Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

What is the most adequate non-invasive oxygen support for acute hypoxaemic respiratory failure due to COVID-19?

During the COVID-19 pandemic, intensive care units have been overwhelmed with COVID-19 patients having life-threatening hypoxaemic respiratory failure. This situation underscored the uncertainty about the initial management of patients with acute hypoxaemic respiratory failure. The optimal initial oxygen support for these patients remains controversial and different approaches have been applied with variable success rates [1–3]. Non-invasive oxygen supports are applied until patients recover or require being intubated and mechanically ventilated, most often to relieve exhaustion due to a prolonged and intense work of breathing. In the context of COVID-19 pandemic, the objectives of non-invasive oxygen supports are at the individual level to decrease risk of nosocomial infections and improve survival by avoiding tracheal intubation, and, at the collective level, to avoid prolonging ICU stay. Standard oxygen using face mask, the oldest oxygen device first described in 1946 [4], remains the most common non-invasive oxygen support used in ICUs around the world, and also during the coronavirus disease 2019 (COVID-19) pandemic [1,3]. In this issue of *Anaesthesia Critical Care and Pain Medicine*, Fujii et al. present a narrative review and summarise the literature on the impact of alternative to standard oxygen, *i.e.*, non-invasive ventilation (NIV) and high-flow nasal cannula oxygen (HFNC), and suggest ways of improving their use in this setting [5].

In addition to determine the optimal oxygen support leading to improved prognosis of patients with COVID-19-induced respiratory failure, another question remains regarding the timing of their initiation. Both NIV and HFNC, to varying degrees, help to unload respiratory muscle activity by decreasing work of breathing via reduction of inspiratory effort and respiratory rate, while also improving oxygenation [6,7]. Thereby, they could mitigate the potentially deleterious effects of spontaneous breathing, as recently elucidated in the concept of patient self-inflicted lung injury (P-SILI); indeed, the efforts generated during spontaneous breathing could lead to an aggravation of lung injury through changes in global or regional pressure, even without any ventilatory support [8]. However, patients having COVID-19-induced respiratory failure present with a remarkable disconnect in rest between profound hypoxaemia yet without proportional signs of respiratory distress, no sensation of dyspnoea or increased respiratory work, and rapid deterioration can occur. This can be illustrated by the comparison between patient population having acute hypoxaemic respiratory failure mainly caused by bacterial pneumonia [9] and with COVID-19- induced respiratory failure [10]. Despite similar intubation rates, 38 and 34%, respectively in the two populations, PaO_2/FiO_2 ratio at enrolment in non-COVID-19 patients was higher, 150−160 mm Hg, higher respiratory rate approximating 33 breaths/min, while patients with COVID-19 had a more severe oxygen impairment, PaO_2/FiO_2 ratio of 102−105 mmHg, with surprisingly less tachypnoea, and a respiratory rate of 28 breaths/min [9,10]. This particular pattern of acute hypoxaemic respiratory failure caused by COVID-19 refers to the concept of "silent" or "happy" hypoxaemia [11,12]. Possible pathophysiological mechanisms include intrapulmonary shunting due to local interstitial oedema, resulting in ventilation-perfusion ratio mismatch and in an alveolar to arterial oxygen gradient, loss of lung perfusion regulation, with involvement of the renin-angiotensin system, intravascular microthrombi favoured by local acute inflammation, and endothelial injury resulting in an imbalance between procoagulant and fibrinolytic activity; these abnormalities lead to impaired diffusion capacity [12]. Because gas exchange abnormalities in some patients with COVID-19 occur earlier than increased mechanical loads and signs of respiratory distress, it is questionable whether there is a need to improve blood oxygenation with non-invasive oxygen supports, such as NIV or HFNC, instead of standard oxygen.

For this purpose, Fujii et al. first revisited the efficacy and impact of non-invasive oxygen supports in acute respiratory failure, and went to explore their indication in the COVID-19 era. Indeed, the use of NIV in acute hypoxaemic respiratory failure delivered either with a continuous positive airway pressure (CPAP) or combining pressure support ventilation plus positive end-expiratory pressure (PEEP) is controversial and was not recommended by international experts in patients with acute respiratory failure not related to COVID-19 [13,14]. However, it has been frequently used to manage patients with COVID-19-related respiratory failure in ICUs as well as in the wards put into place to support overwhelmed ICUs [2]. Whereas NIV has been described as able to reduce inspiratory effort and work of breathing as compared to standard oxygen [6], it may be deleterious due to barotrauma favoured by the high respiratory drive of patients, and synchronisation with the pressure support, which together may result in high tidal volumes. A previous study including patients with acute hypoxaemic respiratory failure reported that tidal volume exceeding 9 ml/kg of predicted body weight under NIV was strongly associated with intubation and mortality [15]. As is the case with invasive ventilation in patients with acute respiratory distress syndrome, NIV may lead to ventilator-induced lung injury (VILI) favoured by high tidal volumes and high

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transpulmonary pressure. This raises the questions of whether NIV could be delivered protectively to avoid VILI, and early to improve oxygenation in the management of COVID-19-induced respiratory failure. In patients with COVID-19-induced respiratory failure, helmet NIV delivered with high PEEP, around 12 cm of water has been shown to reduce intubation rates and increase 28-day invasive ventilation-free days as compared to HFNC [10]. However, this trial did not show any difference in mortality rates between the two strategies; in fact, the mortality rate was higher in patients who failed helmet NIV as compared those who failed HFNC. As developed in this issue of *Anaesthesia Critical Care and Pain Medicine* by Fujii et al. [5], there is no strong evidence favouring use of NIV in COVID-19-induced respiratory failure. Moreover, this last study underlined a need to think about different settings of NIV [9], with higher levels of PEEP or different interface, and did not rule out the use of HFNC.

At the beginning of the COVID-19 pandemic, various organisations offered varying recommendations in their guidelines, and some guidelines warned against the routine use of HFNC due to the risk of dispersal of viral particles in the atmosphere [16,17]. Finally, several simulation studies using manikin model of exhaled dispersion distances and analysing concentrations aerosol from the respiratory tract in room air showed that this risk was not higher under HFNC than NIV or standard oxygen devices [18]. Thereafter, HFNC seemed to be more frequently used to manage patients with COVID-19-induced respiratory failure [1,10]. Several observational studies have shown less intubation with the use of HFNC as compared to standard oxygen, but no difference was reported in mortality rates [19,20]. Therefore, there is no strong evidence of HFNC benefit in terms of survival in this setting, as compared to standard oxygen. Up until now, most published studies were observational and showed essentially that HFNC provided better oxygenation than standard oxygen, with intubation rates varying from 30 to 50%. Several randomised controlled trial are ongoing to assess the efficiency of HFNC in COVID-19-related respiratory failure as compared to standard oxygen or NIV around the world and results of an international mega-trial are expected regarding effects of awake prone position under HFNC on intubation and survival (NCT04358939).

The COVID-19 pandemic has highlighted the need to determine the optimal oxygen strategy to manage patients with severe hypoxaemic respiratory failure with the dual objective of individual benefits, *i.e.*, avoiding intubation, improving comfort and survival, and collective benefits to enable equipment availability and avoid critical shortage of ICU beds.

Competing interests

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References

[1] Clinical characteristics and day-90 outcomes of 4244 critically ill adults with covid-19: a prospective cohort study. Intensive Care Med 2021;47:60–73.

[2] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with sars-cov-2 admitted to icus of the Lombardy region, Italy. JAMA 2020;323:1574–81.

[3] Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with covid-19 in New York City: a prospective cohort study. Lancet (London England) 2020;395:1763–70.

[4] Kent BS. Light-weight oxygen mask of plastic material. Lancet (London England) 1946;2:380.

[5] Fujii T. Non-invasive oxygenation strategies for respiratory failure with COVID-19: A concise narrative review of literature in pre and mid-COVID-19 era. ACCPM 2021;40(4):100897. http://dx.doi.org/10.1016/j.accpm.2021.100897. In this issue.

[6] L'Her E, Deye N, Lellouche F, Taille S, Demoule A, Fraticelli A, et al. Physiologic effects of noninvasive ventilation during acute lung injury. Am J Respir Crit Care Med 2005;172:1112–8.

[7] Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. Am J Respir Crit Care Med 2017;195:1207–15.

[8] Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. Am J Respir Crit Care Med 2017;195:438–42.

[9] Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372:2185–96.

[10] Grieco DL, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, et al. Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with covid-19 and moderate to severe hypoxemic respiratory failure: the henivot randomized clinical trial. JAMA 2021;325:1731–43.

[11] Serrano Ricardo, CX, Rello Jordi. Management of hypoxemia in severe acute respiratory syndrome coronavirus 2 infection: lessons learned from one year of experience, with a special focus on silent hypoxemia. J Intensive Med 2021. http://dx.doi.org/10.1016/j.jointm.2021.02.001. In press.

[12] Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of' happy' hypoxemia in covid-19. Respir Res 2020;21:198.

[13] Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ers/ats clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50.

[14] Luján M, Peñuelas Ó, Cinesi Gómez C, García-Salido A, Moreno Hernando J, Romero Berrocal A, et al. Summary of recommendations and key points of the consensus of spanish scientific societies (separ, semicyuc, semes; secip, seneo, sedar, senp) on the use of non-invasive ventilation and high-flow oxygen therapy with nasal cannulas in adult, pediatric, and neonatal patients with severe acute respiratory failure. Arch Bronconeumol 2021;57:415–27.

[15] Frat JP, Ragot S, Coudroy R, Constantin JM, Girault C, Prat G, et al. Predictors of intubation in patients with acute hypoxemic respiratory failure treated with a noninvasive oxygenation strategy. Crit Care Med 2018;46:208–15.

[16] Raoof S, Nava S, Carpati C, Hill NS. High-flow, noninvasive ventilation and awake (nonintubation) proning in patients with coronavirus disease 2019 with respiratory failure. Chest 2020;158:1992–2002.

[17] Cinesi Gómez C, Peñuelas Rodríguez Ó, Luján Torné M, Egea Santaolalla C, Masa Jiménez JF, García Fernández J, et al. Clinical consensus recommendations regarding non-invasive respiratory support in the adult patient with acute respiratory failure secondary to sars-cov-2 infection. Arch Bronconeumol 2020;56 Suppl 2:11–8.

[18] Li J, Fink JB, Ehrmann S. High-flow nasal cannula for covid-19 patients: low risk of bio-aerosol dispersion. Eur Respir J 2020;55.

[19] Demoule A, Vieillard Baron A, Darmon M, Beurton A, Géri G, Voiriot G, et al. High flow nasal canula in critically ill severe covid-19 patients. Am J Respir Crit Care Med 2020;202(7):1039–42. http://dx.doi.org/10.1164/rccm.202005-2007LE.

[20] Bonnet N, Martin O, Boubaya M, Levy V, Ebstein N, Karoubi P, et al. High flow nasal oxygen therapy to avoid invasive mechanical ventilation in sars-cov-2 pneumonia: a retrospective study. Ann Intensive Care 2021;11:37.

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