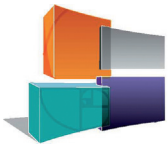
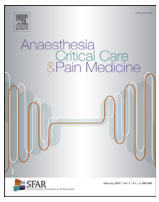
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Anaesth Crit Care Pain Med 39 (2020) 451–452



SFAR
Société Française d'Anesthésie et de Réanimation



Editorial

Treating hypoxemic COVID-19 "ARDS" patients with almitrine: The earlier the better?

ARTICLE INFO

Keywords:
Hypoxemia
Capillary shunt
COVID-19
Almitrine

COVID-19 viral pneumonia (pneumonitis) is an acute respiratory illness associated with a new droplet-borne coronavirus (SARS-CoV-2). To this day, the pandemic has resulted in over 9 million infections worldwide with over 470,000 deaths, and is associated with a profound disruption of the world's health systems and economy. Surprisingly, the majority of infected patients exhibit good thoraco-pulmonary compliance with preserved lung mechanics following intubation and mechanical ventilation (MV) [1,2]. Nevertheless, the dominant respiratory feature is profound and disproportionate hypoxemia [1].

In a recent editorial published in the *JAMA*, Marini and Gattinoni argue that deep sedation and MV should be implemented early on in order to prevent COVID-19 patients from generating spontaneous inspiratory efforts [3]. The authors state that in the early phase of lung infection, the high transpulmonary pressures associated with spontaneous vigorous inspiratory efforts may provoke self-induced lung injuries (P-SILI) [3]. Even if we agree with this present opinion, it is difficult to make the decision to intubate and paralyse not very symptomatic — but profoundly hypoxemic — patients when the main cause of this condition is a severe intrapulmonary oxygen shunt [2,4]. Indeed, it appears that the present SARS-CoV-2 pneumonitis induces a significant intrapulmonary capillary shunt resulting from a loss of hypoxic pulmonary vasoconstriction (HPV, Euler-Liljestrand mechanism) [4–6]. When recalcitrant hypoxemia is present, specific non-ventilatory strategies like body positioning (prone and anti-Trendelenburg) and pharmacological treatments, especially intravenous (IV) almitrine-bismesylate, may be of interest [4].

Almitrine is a scientifically recognised drug that enhances HPV by a vasoconstrictor effect specific to pulmonary arteries via a calcium mediated action [7]. In hypoxemic patients with acute respiratory distress syndrome (ARDS), this medication has been used with success [8,9]. In this regard, in this issue of *Anaesthesia Critical Care Pain Medicine*, the reader will find two interesting articles examining different, but converging prospects of IV almitrine administration on ventilation-perfusion inequalities in COVID-19 ARDS patients. Both authors hypothesised that IV almitrine may restore some blood oxygenation, even partially, when associated with postural manoeuvres and/or nitric oxide (NO) inhalation.

In a landmark first study, Losser et al. presented a prospective small case series of 17 COVID-19 ARDS patients admitted to the ICU for invasive MV [10]. After initial assessment, 10 patients received IV almitrine in the early phase of severe ARDS. The dose was initially 4, then 12 mcg/kg/min, with measurements of lung mechanics and oxygenation under 100% FiO_2 after 45 minutes of each increase in dose. With a PEEP of 10 cmH_2O and a median V_T of 425 ml throughout, respiratory compliance remained at 35.4 ml/cmH_2O with a driving pressure of 12 cmH_2O. PaO_2/FiO_2 ratios increased from 135 to 215 mmHg ($P < 0.05$), with an increase in $ScvO_2$ (73, 81, 85% respectively, $P < 0.05$). Cardiac index and right atrial pressures were not affected by the medication. An absence of spontaneous PaO_2 improvement, over eight hours, in a control group (7 patients) was also observed.

Cardinale et al. report a retrospective analysis of 20 consecutive prone patients in severe COVID-19 ARDS (median PaO_2/FiO_2 at 106 mmHg) and already on ventilation for one week (late phase of severe ARDS) [11]. Ten patients were treated with NO inhalation (between 10 to 20 ppm), 13 with almitrine infusion (loading dose of 0.5 mg/Kg over 30 minutes), and 7 with a combined treatment. The choices of treatments and ventilator settings were left to the discretion of the clinicians. Initial median PEEP was of 16 cmH_20, a respiratory compliance of 33.3 ml/cmH_2O and a median driving pressure of 14 cmH_2O. ABG analysis was performed before starting any of the treatments and was repeated one hour after inhaled NO or immediately after the almitrine infusion. The median increase of PaO_2/FiO_2 ratio was marginal under NO and almitrine, respectively, and under the combined treatment (P = NS).

What do these two studies add to what is already known on this topic? First, the benefit of a combination of NO inhalation and almitrine on PaO_2/FiO_2 ratios is more important in the early exudative phase than in the proliferative phase of severe classical ARDS [8,9,12]. This same timeframe can be found in COVID-19 ARDS and can be explained by the fact that, in the early phase, lung injury probably results from the gas side of the alveolus (alveolar oedaema). The evolution of the COVID-19 (late phase) appears to

https://doi.org/10.1016/j.accpm.2020.07.003

include an important endothelial insult with histological evidence of endothelial dysfunction [13] that mandates an additional vascular and rheological approach [3]. Second, a combination of gravitational and pharmacological intervention (prone positioning and almitrine) improve PaO_2/FiO_2 ratios of severe ARDS patients, principally in the early phase of ARDS [14]. The gravitational posture potentiates HPV induced by an almitrine infusion, which acts to divert pulmonary blood flow away from poorly ventilated alveoli toward well-ventilated areas. However, regrettably in the second investigation [11], there was insufficient echocardiographic assessment needed to exclude a patent *foramen ovale*. Indeed, the haemodynamic effects of almitrine on pulmonary arterial pressure and right ventricular pressures [15] may induce an intracardiac shunt that offsets and abolishes the benefit of the drug on blood oxygenation.

Recently, Barthélémy et al. also completed a retrospective analysis of 19 severe COVID-19 ARDS patients treated with an almitrine infusion of 2 mcg/kg/min, as a rescue therapy for refractory hypoxemia [16]. The median time from ICU admission was four days. PEEP was 10 cmH_2O and C_{rs} 32 ml/cmH_2O. Eighteen patients had at least one session of prone positioning before the almitrine infusion, and 15 had neuromuscular blockers and prone positioning at the time of the infusion. The median PaO_2/FiO_2 ratio increased from 79 before the infusion was started, to 117 mmHg within the first 6 hours ($P = 0.001$). Despite an improvement in oxygenation, the majority of patients under almitrine required additional rescue therapies or died.

What can be learned from the present studies? Reading these articles is stimulating to intensivists and physiologists who are currently facing the unprecedented challenge of treating and ventilating COVID-19 ARDS patients. As already stated above, several features of SARS-CoV-2 pneumonitis distinguish it from typical ARDS. First, patients often display a silent hypoxemia with very few clinical symptoms (dyspnoea) despite low PaO_2/FiO_2 ratios [4]. Such a condition is probably related to an impairment of the carotid body sensors, which physiologically senses hypoxemia and increases the respiratory drive. Second, the severe hypoxemia is mainly due to a large intrapulmonary capillary oxygen shunt linked to loss of HPV. At this point, we turn the question over to the reader: how can we use physiology to treat a failure of the body's homeostatic O_2-sensing system, which includes both the pulmonary circulation and the carotid body sensors [4]? The present question is crucial since the surest way to increase COVID-19 mortality is the liberal use of intubation and MV [1]. Indeed, although frequently life-saving during threatening hypoxemia, MV is also associated with various complications, some of them life-threatening in and of themselves [4]. In this regard, the key factor that could make almitrine administration of great importance in COVID-19 patients is its ability to avoid intubation and MV [17].

Finally, if we revisit recent results in the existing literature, we may say that administration of IV almitrine in the early phase of lung injury and ARDS may be associated with an improvement in arterial blood oxygenation in COVID-19 ARDS patients. As previously stated in another editorial, the proposed pharmacological treatment seems justified as long as its aim is to prevent intubation and MV, or improve MV weaning, without further deterioration of the patient's dangerous state [4].

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Tobin MJ. Basing respiratory management of COVID-19 on physiological principles. Am J Resp Crit Care Med 2020;201(11):1319–20.
[2] Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Resp Crit Care Med 2020;201(10):1299–300.
[3] Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. Jama 2020.
[4] Bendjelid K, Raphael G. Treating hypoxemic patients with SARS-COV-2 pneumonia: back to applied physiology. Anaesth Crit Care Pain Med 2020.
[5] Naeije R, Brimioulle S. Physiology in medicine: importance of hypoxic pulmonary vasoconstriction in maintaining arterial oxygenation during acute respiratory failure. Critical care 2001;5(2):67–71.
[6] Marshall BE, Hanson CW, Frasch F, Marshall C. Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution, 2. Pathophysiology. Intens Care Med 1994;20(5):379–89.
[7] Lumb AB, Slinger P. Hypoxic pulmonary vasoconstriction: physiology and anesthetic implications. Anesthesiology 2015;122(4):932–46.
[8] Papazian L, Roch A, Bregeon F, Thirion X, Gaillat F, Saux P, et al. Inhaled nitric oxide and vasoconstrictors in acute respiratory distress syndrome. Am J Resp Crit Care Med 1999;160(2):473–9.
[9] Gallart L, Lu Q, Puybasset L, Umamaheswara Rao GS, Coriat P, Rouby JJ. Intravenous almitrine combined with inhaled nitric oxide for acute respiratory distress syndrome. The NO Almitrine Study Group. Am J Resp Crit Care Med 1998;158(6):1770–7.
[10] Losser MR, Lapoix C, Delannoy M, Champigneulle B, Payen D. Almitrine as a non-ventilatory strategy to improve intrapulmonary shunt in COVID-19 patients. Anaesth Crit Care Pain Med 2020.
[11] Cardinale M, Esnault P, Cotte J, Cungi PJ, Goutorbe P. Effect of almitrine bismesylate and inhaled nitric oxide on oxygenation in COVID-19 acute respiratory distress syndrome. Anaesth Crit Care Pain Med 2020.
[12] Puybasset L, Rouby JJ. Almitrine and NO in acute respiratory distress syndrome: two pieces of the same puzzle? Eur Respir J 1999;14(6):1244–5.
[13] Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Critical care 2020;24(1):353.
[14] Gillart T, Bazin JE, Cosserant B, Guelon D, Aigouy L, Mansoor O, et al. Combined nitric oxide inhalation, prone positioning and almitrine infusion improve oxygenation in severe ARDS. Can J Anaesth 1998;45(5 Pt 1):402–9.
[15] Michard F, Wolff MA, Herman B, Wysocki M. Right ventricular response to high-dose almitrine infusion in patients with severe hypoxemia related to acute respiratory distress syndrome. Critical care medicine 2001;29(1):32–6.
[16] Barthelemy R, Blot PL, Tiepolo A, Le Gall A, Mayeur C, Gaugain S, et al. Efficacy of almitrine in the treatment of hypoxemia in Sars-Cov-2 acute respiratory distress syndrome. Chest 2020.
[17] Muret J, Clavier N, Beloucif S, Payen D. Intubation and mechanical ventilation avoided by using almitrine bismesylate in an acute hypoxemic pneumonia. Intens Care Med 1997;23(9):1008.

Karim Bendjelid[a,b,c,*], Raphael Giraud[a,b,c], Stephan Von Düring[a,b,c,d]

[a]*Intensive Care Division, Geneva University Hospitals, Geneva, Switzerland*

[b]*Geneva Haemodynamic Research Group, Geneva, Switzerland*

[c]*Faculty of Medicine, University of Geneva, Geneva, Switzerland*

[d]*Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada*

[*]Corresponding author at: Cardiovascular Unit, Intensive Care Division, Geneva University Hospitals, Geneva, Switzerland
E-mail address: karim.bendjelid@hcuge.ch (K. Bendjelid).

Available online 9 July 2020