RESPIRATORY MANAGEMENT PROTOCOL OF PATIENTS WITH SARS-COV-2 (COVID-19)

CPAP
(8 – 10 cmH₂O)

VM
Titrate PEEP

PRONE
RM?

S/F
300
250
200
175
150

P/F
300
250
200
175
150

TITRATE Fio₂ FOR SpO₂ 88 – 97

V̇ₜ = 6 ml/Kg
PEEP 10 cmH₂O
ΔP < 15 cmH₂O
Pplat < 30 cmH₂O
Sedation + NMB

V̇ₜ = 4 – 6 ml/Kg
PEEP 15 – 24 cmH₂O

CONSIDER INO + SYSTEMIC VASOCONSTRICTOR
INTRODUCTION

We are an international group of experts and based on what has been currently published by the Chinese, Italian and the Spanish, we believe it is necessary to develop a unified action criteria in order to optimise resources and apply the most effective therapies for patients with COVID-19.

It appears that in many patients, the type of hypoxemic respiratory failure resulting from COVID-19 may differ from more classic forms of Acute Respiratory Distress Syndrome (ARDS). While many patients have significant loss of end expiratory lung volume, compliance is often relatively preserved with high degrees of alveolar dead-space, suggesting possible alteration of the hypoxic pulmonary vasoconstriction (HPV) reflex, or other mechanisms yet to be found.

In relation to the above we recommend that in patients with respiratory failure related to COVID-19:

1. The degree of oxygen impairment should be measured routinely using pulse oximetry/inspired fraction of oxygen ratio \( (S/F) \). \( (3)(4)(5) \). S/F is recommended to assess patient evolution and is non-invasive, available on all patients. Taking into account the large number of patients to be treated, the S/F will be very useful as it is non-invasive. The \( \text{PaO}_2/\text{FiO}_2 \) ratio \( (P/F) \) is the gold standard\( (3)(6) \) to measure oxygen impairment but it can be reserved for patients with more severe disease, haemodynamic instability.
(needing invasive blood pressure monitoring), or for confirmation of S/F. It is important to instruct medical staff in the proper measurement of the S/F, which includes titration of FiO2 to achieve a saturation between 88 - 97%. [Figure 1]

- In paediatric patients Oxygen Index (OI) and Oxygen Saturation Index (OSI) can be used to guide the treatment approach. (7)

2. **High flow oxygen therapy (HFNC).** High flow oxygen therapy (HFNC) can be considered for patients who do not have severe hypoxemia, particularly if the availability of ventilators is limited. However HFNC may have increased risks for aerosolization of the virus. The response to HFNC must be assessed within 30 – 60 minutes of initiation, and patients who do not improve significantly should not be maintained on HFNC. It is important to remember that HFNC does not produce significant lung recruitment. (8)(9)(10) If a patient on HFNC has sustained moderate/severe hypoxemia (S/F < 220; FiO2 > 0.4 for SpO2 > 92%) escalation to another form of respiratory support (NIV or intubation) should be strongly considered, depending on availability of resources. In the case of using HFNC it is important to remember the high risk of aerosol generation and the potential infection risk to the medical staff. In this sense, the use of HFNC in a negative pressure room is highly recommended if available.

- **Oxygen therapy with mask with a reservoir.** Due to the characteristics of this particular pathology, this type of device should not be used since it does not generate recruitment of the lungs. Furthermore, administering 100% oxygen will cause an increase in PaO2 and SpO2 with no improvement in P/F ratio (shunt, recruitment), which may lead to a delay in the administration of an adequate recruitment therapy. It cannot, therefore, be in any way a substitute for CPAP.

3. **EARLY CPAP/BLPAP.** Should be considered if the patient has significant oxygen need or high work of breathing. The response to CPAP/BLPAP must be assessed within 30 minutes of initiation, and those who do not improve significantly should be intubated. If the patient on NIV has sustained moderate/severe hypoxemia (S/F < 200; FiO2 > 0.4), intubation should be strongly considered, depending on availability of resources. The helmet (11) is recommended as the first line interface to be used, if available. When CPAP is provided using home care ventilators, it is important to remember the limitation in the administration of FiO2 (i.e. due to T piece). In this case close patient monitoring (S/F) should be performed.
• In the event that a helmet is not available, the second best option will be the full face mask, although self-protection measures must be used because of the increase of aerosols.

4. **INTUBATION.** If resources are available, the patient should be intubated if they maintain a P/F or S/F ≤ 200 (FiO₂ > 0.4) after initiation of non-invasive therapy. If the patient is treated with NIV or HFNC and presents with high work of breathing (WOB) even if P/F or S/F is > 200 (FiO₂ < 0.4 for SpO₂ > 92%), they should be intubated. A surrogate marker which can be used for guidance about work of breathing is the ROX index [(S/F) / RR] (12). If the patient has a ROX index ≤ 5 intubation is strongly advised. Chest X-Ray or lung ultrasound or chest CT should be performed to assess for ground glass opacities and the distribution of pulmonary opacifications. Static lung compliance (C) (13) should also be evaluated after intubation, with no spontaneous breathing present (flow zero).

5. **INITIAL SETTINGS.** **Protective Ventilation.** Since many of these patients have normal or high C, it is recommended (14):

   a. Standard sedation (controlled by SAS / RASS) + Neuromuscular Blockers. Continuous neuromuscular blockade should be considered for the first 24 – 48 hours after intubation (15)
   b. Initial PEEP: 10 cmH₂O. (16) (17)
   c. VT: 6 ml/kg of IBW. (18) (19)
   d. Driving Pressure: < 15 cmH₂O. (20) (21)
   e. Pplat: < 30 cmH₂O. (22) (23)
   f. FiO₂ to achieve oxygen saturation between 88-97%

6. **NO IMPROVEMENT.** If P/F ratio remains < 200, consider the following:

   A. If P/F between 151 – 200 or S/F 176 – 200 (FiO₂ 0.4 – 0.5), perform a **PEEP express titration** (24)(25)(26)(27) [Figure 2]:

      a. Initial PEEP: 10 cmH₂O. (28)
      b. Increase PEEP 2 cmH₂O, every 2 minutes. Measure plateau pressure, and monitor oxygenation response (S/F ratio).
      c. Set the highest PEEP that maintains or improves S/F ratio and allows a Pplat of ≤ 30 cmH₂O.
B. If $P/F \leq 150$ or $S/F \leq 175$ ($FiO_2 > 0.5$). The following therapeutic options would be recommended:

a. **PRONE POSITIONING.** (29) (30) (31) (32) Should be considered as the first line of treatment if resources in the ICU are available. The evidence suggests it is most useful for patients with $P/F \leq 150$, and is not recommended if $P/F$ is above. Recommended approach (2 options):

- Place Prone and evaluate response: If improvement in $P/F - S/F$ ratio when placing prone, maintain in prone position for at least 16 hours and until $P/F$ or $S/F$ ratio $>200$ for at least 4 hours. Turn supine. If patient able to maintain $P/F >150$ or $S/F > 175$ for at least 4 hours remain supine. Otherwise prone again for at least 16 hours and re-evaluate.
- If resources are available, rotation between prone and supine positioning should be considered following the recommendations above, with duration of prone ranging from 16-20 hours a day.
- It is important to considerer that most patients can suffer a decrease of $P/F$ ratio after changing from prone to supine position.

b. **RECRUITMENT MANEUVRRES.** (33) (34) (35) (36) They could be considered prior to prone positioning if resources are limited. They may also be considered for patients that are Prone but persist with $P/F < 150$ or $S/F < 175$. Careful consideration of haemodynamics must be considered before and during the recruitment maneuvers. Recruitment manoeuvres should be performed under careful monitoring.

- We suggest increasing the PEEP initially 10, then 15 and finally up to 20 cmH$_2$O for 60 seconds in total, in PCV mode. Then titrate the PEEP decrementally by the lowest Driving Pressure. One option would be to follow the modified Amato algorithm [Figure 3].

- Different methods of recruitment can be attempted as per usual local practice, but no single method can be recommended based on current evidence. Safety of the patient has to be ensured during any RM(33). RM should
be used with extreme caution in patients with cardiac disease or hemodynamic instability.

- Cardiac ultrasound in addition to lung ultrasound is highly recommended when PEEP level is being titrated or during recruitment manoeuvres. Many patients, depending on their lung condition (normal C), can suffer an increase in pulmonary arterial pressure (PAP) when the PEEP is higher than 15 cmH$_2$O.

7. **If hypoxemia is refractory** (P/F < 150 or S/F < 175) despite prone and RM, two options should be considered:

1. **ARDS with a predominance of alteration of the HPV reflex.** (37) (38) This possibility should be considered in a patient with few alveolar-interstitial infiltrates (“Black X-ray”) and poor response to recruitment techniques (PEEP increments, proning and recruitment manoeuvres). In this case, the use of iNO + systemic vasoconstrictors (39) (40) should be considered, particularly if there is signs of the pulmonary hypertension on echography. The chest X-ray does not often reveal the extent of the problem. In many cases the X-ray is relatively normal, but the CT is very altered. Lung ultrasound is recommended for the diagnosis and to guide the treatment approach.(41) The use of ECMO as an initial treatment strategy is not recommended; this should be is left to the evaluation by medical staff on a case by case basis.

2. **Classic ARDS.** Chest X-ray with a clear bilateral alveolar-interstitial infiltrate pattern and low C. (42)(43) A higher PEEP and lower tidal volume strategy should be considered:

   - PEEP = 12 - 24 cmH$_2$O. (44)
   - VT = 4 – 6 ml/kg IBW.
   - Driving Pressure: < 15 cmH$_2$O.
   - Pplat: < 30 cmH$_2$O.

   - As guidance, patients responding to the increase in PEEP can be considered those in whom an increase >25 points in the P/F is observed. If this improvement in the P/F ratio is not observed after the increase in the PEEP level, it
would be advisable to maintain the previous level of PEEP. (45)

- Although some patients with a typical ARDS may need a higher level of PEEP. If it is necessary to increase this level above 15 – 18 cmH₂O it should be performed with precaution.
S/F concept
(Figure 1)

Titrte FiO₂ for SpO₂ = 95% ⇒ PaO₂ = 80 mmHg

<table>
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<th>FiO₂</th>
<th>S/F</th>
<th>P/F</th>
<th>SHUNT</th>
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<tr>
<td>1</td>
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High PEEP Recommended Strategy Express
(Figure 2)
Decreasing titration of PEEP Protocol Prof. Amato (modified) (Figure 3)

- Individualized PEEP
- Ventilatory mode at clinical criteria
- PIP enough to generate 6 ml/Kg of Vr

PC-CMV's
DP = 15 cmH₂O

VC-CMV's
\( V_T = 6 \text{ ml/kg IBW} \)

PC-CMV's
DP = 15 cmH₂O
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