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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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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.

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

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

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

35 Patients' Management

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

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

47 Statistical Analysis

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

51 Results

52 Patients

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

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

60 Efficacy of Almitrine

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

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

65 Safety of Almitrine

66 The median arterial lactate level increased from 1.2 [0.9–1.4] to 1.5 [1.1–1.7] mmol.L⁻¹ after
67 almitrine infusion (p=0.002). RAP did not change after almitrine infusion (9 [8–11] to 10 [9–
68 11] mmHg, p=0.174).

69 Alanine Transaminase, Alkaline Phosphatase and Gamma Glutamyl Transpeptidase did not
70 change during the 48h following almitrine infusion. Peak values were respectively 60 [37–
71 78], 111 [76–142] and 116 [103–154] IU.L⁻¹.

72 Discussion

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

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

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

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

91 Conclusion

92 In this monocenter retrospective study, we found that almitrine at the dose of 2
93 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ was associated with an increased $\text{PaO}_2/\text{FiO}_2$ ratio in the following 6 hours in
94 Sars-Cov-2 ARDS patients.

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Figure Legend

Figure 1: Evolution of PaO₂/FiO₂ Ratio Following Almitrine Infusion

Circles (o) represent individual PaO₂/FiO₂ ratio at FiO₂ 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 PaO₂/FiO₂ ratio up to 3 hours before almitrine infusion was taken as baseline value. Peak PaO₂/FiO₂ 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.



