative variables distribution at different timepoints will be assessed with ANOVA for repeated measures.

Prespecified subgroup analyses according to the following characteristics will be performed:

- Patients with AHRF due to COVID-19
- Patients with bilateral pulmonary infiltrates at study inclusion
- History or no history of cardiac failure
- Patients older than 65 years.
- Patients with PaCO2≥40 at study inclusion
- Respiratory rate≥35 at study inclusion (measure at the moment of the oxygenation criteria validation while receiving 50 L/min of 50% oxygen via a face mask).
- P/F≤120 at study inclusion.
- Immunocompromised patients.

All analyses will be performed applying a bilateral hypothesis.

Appendix

Table 1. Helmet size according to neck circumference.

Neck circumference (cm)	Helmet Size
17-227	Extra small
27-34	Small
34-40	Medium
40-47	Large
> 45	Extra large

Criteria for undergoing a spontaneous breathing trial

During invasive mechanical ventilation, spontaneous breathing trial will be initiated as the following criteria are met:

a) improvement or resolution of the underlying cause of acute respiratory failure,

b) normal sensorium (alertness and ability to communicate),

c) correction of arterial hypoxemia ($PaO_2 \geq 60$ mmHg at a $FiO_2 \leq 40\%$ with PEEP ≤ 5 cmH_2O);

d) absence of fever (≥ 38 °C) or sepsis;

e) blood hemoglobin concentration of 7 g/dL or more;

f) hemodynamic stability without cardiac ischemia or arrhythmias (norepinephrine<0.1 gamma/kg/min).

Success of the spontaneous breathing trial will be defined as presence of the following criteria: 1) respiratory rate < 35/min, 2) arterial oxygen saturation ≥ 90%, 3) heart rate < 120/min, 4) systolic blood pressure > 90 and < 160 mmHg, 5) adequate cough. If the spontaneous breathing trial is successful, the patient will be extubated.

In case of SBT failure, mechanical ventilation will be resumed and new spontaneous breathing trials will be performed on a daily basis. The use of pressure support ventilation and proportional assist ventilation, as compared to assist-control modes, will be encouraged during the weaning phase.

509 **Figure 1.** VAS scale for dyspnea

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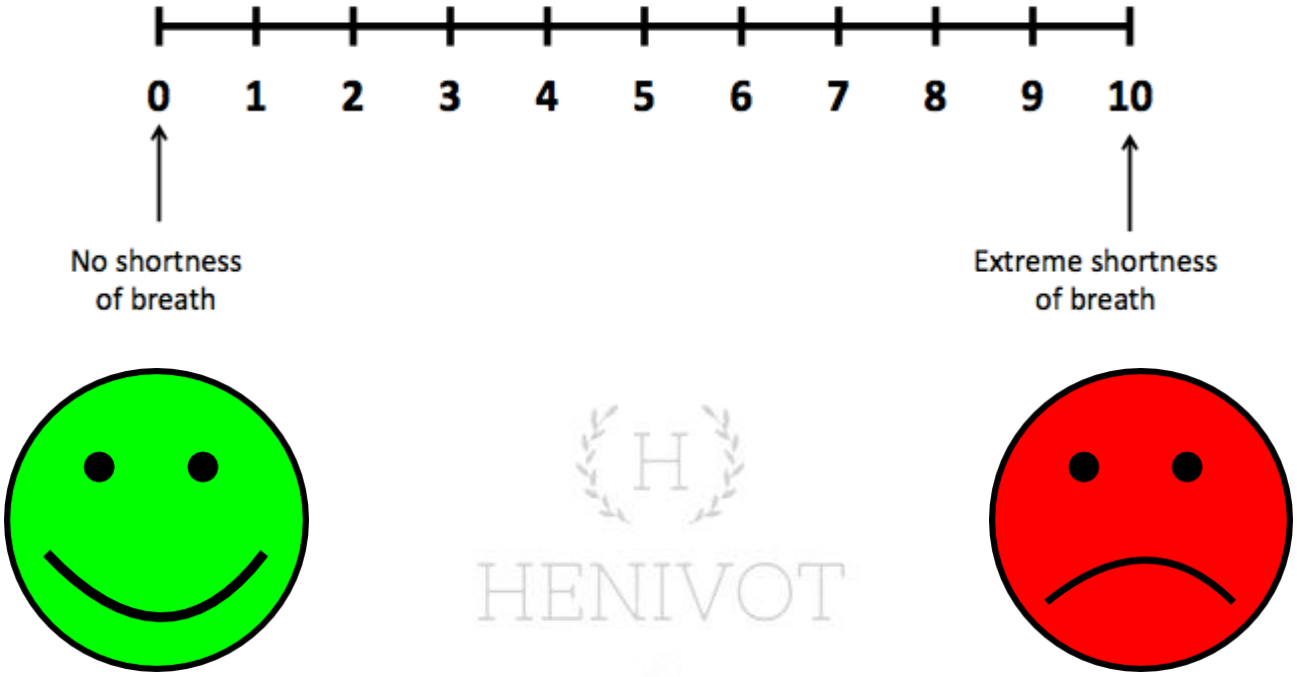
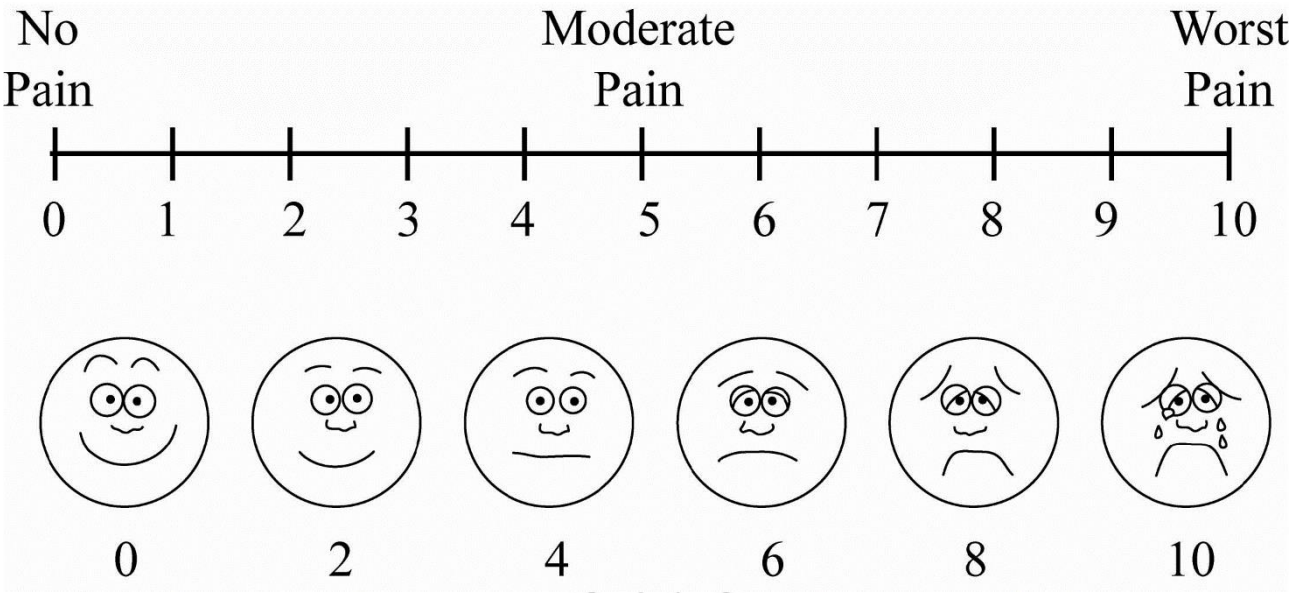


513 **Figure 2**. Discomfort scale [43]



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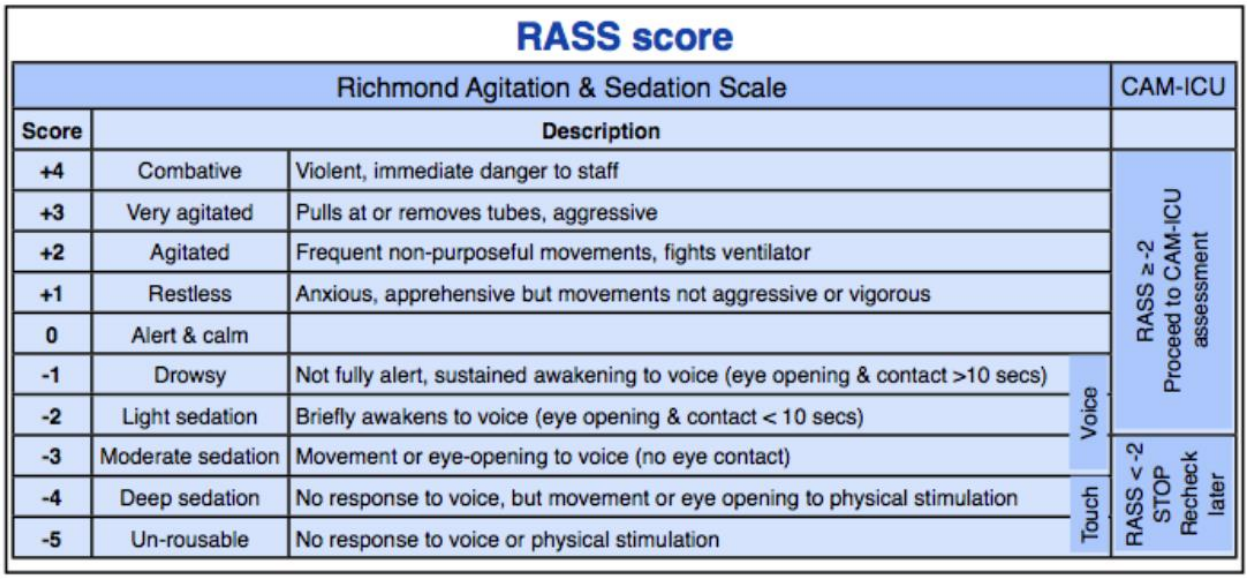
526 **Figure 3**. Richmond agitation and sedation scale



RASS score

Richmond Agitation & Sedation Scale				CAM-ICU
Score	**Description**			
+4	Combative	Violent, immediate danger to staff		RASS ≥ -2 Proceed to CAM-ICU assessment
+3	Very agitated	Pulls at or removes tubes, aggressive		
+2	Agitated	Frequent non-purposeful movements, fights ventilator		
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous		
0	Alert & calm			
-1	Drowsy	Not fully alert, sustained awakening to voice (eye opening & contact >10 secs)	Voice	
-2	Light sedation	Briefly awakens to voice (eye opening & contact < 10 secs)		
-3	Moderate sedation	Movement or eye-opening to voice (no eye contact)		RASS < -2 STOP Recheck later
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Touch	
-5	Un-rousable	No response to voice or physical stimulation		

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529 Table 1. Sequential Organ Failure Assessment (SOFA) score

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SOFA score	**0**	**1**	**2**	**3**	**4**
Respiration PaO_2/FIO_2 (mmHg)	>400	<400	<300	<200	<100
Coagulation Platelets $10^3/mm^3$	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular[b] Hypotension	No hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine≤0.1	Dopamine>15 or norepinephrine>0.1
CNS Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

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Table 2. The modified clinical pulmonary infection score

CPIS Points	**0**	**1**	**2**
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature, °C	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39 or ≤ 36
Leukocytes count, per mm^3	≥ 4,000 and ≤ 11,000	< 4,000 or > 11,000	< 4,000 or > 11,000 + band forms ≥ 500
PAO2/FIO2, mm Hg	> 240 or ARDS		≤ 240 and no evidence of ARDS
Microbiology	Negative		Positive

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