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Efficacy of Almitrine in The Treatment of Hypoxemia in Sars-Cov-2 Acute Respiratory Distress Syndrome

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Author's Contribution

RB and PLB contributed equally. RB, PLB, and BGC designed the study, participated in the collection of the data, performed the statistics, participated in the interpretation of the data and drafting of the manuscript. AT, ALG, CM, SG, and LM participated in the collection of the data and drafting of the manuscript. EG and AM participated in the interpretation of the data and drafting of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

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Word Count

991

1 Research Letter

2 Dear Editor,

3 Critically ill Covid-19 patients frequently present profound hypoxemia with Acute
4 Respiratory Distress Syndrome (ARDS) requiring mechanical ventilation (MV)¹. According to
5 recently published Covid-19 guidelines², ventilatory support aims at increasing alveolar
6 oxygen partial pressure with non-invasive methods and eventually MV. Ventilator settings
7 are optimized in order to recruit collapsed alveoli and reduce ventilator-induced lung injury.

8 However, in Sars-Cov-2 ARDS, it has been hypothesized that recruitment strategies may be
9 hazardous because of a preserved compliance³ and a poor response to PEEP⁴ whereas
10 physiological measurements rather show increased intrapulmonary shunt⁵. Abnormal
11 pulmonary vascular dilation and increased perfusion surrounding areas of lung opacity have
12 been identified with dual-energy CT imaging, suggesting that insufficient hypoxic pulmonary
13 vasoconstriction (HPV) may play a major role in the onset of hypoxemia⁶.

14 Almitrine, a drug that used to decrease intrapulmonary shunt by enhancing HPV, improves
15 gas exchange in ARDS⁷. We hypothesized that almitrine could improve hypoxemia in Sars-
16 Cov-2 ARDS patients.

17 Materiel and methods

18 Study Design

19 This monocenter retrospective study aimed to evaluate the association between almitrine
20 introduction and improvement of oxygenation in Sars-Cov-2 ARDS. The study was conducted
21 in a 36-bed ICU (Hôpital Lariboisière, Paris, France) fully dedicated to the Covid-19 outbreak.

The medical records of all patients admitted between March 14th 2020 and April 11th 2020 were reviewed.

Inclusion criteria in the study were: admission for respiratory failure, a diagnosis of ARDS according to Berlin criteria⁸, laboratory confirmed Sars-Cov-2 infection, almitrine infusion in ICU. The primary endpoint was the arterial oxygen partial pressure (PaO₂) to fraction of inspired oxygen (FiO₂) ratio between baseline value and peak value during the 1st–6th hour timeframe after introduction of almitrine. PaO₂/FiO₂ ratio was measured with FiO₂ 1. The other endpoints were incidence of treatment failure at 24h, 48h, 72h and 96h, and safety. Treatment failure was defined as death, or the need for additional rescue therapy. Increase in right atrial pressure (RAP) and lactate during the first 6 hours and peak values for liver tests during the first 48h were reported as safety data.

This study was approved by an institutional ethics committee: Institutional Review Board (IRB 00006477) of HUPNVS, Paris 7 University.

Patients' Management

Patients were managed according to local protocol based on international guidelines⁹. Intrapulmonary shunt is confirmed after exclusion of a patent *foramen ovale*. Pleural effusions are considered for drainage. Hemodynamic optimization is performed to address low PvO₂ effect. Early respiratory management includes limitation of tidal volume and plateau pressure, systematic neuromuscular blockade and prone positioning session of at least 16h. PEEP is individualized to improves oxygenation without deteriorating compliance and cardiac output. In case of persistent refractory hypoxemia, we usually consider almitrine infusion (initial dose 2 µg.kg⁻¹.min⁻¹) and/or inhaled nitric oxide (iNO). Almitrine and iNO use are decided after collegial discussion on a case-by-case basis. If severe hypoxemia persists

despite the latter treatments, extracorporeal membrane oxygenation (ECMO) team is called to evaluate the indication of the device.

Statistical Analysis

Continuous variables before and after almitrine infusion were compared by a Wilcoxon Rank Sum test for paired data. All statistical analyses were performed using R statistical software version 3.6.1.

Results

Patients

Eighty-six patients were admitted to our ICU during the studied period. Nineteen of the 20 patients that met inclusion criteria had complete data and were analyzed (age 63 [54–67] years, sex-ratio 2.8, body mass index 28 [26–32] kg.m⁻²). Median time from ICU admission was 4 [2–6] days.

At the time of almitrine infusion, 15/19 (79%) were under MV with neuromuscular blockade. PEEP was set at 10 [10–12] cmH₂O and static compliance was 32 [28–35] mL.cmH₂O⁻¹. Eighteen patients (95%) had at least one session of prone positioning before almitrine.

Efficacy of Almitrine

The median PaO₂/FiO₂ ratio increased from 79 [64–100] at baseline to 117 [81–167] after almitrine (p=0.001) (Figure 1).

Figure 2 shows that almitrine infusion remained associated with an incremental need of supportive treatments in the following 96 hours.

Safety of Almitrine

The median arterial lactate level increased from 1.2 [0.9–1.4] to 1.5 [1.1–1.7] mmol.L⁻¹ after almitrine infusion (p=0.002). RAP did not change after almitrine infusion (9 [8–11] to 10 [9–11] mmHg, p=0.174).

Alanine Transaminase, Alkaline Phosphatase and Gamma Glutamyl Transpeptidase did not change during the 48h following almitrine infusion. Peak values were respectively 60 [37–78], 111 [76–142] and 116 [103–154] IU.L⁻¹.

Discussion

This is the first study describing therapeutic effects of almitrine in Sars-Cov-2 ARDS. In our observational study, almitrine was associated with an increase in PaO₂/FiO₂ ratio after treatment. However, this improvement of hypoxemia seems to be heterogenous amongst patients. Furthermore, despite an associated improvement in PaO₂/FiO₂ ratio, the majority of patients receiving almitrine went on to needing additional rescue interventions or died. This may be explained by the fact that, in our study, almitrine has been used as a rescue therapy in severe patients with worsening hypoxemia and very low PaO₂/FiO₂ ratio.

Even though this is a small sample study without control group, our data shows that enhancing HPV is an encouraging strategy to reduce hypoxemia in Sars-Cov-2 ARDS. This could at least be helpful to secure intra- or inter-hospital transfers in the most severe patients, or gain precious time until a more invasive life support is available.

The ideal time to start almitrine also remains to be determined. Almitrine could be used earlier in the treatment of Sars-Cov-2 hypoxemia to reduce the need or duration of MV, a scarce resource in the setting of worldwide outbreak. However, improvement in hypoxemia

is not necessarily associated with improved outcome. On the other hand, almitrine has been identified as a potential candidate against targeted proteins of SARS-Cov-2 with expected inhibitory effect¹⁰. Altogether, we believe that almitrine should be evaluated in clinical trials aiming at improving patient centered outcome for Covid-19 patients.

Conclusion

In this monocenter retrospective study, we found that almitrine at the dose of 2 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$ was associated with an increased $\text{PaO}_2/\text{FiO}_2$ ratio in the following 6 hours in Sars-Cov-2 ARDS patients.

References

1. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA*. Published online April 6, 2020. doi:10.1001/jama.2020.5394
2. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. Published online March 28, 2020. doi:10.1007/s00134-020-06022-5
3. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. Published online April 14, 2020. doi:10.1007/s00134-020-06033-2
4. Pan C, Chen L, Lu C, et al. Lung Recruitability in SARS-CoV-2 Associated Acute Respiratory Distress Syndrome: A Single-center, Observational Study. *Am J Respir Crit Care Med*. Published online March 23, 2020.

- 108 5. Gattinoni L, Coppola S, Cressoni M, Busana M, Chiumello D. Covid-19 Does Not Lead
109 to a “Typical” Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med*. Published
110 online March 30, 2020.
- 111 6. Lang M, Som A, Mendoza DP, et al. Hypoxaemia related to COVID-19: vascular and
112 perfusion abnormalities on dual-energy CT. *The Lancet Infectious Diseases*. 2020;0(0).
113 doi:10.1016/S1473-3099(20)30367-4
- 114 7. Payen D, Muret J, Beloucif S, et al. Inhaled nitric oxide, almitrine infusion, or their
115 coadministration as a treatment of severe hypoxemic focal lung lesions. *Anesthesiology*.
116 1998;89(5):1157-1165. doi:10.1097/00000542-199811000-00016
- 117 8. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory
118 distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-2533.
119 doi:10.1001/jama.2012.5669
- 120 9. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute
121 respiratory distress syndrome. *Ann Intensive Care*. 2019;9(1):69. doi:10.1186/s13613-019-
122 0540-9
- 123 10. Wu C, Liu Y, Yang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and
124 discovery of potential drugs by computational methods. *Acta Pharmaceutica Sinica B*.
125 Published online February 27, 2020. Accessed March 28, 2020.
126 <http://www.sciencedirect.com/science/article/pii/S2211383520302999>

Figure Legend

Figure 1: Evolution of $\text{PaO}_2/\text{FiO}_2$ Ratio Following Almitrine Infusion

Circles (o) represent individual $\text{PaO}_2/\text{FiO}_2$ ratio at FiO_2 1 of patients under mechanical ventilation. Triangles (Δ) are for patients who are spontaneously breathing. Solid circles (●) are for the 3 mechanically ventilated patients that had concomitant inhaled nitric oxide started along with almitrine. Segments connect baseline and almitrine value for each individual patient. Boxes represent interquartile range and horizontal lines inside the boxes represent median values. The closest available $\text{PaO}_2/\text{FiO}_2$ ratio up to 3 hours before almitrine infusion was taken as baseline value. Peak $\text{PaO}_2/\text{FiO}_2$ ratio measured from the 1st to the 6th hour after the start of the infusion was taken as almitrine value. During this period, there was no change in patient positioning and no additional rescue therapy was started.

Figure 2: Type of Respiratory Support and Cumulative Incidence of Almitrine Failure During the First 96h

Treatment failure is defined as death, or the need for any of the following additional rescue therapy: new endotracheal intubation if the patient was not under mechanical ventilation, administration of inhaled nitric oxide in a patient that was not treated with it, or extracorporeal membrane oxygenation (ECMO) cannulation. Cumulative incidence reports the absolute number of patients with reported treatment failure from the start of the almitrine infusion to the evaluation time.



