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REVIEW

Early *versus* late tracheal intubation in COVID-19 patients: a "pros/cons" debate also considering heart-lung interactions

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ABSTRACT

The best timing of orotracheal intubation and invasive ventilation in COVID-19 patients with acute respiratory distress syndrome is unknown. The use of non-invasive ventilation, a life-saving technique in many medical conditions, is debated in patients with ARDS since prolonged NIV and delayed intubation may be harmful. Shortage of intensive care beds and ventilators during a respiratory pandemic can trigger a widespread use of early non-invasive ventilation in many hospitals but which is the best way to ventilate patients with severe bilateral pneumonia and severely increased spontaneous ventilation is controversial. Moreover, viral spreading to health-care workers and other hospitalized patients is an issue for any device used to administer oxygen. Even if protective mechanical ventilation is currently the gold standard for the management of acute respiratory distress syndrome, tracheal intubation is not without risks and is associated with delirium, hemodynamic instability, immobilization and post intensive care syndrome. Both invasive and non-invasive ventilation are associated with advantages and limitations that should be carefully considered when patients with COVID-19-ARDS need our attention. In the absence of strong evidence, in this review we highlight all the pro and con of these two different approaches.

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The ongoing pandemic of coronavirus disease 2019 (COVID-19) is characterized by a relevant number of patients suffering from moderate to severe acute respiratory failure (ARF).[1] In the most hit countries the demand for intensive care beds and ventilators was (and often still is) dramatically high.[2-6] Not rarely a shortage of these resources has been reported, leading to difficult ethical dilemmas.[7-9] Despite every effort to face the pandemic, many health systems even in developed countries became overwhelmed. In accordance with well established guidelines on ARDS treatments, a short trial of non-invasive ventilation (NIV) or high-flow nasal cannula

(HFNC) oxygen has been recommended -also in COVID-19 patients- when standard oxygen therapy by mask is insufficient to correct hypoxemia;[10-13] however, prompt intubation in case of NIV failure has been suggested, based on the common observation that patients failing NIV present a higher mortality. Furthermore, early tracheal intubation is intended to prevent too vigorous patient's respiratory efforts causing dangerous transpulmonary pressure and avoidable lung injury.[14] In the absence of strong evidence on COVID-19 management, the timing of tracheal intubation remains a controversial topic. In this manuscript, arguments pro and contra early tracheal intubation will be presented (Table I).

TABLE I.—*Key points to decide intubation timing in COVID-19 patients.*

General concepts
Preserved patient's consciousness helps clinician to discuss the therapeutic plan with the patient (nevertheless, anxiety and discomfort must be appropriately treated).
The outbreak of COVID-19 pandemic is very recent, few randomized trials have been conducted so far and available evidence is limited. It is premature to offer strong recommendations on COVID-19 treatment.
Favors NIV
Sedation is often required for intubation and may impair hemodynamics and predispose to delirium, neurocognitive dysfunction, immunosuppression and post intensive care syndrome.
MV, especially when associated with high PEEP levels, may have a detrimental impact on hemodynamics by reducing the pressure gradient for venous return and increasing RV afterload.
NIV has been successfully tested in awake patients in the prone position even outside the ICU.
NIV may permit to buy time allowing anti-inflammatory/anti-interleukin agent therapies to improve the clinical status.
A short trial of NIV or HFNC oxygen is recommended -also in COVID-19 patients- when standard oxygen therapy by mask is insufficient to correct hypoxemia.
Unnecessary intubation and MV of patients who would have otherwise improved on noninvasive techniques should be avoided.
NIV resulted effective also when applied in ordinary wards and when considering long-term outcomes.
Tracheal intubation maneuver is considered an aerosol-generating procedure that may expose the healthcare staff involved in the procedure to a high viral load with a relevant risk of viral transmission.
NIV is extremely useful during a pandemic in which a dramatic shortage of ICU beds, mechanical ventilators, trained intensivists, nurses, respiratory therapists, and drugs (e.g., sedatives, neuromuscular blockade drugs) occurs.
NIV can be applied outside the ICU, through easy-to-use, cheap ventilators or devices.
A too liberal approach to tracheal intubation implies the possibility that another patient (not necessary a COVID-19 patient) will be denied ICU admission.
Tracheal intubation is not without risks for COVID-19 patients and healthcare workers. Among 202 consecutive tracheal intubations in COVID-19 critically ill patients, peri-procedural hypoxemia was observed in 73% of cases, hypotension in 40% and cardiac arrest in 2% of cases; moreover, pneumothorax occurred in 6% of patients and death in the first 24 hours after intubation was 10%.
Beside risks associated to tracheal intubation, mortality of mechanically ventilated COVID-19 patients is not encouraging.
Favors early intubation and invasive ventilation
Prompt intubation in case of NIV failure has been suggested, based on the common observation that patients failing NIV present a higher mortality
The low PEEP usually applied during HFNC/NIV (2-7 cmH2O) may not prevent atelectrauma (alveolar opening and closing)
Early tracheal intubation is intended to prevent too vigorous patient's respiratory efforts causing dangerous transpulmonary pressure and avoidable lung injury (P-SILI)
During NIV, high inspiratory efforts may damage the diaphragm, stressed by mechanical forces, causing sarcolemma ruptures, sarcomere disarray and inflammation. All these mechanical effects may negatively affect short- and long-term clinical outcome
Endotracheal intubation should not be delayed because when COVID-19-ARDS patients are intubated in emergency conditions, the maneuver can be hampered by severe complications, including worsening hypoxia, hypotension, and cardiac arrest
Endotracheal intubated patients do not spread viruses to health-care workers and other hospitalized patients
During COVID-19-ARDS, highly increased respiratory drive and intense inspiratory efforts may induce uncontrolled swings in transpulmonary pressure and generate delivery of excessive tidal volumes, eventually favoring the worsening of lung injury

HFNC: high-flow nasal cannula; ICU: Intensive Care Unit; MV: mechanical ventilation; NIV: non-invasive ventilation; PEEP: positive end expiratory pressure; P-SILI: patients self-inflicted/induced lung injury; PEEP: positive end expiratory pressure.

PRO – Timing of endotracheal intubation in COVID-19 patients: the sooner the better

Deciding whether and when "to do or not to do something" is a major issue affecting many aspects of critical care medicine. Renal replacement therapy in acute kidney injury, norepinephrine in septic shock, tracheostomy, NIV *versus* endotracheal intubation and mechanical ventilation (MV) are just few examples. Complexity and heterogeneity are the main obstacles to the definition of a specific threshold that may trigger an action. The Severe Acute Respiratory Syndrome Coronaviruses-2 (SARS-CoV-2) outbreak represents a new challenge for intensive care physicians. Coronavirus Disease 2019 is a clinical syndrome characterized by respiratory symptoms with variable degrees of severity, ranging from mild upper respiratory illness to severe interstitial pneumonia and acute respiratory distress syndrome (COVID-19-ARDS) with multiorgan involvement.[15] The variability of clinical manifestations eventually leads to differences among patients regarding their needs in terms of oxygen therapy, ventilation requirements and organ support. Although guidelines and recommendations are constantly evolving as new trials are concluded, conflicting statements currently exist. The COVID-19 guidelines of the Surviving Sepsis Campaign recommend using supplemental conventional oxygen and, if insufficient, HFNC or NIV to maintain SpO_2 between 92 and 96%.[13] It also recommended close monitoring of the respiratory status and early intubation if worsening occurs.[13] Differently, the Faculty of Intensive Care Medicine, Intensive Care Society, Association of Anesthetists and Royal College of Anesthetists stated that "high-flow nasal oxygen or similar devices should be avoided", remarking that there is "no survival benefit compared to conventional oxygen therapy, and the risk of environmental viral contamination may be higher" and "use of CPAP or NIV should be confined to short periods (about 1-hr) using a well-fitting interface (full face mask or helmet) as a bridge to invasive mechanical ventilation."[16] Other recommendations suggested reserving use of HFNC or NIV for mild hypoxemia, with airborne precautions, and adopting a low threshold for intubation to avoid viral nosocomial transmission to staff.[17] As a general concept, early intubation of a patient with respiratory distress could result in unnecessary intubation and MV of patients who would have otherwise improved on non-invasive techniques. On the other hand, delaying intubation may lead to further deterioration of clinical conditions eventually contributing to worsened outcomes.[18, 19] In particular, concern exist regarding the impact of prolonged NIV in the absence of quick respiratory status improvement, which may result in potentially late tracheal intubation and MV. In this regard, previous studies showed that patients who underwent late intubation had markedly higher mortality rates compared to early intubated patients.[18, 19] A Chinese retrospective study showed that when COVID-19-ARDS patients are intubated in emergency conditions, the manoeuvre can be hampered by severe complications, including worsening hypoxia, hypotension, and cardiac arrest.[20] Therefore, HFNC/NIV *vs*. invasive MV is just another clear example of "one size does not fit all". Overall, this should serve as a warning to realize the need of careful evaluation under pathophysiological evidence while planning a supportive strategy for patients with moderate-to-severe hypoxemia due to COVID-19-ARDS. Although respiratory transmission of SARS-CoV-2 occurs via inhalation, COVID-19-ARDS appears to mainly originate from the vascular side of the alveolus, at least during the early stages of respiratory failure, with impairment of pulmonary vasoregulation, ventilation-perfusion (V/Q) mismatch, hypoxemia, and thrombogenesis.[21, 22] As the respiratory disease advance, lung edema increase and the lung damage progress, resulting some patients in a more "classic" ARDS.[23-25] Therefore, depending on the stage or phase of the disease (and other factors including the host response, physiological reserve, and comorbidities), COVID-19-ARDS could be characterized by significant non-uniformity.[25] As a consequence, variable ventilation techniques are adopted. Reports suggest that HFNC, NIV and invasive MV were used in many critically ill patients with COVID-19 in China,[1, 26, 27] Italy[6, 28] and the United States[29, 30] with significant variability among centers. Endotracheal intubation has not been identified as a risk factor for mortality in previous reports on COVID-19.[31-34] Moreover, use of noninvasive respiratory supports in ARDS is controversial and the balance between benefits and harms of spontaneous breathing in these patients is still debated. In general, potential advantages of NIV in the management of patients with respiratory failure, including those with ARDS, mainly involve avoidance of deep sedation complications (*e.g.,* delirium, hemodynamic depression, immunosuppression, immobilization),[35] muscle paralysis, and ventilator-associated complications of endotracheal intubation and invasive MV. Among patients less likely to benefit from noninvasive respiratory support are patients with acute hypoxemic non-hypercapnic respiratory failure due to conditions other than acute cardiogenic pulmonary edema (*e.g.,* COVID-19 patients). Even if the reduction in ventilator-induced lung injury is one of the potential benefits of NIV,[36] the possibility of injurious spontaneous breathing during noninvasive respiratory support has emerged and several mechanisms that may harm the patient have been described.[37] Like in COVID-19-ARDS, the physiologic response to hypoxemia is represented by an increase in both tidal volume and respiratory rate. In addition, we observe an increased respiratory drive and work of breathing due to the inflammatory response to viral infection.[38] Development of HFNC/NIV-associated high stress and strain within the lung may lead to patient self-inflicted lung injury (P-SILI).[39] The concept of P-SILI summarizes all those conditions where maintenance of spontaneous breathing in patients with damaged lungs and high respiratory drive may result in global/regional pressure/volume changes and possible aggravation of initial lung injury.[40] Based on the P-SILI concept, when the patient is spontaneously breathing (*e.g.* under HFNC/NIV) airway pressure is lower than during controlled MV, but this does not necessarily translate into lower transpulmonary pressure, where the inspiratory effort is the major determinant (usually strong in COVID-19-ARDS patients). Inspiratory effort can be precisely estimated from the negative deflection in esophageal pressure measured with the esophageal balloon technique. However, the esophageal balloon is difficult to use during noninvasive ventilatory support.[41] An alternative to estimate the transpulmonary pressure in these patients is represented by central venous pressure (CVP) trace which reflects changes in intrathoracic pressure[42] and shows ventilation-dependent oscillations characterized by low frequency. Indeed, changes in CVP during pressure support ventilation were correlated to changes in esophageal pressure and could thus be used for continuous monitoring of respiratory mechanics.[43, 44] During COVID-19-ARDS, highly increased respiratory drive and intense inspiratory efforts may induce uncontrolled swings in transpulmonary pressure and generate delivery of excessive tidal volumes, eventually favoring the worsening of lung injury. Recently, a bench and human study demonstrated the possibility to measure tidal volume during noninvasive ventilation delivered with a helmet by applying a turbine-driven ventilator and an intentional leak single-limb vented circuit.[45] Endotracheal intubation and MV have many advantages in ARDS patients: precise respiratory monitoring, limited air leaks, PEEP optimization, control of tidal volumes in case of spontaneous/supported breathing or setting of precise tidal volumes in case of controlled ventilation, facilitated prone positioning,[3] transportation and performance of diagnostic procedures outside the ICU. In fact, careful setting of ventilator parameters has been strongly recommended in COVID-19-ARDS patients:[13, 24, 46, 47] PEEP of 8-10 cmH_2O (gradually up-titrated to about 15 cmH_2O if needed), driving pressure <15 cm H_2O, and a tidal volume of 8 ml/kg of predicted body weight. The low PEEP usually applied during HFNC/NIV (2-7 cmH_2O) may not prevent atelectrauma (alveolar opening and closing).[48] Furthermore, large negative deflections in pleural pressure can increase vascular transmural pressure and vessels permeability (already damaged by virus penetration),[22] thus worsening pulmonary edema (negative pressure pulmonary edema)[49] and favoring the progression of ARDS from a "L-type" (Low elastance (= high compliance), limited PEEP response and low recruitability, low ventilation–perfusion (V/Q) matching) to a "H-type" (High elastance (= low compliance), higher recruitability and PEEP response, and a high right-to-left shunt)[23, 25] (Figure 1, 2). Additionally, spontaneous effort during mechanical

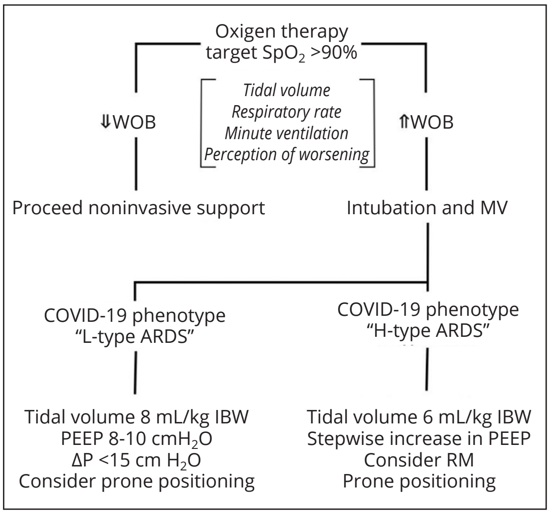

Figure 1.—Ventilation strategy for COVID-19-ARDS. ARDS: acute respiratory distress syndrome; ΔP: driving pressure; IBW: ideal body weight; RM: recruitment maneuvers; WOB: work of breathing; PEEP: positive end-expiratory pressure.

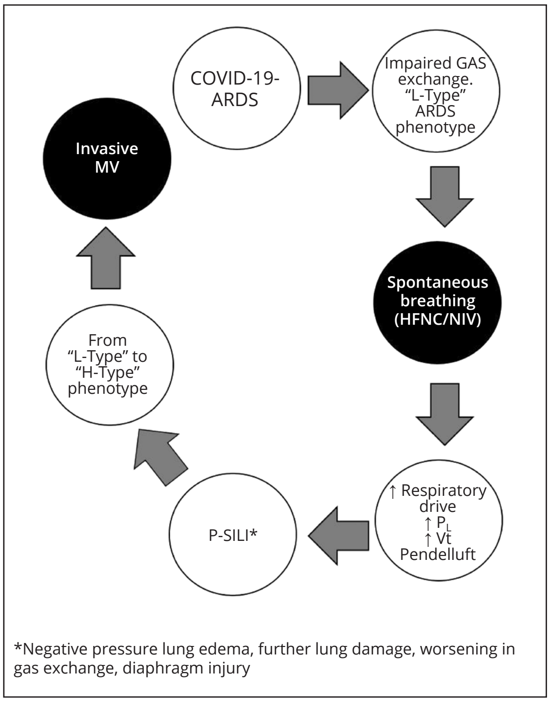

Figure 2.—Potential progression of COVID-19-ARDS. Role of patient self-inflicted lung injury (P-SILI).
ARDS: acute respiratory distress syndrome; PL: transpulmonary pressure; Vt: tidal volume: P-SILI patient self-inflicted lung injury.

ventilation can cause the so called "pendelluft" phenomenon (displacement of gas from nondependent -more recruited- lung to dependent -less recruited- lung during early inspiration). On the one hand, pendelluft may improve gas exchange, but on the other hand, because of tidal recruitment, it may contribute to P-SILI[50] during spontaneous breathing but not during paralysis and fully controlled ventilation.[39] Finally, during high inspiratory efforts, the diaphragm can be damaged by mechanical forces, sarcolemma rupture, sarcomere disarray and inflammation all negatively affect short- and long-term clinical outcome.[51] P-SILI is mitigated by higher levels of PEEP which, however, could be difficult to maintain during NIV due to air leaks, unless the treatment is delivered using the helmet interface. On the other hand, hemodynamic effects of invasive positive pressure ventilation and right ventricular function should be carefully monitored in COVID-19 patients in which a prothrombotic state affects pulmonary vasculature.[52] Mechanical ventilation, especially when associated with relatively high PEEP levels, may have a detrimental impact on hemodynamics by reducing the pressure gradient for venous return eventually leading to low cardiac output states especially in conditions of hypovolemia due to diuretics use (a strategy often applied in ARDS). Moreover, PEEP administration may increase right ventricular afterload contributing to right ventricular failure that should be carefully evaluated with echocardiography.[53, 54] It is also important to underline that experience in patients with ARDS indicates that inhaled nitric oxide (iNO) might reduce mean pulmonary artery pressure and improve oxygenation. Only intubated patients may receive iNO. Furthermore, previous in vitro studies on antiviral activity against SARS-CoV suggests a potential efficacy of iNO.[55] Some trials, evaluating iNO for COVID-19 are planned or underway (NCT04305457, NCT04306393, NCT04312243). Interestingly, FDA has recently granted access allowing iNO delivery systems to be immediately used for the treatment of COVID-19. In conclusion, ventilation support for COVID-19-ARDS patients is challenging, mainly because of heterogeneous respiratory dysfunctions and lung pathologies that require individualized lung-protective ventilation strategies to improve outcomes. The choice, timing and setting of the ventilatory support should be carefully tailored to patients' specific requirements and should consider disease phase and progression.

CON – Tracheal intubation in COVID-19: stop and think before grabbing the laryngoscope

The outbreak of the COVID-19 pandemic is very recent, few randomized trials have been conducted so far and available evidence is limited. Moreover, the disease is different from other better known viral respiratory disease like H1N1 flu. Severe COVID-19 ARF presentation has unusual peculiarities: hypoxemia can be marked, and chest imaging can show the typical picture of severe ARDS, but patients often tolerate surprisingly well very low oxygen values.[56] It is premature to offer strong recommendations on COVID-19 treatment; nevertheless, some considerations can be of help. Particularly, in our opinion some issues should be considered before taking the decision to intubate a patient affected by COVID-19 severe ARF as early intubation might not be in the best interest of the patient, carrying more risks than benefits. In the following paragraphs we will briefly address the most relevant points to be considered. First, tracheal intubation is not without risks for COVID-19 patients and healthcare workers. Among 202 consecutive tracheal intubations in COVID-19 critically ill patients, peri-procedural hypoxemia was observed in 73% of cases, hypotension in 40% and cardiac arrest in 2% of cases; moreover, pneumothorax occurred in 6% of patients and death in the first 24 hours after intubation was 10%.[20] Furthermore, tracheal intubation is considered an aerosol-generating procedure – actually, the worst one:[57] hence, it exposes the healthcare staff involved in the procedure to a high viral load with a relevant risk of viral transmission. Personal protective equipment (PPE) is clearly mandatory, but it is only one piece of a full system aimed at preventing contamination: the right intubation equipment, deep knowledge of the recommended protocols, a careful planning, and extensive training are also needed.[57] Despite any precautions, however, tracheal intubations in this setting remains a complex procedure with relevant risks for patients and operators.[58] Beside risks associated to tracheal intubation, mortality of mechanically ventilated patients is not encouraging.[59] In one of the first report from Wuhan, China, among 22 patients treated by mechanical ventilation the mortality rate was 86%.[1] In 344 consecutive intensive care patients from another Chinese hospital, Wang reported a 28-day mortality of 97% among 100 mechanically ventilated patients.[31] In a multicenter study from New York on the first 5700 COVID-19 patients, Richardson reported a mortality of 88% in 282 mechanically ventilated patients (97% of patients were older than 65 years).[30] Lastly, the availability of ventilators can be a major issue in resource-limited settings or during pandemics.[2, 56, 60] NIV and HFNC proved to be helpful in hypoxemic patients;[61, 62] NIV resulted effective also when applied in ordinary wards and when considering long-term outcomes.[63, 64] NIV and HFNC have been proposed in guidelines as useful measures also in the treatment of COVID-19 patients, provided close monitoring in the ICU with early intubation in case of no improvement after a 1-2-hour test.[11-13] So far, pilot small studies suggested that NIV might be applied also for longer periods, sometimes resulting (in selected patients) an alternative to tracheal intubation and mechanical ventilation.[4, 65] In particular, continuous positive airway pressure could offer several advantages, above all when using helmet as interface and the simple, cheap high-flow devices instead of ventilators.[66] Interestingly, NIV has also been successfully tested in awake patients in the prone position even outside the ICU:[67-70] prone positioning improved survival in ARDS patients,[71] and has been included in recent guidelines on treatment of COVID-19 severe ARF.[13] Recruitment of dorsal lung areas with improved ventilation/perfusion ratio and reduction of ventilation induced lung injury are among the main relevant beneficial mechanisms.[72] NIV can also permit to buy time and allow potent anti-inflammatory/anti-interleuchin agents to improve patient general and respiratory status.[28, 73-75] NIV and HFNC pose some concerns regarding safety of health care workers and other patients: precautions to minimize the problem have been proposed,[76, 77] and so far no case of viral transmission due to these treatments has been reported. On the other hand, NIV offers several advantages when compared to tracheal intubation: it can be applied outside the ICU, through easy-to-use, cheaper ventilators or devices, deep sedation is not required, and risks associated to tracheal intubation and prolonged mechanical ventilation are avoided.[78] In brief, the superiority of a strategy based on early intubation over prolonged NIV or HFNC in COVID-19 patients is still to be demonstrated, above all during a pandemic in which a dramatic shortage of ICU beds, mechanical ventilators, trained intensivists, nurses and respiratory therapists, sedatives, neuromuscular blockade drugs, and so on, is reported even in most developed countries.[7-9] Finally, ethical aspects must be carefully considered when evaluating the indication to tracheal intubation. As above reported, mortality in mechanically ventilated patients is very high; older and fragile patients present an even lower survival rate.[1] Moreover, even if we have not yet data on long-term outcomes of COVID-19 invasively ventilated patients, but it is well known that most patients undergoing prolonged mechanical ventilation suffer by several relevant sequelae, summarized as "postintensive care syndrome," including physical, cognitive, mental and social elements commonly with marked worsening of the quality of life for many years. Furthermore, even if an exhaustive description of all the ethical dilemmas emerged during the pandemic is beyond the scope of the present article, it is intuitive that a too liberal approach to tracheal intubation implies the possibility that another patient (not necessary a COVID-19 patient) will be denied ICU admission.[7-9] More importantly, most COVID-19 patients are fully conscious at hospital admission and commonly consciousness is preserved for days while ARF worsens: we should take advantage of this period to involve patients in a comprehensive discussion, exposing all options and exploring patient's preferences.[7-9] Palliation should clearly be part of the offered alternatives to tracheal intubation. In conclusion, in our opinion in times of pandemic causing shortage of ICU beds and ventilators, and above all considering the dismal outcome of mechanically ventilated patients, physicians should carefully consider every options (like using NIV as ceiling treatment, followed by palliation in case of NIV failure) and avoid automatic reactions (sometimes unfortunately guided by a defensive attitude due to medico-legal fears) to hypoxemia or a hurried adoption of algorithms developed for different conditions. Patient's preferences should be explored well in advance before critical hypoxemia is reached. In brief, serving the best interest of patients in this complex, dramatic scenario while preserving the safety of the staff and a rationale, fair use of the resources should be the rule for our behavior as physicians.

Discussion

While avoidance of intubation may improve survival, maintenance of spontaneous breathing may worsen lung injury and gas exchange and increase mortality. Based on pathophysiology of COVID-19-ARDS, one could speculate that in those patients with mild oxygenation impairment and no clinically evident severely elevated work of breathing, the maintenance of spontaneous breathing supported by HFNC/NIV can be a safe and maybe preferable procedure. At the same time, it would be more prudent when dealing with these patients to initiate HFNC/NIV early, at first stages of ARF, while adopting a low threshold for trigger intubation in case of further deterioration of hypoxemia or work of breathing. Differently, in cases of severe hypoxemia and when there is clinical evidence for disease progression and theoretical risks of P-SILI, invasive MV should be promptly considered. Controlled MV, muscle paralysis, sedation, prone positioning, precise control and monitoring of ventilation parameters may help to improve outcomes of COVID-19-ARDS patients. The potential benefits of prolonged HFNC/NIV therapy in moderate to severe hypoxemia should be evaluated in the context of a clinical trial, aimed also at investigating viral transmission to health care workers.

Conclusions

In conclusion, while waiting for more evidence on the topic, a personalized approach adopting early tracheal intubation in more severe cases, reserving to other cases a HFNC/NIV trial (not necessarily limited to 1 hour) in a well monitored setting could be the best choice. On the other hands, full involvement of patients to explore their preferences should be part of the doctor-patient relationship from the beginning.

Key messages

- Non-Invasive Ventilation (NIV) and High-Flow Nasal Cannula (HFNC) oxygen may allow to buy time for therapies aimed at improving the clinical status. Therefore, a trial of NIV or HFNC is recommended when standard oxygen therapy by mask is insufficient.
- Unnecessary intubation and mechanical ventilation of patients who would have otherwise improved on NIV should be avoided. Moreover, tracheal intubation maneuver is an aerosol-generating procedure that may expose healthcare staff to a high viral load. At the same time, prompt intubation in case of NIV failure has been suggested.

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