Almitrine Infusion in Severe Acute Respiratory Syndrome Coronavirus 2-Induced Acute Respiratory Distress Syndrome: A Single-Center Observational Study

Morgan Caplan, MD[1]

Julien Goutay, MD[1]

Anne Bignon, MD[2]

Emmanuelle Jaillette, MD[1]

Raphael Favory, MD, PhD[3]

Daniel Mathieu, MD, PhD[1]

Erika Parmentier-Decrucq, MD[1]

Julien Poissy, MD, PhD[4]

Thibault Duburcq, MD[1]

on behalf of the Lille Intensive Care COVID-19 Group

OBJECTIVES: Treating acute respiratory failure in patients with coronavirus disease 2019 is challenging due to the lack of knowledge of the underlying pathophysiology. Hypoxemia may be explained in part by the loss of hypoxic pulmonary vasoconstriction. The present study assessed the effect of almitrine, a selective pulmonary vasoconstrictor, on arterial oxygenation in severe acute respiratory syndrome coronavirus 2-induced acute respiratory distress syndrome.

DESIGN: Single-center retrospective observational study.

SETTING: ICU of Lille Teaching Hospital, France, from February 27, 2020, to April 14, 2020.

PATIENTS: Patients with coronavirus disease 2019 pneumonia confirmed by positive reverse transcriptase-polymerase chain reaction for severe acute respiratory syndrome-coronavirus 2 and acute respiratory distress syndrome according to Berlin definition. Data focused on clinicobiological features, ventilator settings, therapeutics, outcomes, and almitrine-related adverse events.

INTERVENTIONS: Almitrine was considered in patients with severe hypoxemia (Pao_2/Fio_2 ratio < 150 mm Hg) in addition to the recommended therapies, at an hourly IV delivery of 10 μg/kg/min. Comparative blood gases were done before starting almitrine trial and immediately after the end of the infusion. A positive response to almitrine was defined by an increase of Pao_2/Fio_2 ratio greater than or equal to 20% at the end of the infusion.

MEASUREMENTS AND MAIN RESULTS: A total of 169 patients were enrolled. Thirty-two patients with acute respiratory distress syndrome received an almitrine infusion trial. In most cases, almitrine was infused in combination with inhaled nitric oxide (75%). Twenty-one patients (66%) were responders. The median Pao_2/Fio_2 ratio improvement was 39% (9–93%) and differs significantly between the responders and nonresponders (67% [39–131%] vs 6% [9–16%], respectively; $p < 0.0001$). The 28-day mortality rates were 47.6% and 63.6% ($p = 0.39$) for the responders and nonresponders, respectively. Hemodynamic parameters remained similar before and after the trial, not suggesting acute cor pulmonale.

CONCLUSIONS: Almitrine infusion improved oxygenation in severe acute respiratory syndrome coronavirus 2-induced acute respiratory distress syndrome without adverse effects. In a multistep clinical approach to manage severe hypoxemia in this population, almitrine could be an interesting

therapeutic option to counteract the loss of hypoxic pulmonary vasoconstriction and redistribute blood flow away from shunting zones.

KEY WORDS: acute respiratory distress syndrome; almitrine bismesylate; coronavirus disease 2019; hypoxemia; hypoxic pulmonary vasoconstriction; intrapulmonary shunt

Since the first cases were reported in Wuhan, China, in December 2019, the severe acute respiratory coronavirus 2 (SARS-CoV-2) has become a global health issue. Coronavirus disease 2019 (COVID-19) varies widely from asymptomatic carriage to refractory hypoxemia, requiring intensive care admission. Because of a lack of knowledge about the underlying physiopathology, hypoxemia remains a challenge to treat. Although falling within the Berlin criteria of acute respiratory distress syndrome (ARDS), these viral pneumonias present an atypical form of the syndrome. The dissociation between a relatively well-preserved lung mechanics and the severity of hypoxemia may be explained by the loss of lung perfusion regulation and hypoxic pulmonary vasoconstriction (HPV) (1). Dual-energy CT imaging confirmed perfusion abnormalities suggesting intrapulmonary shunting, resulting in a worsening ventilation-perfusion (V/Q) mismatch and clinical hypoxia (2). We may reconsider the usual recommended therapies for severe ARDS ventilation, such as recruiting previously collapsed lung units with high levels of positive end-expiratory pressure (PEEP), or prone positioning. Almitrine bismesylate, a selective pulmonary vasoconstrictor, could be an interesting therapeutic option to counteract the loss of HPV. Indeed, by decreasing the perfusion of nonventilated lung areas, almitrine decreases pulmonary shunt and indirectly reduces alveolar dead-space-to-tidal-volume ratio by increasing the perfusion of ventilated lung areas (3). The aim of this study was to assess the effect of almitrine infusion on the arterial oxygenation of patients with SARS-CoV-2-induced ARDS.

MATERIALS AND METHODS

Patients with COVID-19 pneumonia confirmed by positive reverse transcriptase-polymerase chain reaction for SARS-CoV2, admitted in the ICU of Lille Teaching Hospital, France, were enrolled from February 27, 2020, to April 14, 2020. Criteria for ICU admission were acute respiratory failure, requiring conventional oxygen therapy with a gas flow greater than or equal to 6 L/min, high-flow nasal oxygen, non-invasive mechanical ventilation (MV), invasive MV, or refractory hypoxemia (Pao_2/Fio_2 ratio < 80 mm Hg) requiring venovenous extracorporeal membrane oxygenation (VV-ECMO). ARDS was defined according to Berlin definition. French institutional authority for personal data protection (National Commission for Information technology and freedom, registration no DEC20-086) and appropriate ethic committee (ID-CRB 2020-A00763-36, reference 2020/30) approved the study.

As recommended for the management of ARDS, in the case of severe hypoxemia (Pao_2/Fio_2 ratio < 150 mm Hg), a multistep clinical approach that may include the use of protective ventilation strategy with PEEP titration, neuromuscular blockers, inhaled nitric oxide (iNO), and prone position was performed. If severe hypoxemia persisted, clinicians could consider the infusion of almitrine. Thereby, almitrine was used alone or in combination with iNO in order to amplify the intrapulmonary gradient between the regional vascular tones, and to divert more blood flow toward normal zones (4). At last, VV-ECMO could be proposed for persistent severe hypoxemia and/or in the case of hypercapnia despite maximum optimal ventilatory support similar to what was described by the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial group (IDRCB 2009-A01026-51) (5).

Almitrine trial was performed at an hourly IV delivery of 10 μg/kg/min, in supine position with constant ventilation settings. Comparative blood gases were done before starting almitrine trial and immediately after the end of the infusion. A positive response to almitrine was defined by an increase in the Pao_2/Fio_2 ratio greater than or equal to 20% at the end of the infusion (6) and was followed by a continuous infusion. The duration of the almitrine infusion was determined by physicians according to the clinical evolution of the patient. Almitrine trial required normotensive patients with stable hemodynamic (no increase in vasopressor for at least 6 hr), monitoring central venous pressure (CVP), and evaluation by a transthoracic echocardiography (TTE). In the case of acute cor pulmonale (ACP) (7), almitrine was contraindicated. In the case of right ventricular failure, the decision was left to

the physician in charge. During almitrine infusion, hemodynamics, CVP, and lactatemia were monitored to detect signs of poor tolerance and guide the realization of a control TTE. Other contraindications included pregnancy, lactic acidosis, and acute liver failure (8). Data focused on demographic characteristics, clinical and biological findings, therapeutics, and outcomes. Trained physicians reviewed medical electronic records and collected ventilator settings (adjusted tidal volume [Vt], PEEP, driving pressure [ΔP], and respiratory system compliance) and possible adverse events related to almitrine infusion.

The primary aim of this study was to assess the occurrence rate of a positive response to almitrine. Secondary objectives compared clinical characteristics, therapeutics, ventilator settings, and blood gases results between the responders and nonresponders, and safety monitoring. We reported categorical and quantitative variables as numbers (%) and medians (interquartile range). We compared responders with nonresponders using χ^2 or Fisher exact tests for categorical variables, and Mann-Whitney U test for continuous variables. Paired comparisons were realized by a Wilcoxon signed rank test. Tests were two-tailed, with an α level at 0.05. We performed analyses with the GraphPad-Prism-6 software (San Diego, CA).

RESULTS

We enrolled 169 COVID-19 patients during the study period. Among the 32 patients who had an almitrine trial, 30 (94.0%) were intubated and two (6.0%) received continuous positive airway pressure (CPAP). All presented bilateral pulmonary infiltration with diffuse ground glass opacity, and 22 (68.7%) had consolidation on chest x-ray. The main characteristics of the population are presented in **Table 1**. In most cases, almitrine was infused in combination with iNO, which started 1 hour ($n = 18$, 75%), 24 hour ($n = 3$), and 48 hour ($n = 3$) before. Pretest TTE of the whole population was found: right-ventricular-to-left-ventricular-diameter ratio at 0.7 (0.6–0.8), tricuspid annulus plane systolic excursion at 21 mm (20–24 mm), and tricuspid S' wave at 14 cm/s (11–16 cm/s).

Twenty-one patients (66%), including the two patients with CPAP, were responders with a median Pao_2/Fio_2 ratio improvement of 67% (39–131) (**Fig. 1** and **Table 2**). The 28-day mortality rates were 47.6% and

63.6% ($p = 0.39$) for responders and nonresponders, respectively. In responders, the median almitrine duration was 2 days (1.5–5 d), with a mean dose of 1.65 ± 0.4 µg/kg/min. Almitrine was stopped before 2 days in 11 patients (three died, four was placed under ECMO, and four improved oxygenation sufficiently). In the 10 remaining patients, the median duration was 5 days (3.75–6 d). A total of 89 prone positioning sessions was done on the whole population with 76 sessions (85.4%) before and 13 sessions (14.6%) after almitrine.

ECMO therapy was implanted in 11 patients (34%). Arterial blood gases performed at $Fio_2 = 1$ before ECMO found a median Pao_2/Fio_2 at 78 mm Hg (63–90 mm Hg) and a median $Paco_2$ at 60 mm Hg (39–63 mm Hg). The indications were more frequently persistent severe hypoxemia ($n = 7$) than hypercapnia despite maximum ventilatory support ($n = 4$). The median duration of ECMO was 11 days (4–13 d) without significant difference between responders and nonresponders. Compared with the whole population receiving almitrine, the responders placed under ECMO after almitrine trial ($n = 5$) had a low median Pao_2/Fio_2 ratio (73 cm H_2O [60–79 cm H_2O]) and a high driving pressure (21 cm H_2O [16–23 cm H_2O]) before the test. The median time between almitrine trial and ECMO implantation was 1 day [0.25–2.75 d].

Hemodynamic parameters remained similar before and after the trial not suggesting ACP: mean arterial pressure (78 mm Hg [70–88 mm Hg] vs 77 mm Hg [71–85 mm Hg]; $p = 0.51$), heart rate (86 beats/min [75–99 beats/min] vs 87 beats/min [78–105 beats/min]; $p = 0.17$), urine output (0.5 mL/kg/hr [0.04–0.8 mL/kg/hr] vs 0.4 mL/kg/hr [0.02–0.9 mL/kg/hr]; $p = 0.66$), lactate level (1.3 mmol/L [0.9–1.7 mmol/L] vs 1.4 mmol/L [0.9–1.6 mmol/L]; $p=0.86$), and CVP (14 mm Hg [12–16 mm Hg] vs 15 mm Hg [12–18 mm Hg]; $p = 0.61$). Three patients (with previous hepatic cytolysis) presented a transient and moderate increased aminotransferase levels, without acute liver failure. The pulmonary embolism prevalence in our study group ($n = 8/32$, 25%) was similar to a control population not receiving almitrine with at least one Pao_2/Fio_2 less than 150 mm Hg and one prone positioning session ($n = 7/27$, 25.9%). However, this control population seemed less severe with a lower 28-day mortality at 30% (more information available in **additional table**, Supplemental Digital Content 1, http://links.lww.com/CCM/F934).

TABLE 1.

Main Characteristics of the Whole Population Before the Almitrine Trial and Comparisons Between Responder and Nonresponder Groups

Variables	Whole Population ($n = 32$)	Responders ($n = 21$)	Nonresponders ($n = 11$)	p
Age (yr)	63 (52–69)	58 (46–72)	67 (57–68)	0.30
Male sex, n (%)	25 (78)	16 (75)	9 (82)	1
Body mass index (kg/m²)	33.3 (27.4–36.8)	34.2 (28.7–37.6)	30.1 (27.3–36.3)	0.56
Simplified Acute Physiology Score II	56 (39–68)	43 (40–68)	62 (39–72)	0.51
Sepsis-Related Organ Failure Assessment score	7 (4–10)	7 (4–9)	9 (5–12)	0.33
Comorbidities, n (%)				
Any	7 (22)	3 (14)	4 (36)	0.20
Hypertension	17 (53)	12 (57)	5 (46)	0.71
Diabetes	10 (30)	6 (29)	4 (36)	0.70
Respiratory disease	9 (28)	6 (29)	3 (27)	1
Delay symptoms-trial (d)	15 (12–22)	15 (12–21)	18 (14–23)	0.34
Delay admission-trial (d)	5 (2–11)	7 (2–11)	5 (4–12)	0.70
Delay intubation-trial (d)	7 (4–12)	7 (4–12)	5 (4–12)	0.77
Norepinephrine, n (%)	15 (47)	8 (38)	7 (64)	0.27
iNO, n (%)	24 (75)	16 (76)	8 (72)	1
iNO (parts per million)	10 (10–15)	10 (10–15)	10 (10)	0.31
Prone positioning, n (%)	29 (90.6)	18 (85.7)	11 (100)	0.53
Neuromuscular blockers, n (%)	21 (66)	13 (62)	8 (73)	0.70
Biological data				
WBC count, × 10⁹/L	13.3 (9.1–17.6)	13.2 (8.9–17.2)	13.4 (10.1–22)	0.37
Lymphocyte count, × 10⁹/L	0.8 (0.6–1.1)	0.7 (0.6–1.1)	0.9 (0.5–1.2)	0.62
Platelet count, × 10⁹/L	275 (183–383)	278 (210–418)	271 (140–365)	0.25
Fibrinogen, g/L	7.8 (7–9.3)	7.8 (6.9–9.4)	7.8 (6.9–9.4)	0.97
Prothrombin time, s	15.9 (15.2–17.3)	15.7 (14.8–17.20)	16.8 (15.6–17.5)	0.21
Activated clotting time, s	43 (38–66)	47 (41–67)	40 (37–66)	0.15
D-dimer, μg/mL	3.9 (2.8–5.6)	4 (2.3–5.3)	3.6 (2.8–15.6)	0.71
Lactate dehydrogenase, U/L	504 (375–648)	426 (364–591)	629 (446–838)	0.19
C-reactive protein, mg/L	201 (104–273)	130 (61–233)	237 (196–334)	0.01
Procalcitonin, ng/mL	0.82 (0.23–1.83)	0.6 (0.14–1.44)	1 (0.7–11.6)	0.13

iNO, inhaled nitric oxide.

Data are expressed as number (%) or median (interquartile range). Comparisons between responders and nonresponders were realized with χ^2 or Fisher exact tests for categorical variables and Mann-Whitney U test for continuous variables.
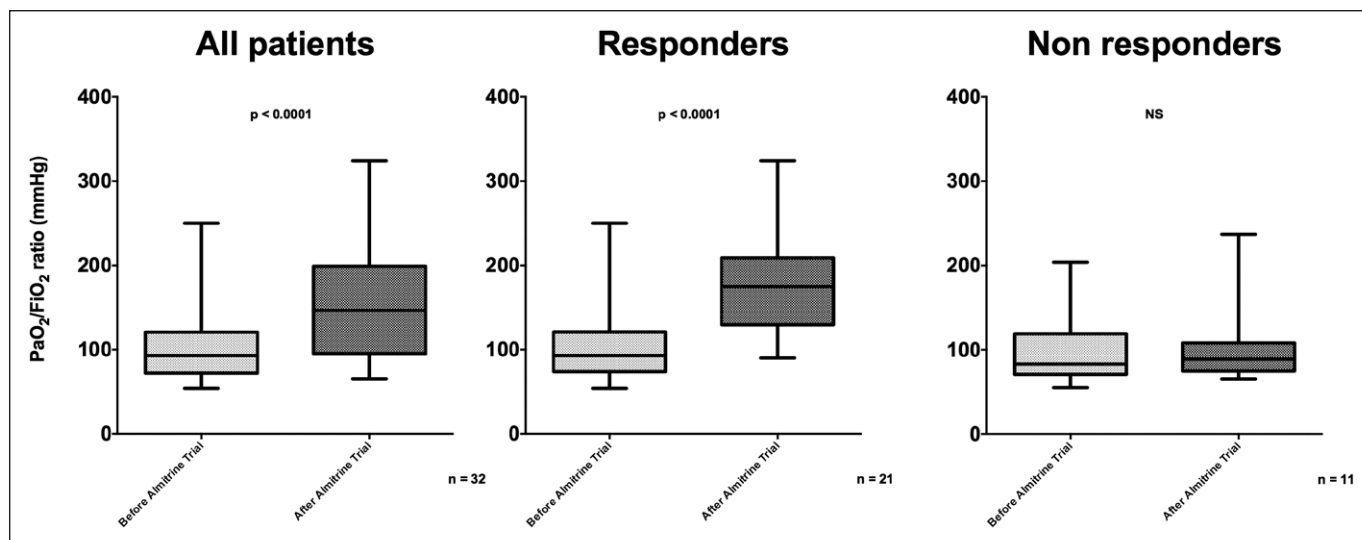
Figure 1. Distribution of Pao_2/Fio_2 ratio before and after the almitrine trial. *Boxplots* represent the distribution of Pao_2/Fio_2 ratio in the global population (32 patients), in responders (21 patients) and in nonresponders (11 patients) to an almitrine infusion of 0.6 mg/kg. A positive trial was defined by an increase in the Pao_2/Fio_2 ratio ≥ 20% at the end of the infusion. NS = not significant.

DISCUSSION

To our knowledge, this is the largest cohort assessing the impact of almitrine infusion on the arterial oxygenation of SARS-CoV-2-induced ARDS. We observed a positive response to almitrine for 66% patients, without significant adverse effects. Our results are consistent with two other studies (9, 10).

The severity of hypoxemia in COVID-19 may be partly explained by the loss of HPV, which is a potent adaptation to hypoxemia in humans. This mechanism drives away the circulating blood flow from hypoxic alveoli in order to optimize the V/Q ratio (11). Dual-energy CT (2) and subtraction CT imaging (12) of COVID-19 pneumonia highlighted pulmonary vascular dilation surrounding peripheral areas of consolidation. High perfusion in nonaerated lung (low V/Q ratio) might be due to the loss of HPV consecutive to an overactivation of a regional vasodilatation cascade due to proinflammatory factors and vasoplegia as in patients with ARDS and sepsis. In such situations, pulmonary vessels exposed to hypoxia may become particularly sensitive to almitrine (13). In our cohort, we found a high rate of response to almitrine infusion (66%). COVID-19 is a systemic disease that injures the vascular endothelium. The host cell entry of SARS-CoV-2 depends on the angiotensin-converting enzyme 2 (ACE2) receptor, expressed in several organs including the endothelial cells. Recent histological findings suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis (14). Endothelial cell dysfunction, systemic ACE2 deprivation could explain the impaired microcirculatory function in pulmonary vascular bed (15). Furthermore, according to general enzymatic kinetics, high angiotensin 2 levels elicited by ACE2 reduction would down-regulate ACE, an enzyme responsible for bradykinin degradation, an inflammatory mediator with strong vasodilatation role that could be implicated on the local intrapulmonary vasodilatation (16).

Interestingly, in addition to the loss of HPV in the nonaerated lung areas, subtraction CT revealed high V/Q ratio in the areas of apparently healthy lung secondary to prominent vasoconstriction, which worsens in more severe cases of COVID-19 pneumonia (12). These changes in vascular resistance lead to a shunt of vascular flow toward the areas of nonaerated hyperperfused lung. These findings may support the early use of pulmonary vasodilators, such as iNO to improve the V/Q mismatch. In our study, iNO was used in combination with almitrine in most patients (75%). Finally, the combination of a vasodilatation of normal zones added to a predominant vasoconstriction of hypoxic zones could act synergistically and redistribute blood flow away from shunting zones and further improve Pao_2 (4). In the case of life-threatening refractory hypoxemia, almitrine alone or in combination with iNO could be a good time-saver. Nevertheless, despite a median Pao_2/Fio_2 ratio improvement of 67% [59–146%],

TABLE 2.

Main Respiratory Parameters Before and After the Almitrine Trial and Comparisons Between Responders and Nonresponders Groups

Variables	Whole Population (n = 32)	Responders (n = 21)	Nonresponders (n = 11)	p
Before almitrine trial				
Number of prone positioning sessions	2 (1–3)	1 (1–2.5)	3 (2–4)	0.05
VV-ECMO, n (%)	3 (9.6)	0	3 (27.3)	0.03
Respiratory system compliance (mL/cm H_2O)	25 (19–28)	26 (20–29)	23 (15–27)	0.26
PEEP (cm H_2O)	13 (10–18)	14 (9–18)	12 (10–20)	0.88
Plateau pressure (cm H_2O)	32 (27–36)	32 (28–36)	31 (27–36)	0.91
Driving pressure (cm H_2O)	17 (14–22)	16 (14–22)	17 (12–25)	0.73
Vt (mL/kg)	6.3 (5.5–7.1)	6.4 (5.9–7.2)	6 (4.6–6.7)	0.12
RR (per min)	30 (26–32)	30 (25–32)	28 (26–30)	0.25
F_{IO_2} (%)	90 (70–100)	80 (65–100)	90 (80–100)	0.41
Pa_{O_2}/F_{IO_2} ratio	93 (72–120)	93 (74–121)	83 (71–119)	0.54
pH	7.35 (7.28–7.42)	7.36 (7.29–7.45)	7.34 (7.27–7.38)	0.58
Pa_{O_2} (mm Hg)	77 (66–93)	77 (68–92)	81 (59–94)	0.79
Pa_{CO_2} (mm Hg)	54 (43–59)	55 (42–64)	53 (49–57)	0.99
After almitrine trial				
Number of prone positioning sessions	0 (0–0.75)	0 (0–1)	0 (0–0)	0.22
VV-ECMO, n (%)[a]	8 (27.6)	5 (23.8)	3 (37.5)	0.65
Respiratory system compliance (mL/cm H_2O)	25 (20–30)	26 (20–31)	23 (17–30)	0.32
PEEP (cm H_2O)	14 (10–18)	14 (9–18)	13 (10–20)	0.88
Plateau pressure (cm H_2O)	31 (27–36)	31 (27–36)	31 (27–37)	0.82
Driving pressure (cm H_2O)	16 (14–22)	16 (13–22)	17 (14–23)	0.68
Vt (mL/kg)	6.3 (5.4–7.2)	6.4 (5.6–7.2)	6 (4.8–6.7)	0.18
RR (per min)	30 (26–32)	30 (26–32)	28 (26–31)	0.50
F_{IO_2} (%)	90 (70–100)	80 (65–100)	90 (80–100)	0.41
Pa_{O_2}/F_{IO_2} ratio	147 (95–199)	175 (130–209)	89 (75–108)	< 0.001
pH (mm Hg)	7.35 (7.29–7.42)	7.35 (7.31–7.46)	7.32 (7.26–7.41)	0.30
Pa_{O_2} (mm Hg)	117 (78–169)	134 (112–178)	70 (65–94)	**0.0001**
Pa_{CO_2} (mm Hg)	51 (43–59)	51 (41–60)	56 (46–58)	0.63

PEEP = positive end-expiratory pressure, RR = respiratory rate, Vt = tidal volume, VV-ECMO, venovenous extracorporeal membrane oxygenation.

[a]Number of VV-ECMO initiated after almitrine trial for the 29 patients not under ECMO support (responders n = 21; nonresponders n = 8). Data are expressed as number (%) or median (interquartile range). Comparisons between responders and nonresponders were realized with χ^2 or Fisher exact tests for categorical variables and Mann-Whitney U test for continuous variables.

five patients needed ECMO. This may be explained by the fact that almitrine was used as a rescue therapy in extremely severe patients with worsening disease and interrogates about the ideal timing for almitrine.

Gattinoni et al (1) described a transition between two phenotypes during the course of COVID-19 pneumonia. At the early phase of the disease, isolated viral pneumonia (type L) presents with near normal compliance, low V/Q ratio, and low lung recruitability. At this stage, almitrine should be interesting to reverse hypoxemia and to avoid the lung injury attributable to high-stress ventilation. In our study, among the six patients with normal compliance (> 50 cm H_2O) before almitrine trial, five (83%) were responders. Afterward, COVID-19 pneumonia (type H) fully fits the severe ARDS criteria with low compliance and potential for recruitment. Although the use of almitrine is actually not recommended, studies in ARDS have shown an improvement in patient oxygenation (13, 17). We report in our study a late almitrine use (median delay between the intubation and almitrine trial of 7 days [4–12 d]). Most of the patients (81%) had a type H COVID-19 pneumonia with respiratory system compliance less than 40 cm H_2O. Among these patients, sixteen (61.5%) were still responders. Almitrine seems to be an effective therapy whatever the phase of the disease.

Our study has several limitations. First, it was a retrospective design. Nevertheless, few data have been published on the subject, and an interesting physiologic rationale warranted the almitrine trial. The 28-day mortality rate was lower in responders, but these patients might be less severe with lower age, norepinephrine requirements, and severity scores compared with nonresponders. Anyway, the observational design with nonrandomized groups does not allow conclusions on the prognosis. Second, almitrine was not integrated in a therapeutic algorithm, and its infusion was performed at a different stage of the disease. This could lead to a selection bias. However, the almitrine trial were standardized to limit confounding factors. Additionally, all patients received almitrine in addition to the usual therapies for severe ARDS, except for two nonintubated patients who received almitrine to avoid intubation. Third, systematic TTE was not performed after almitrine. The benefit-to-risk ratio must be balanced before prescribing almitrine and need to be careful with right ventricle loading conditions (18) because

of the increased prevalence of pulmonary thromboembolism in COVID-19 patients (19). In our cohort, despite the confirmation of the high prevalence of pulmonary thromboembolism, almitrine did not seemed responsible for major side effects such as ACP. In fact, CVP was reliable to assess the evolution of right-sided cardiac filling pressure, as no other changes were made during almitrine trial. Then, almitrine was often used in combination with iNO. The potential side effects of almitrine on the right ventricle function could have been counterbalanced by iNO. Fourth, although the basal status of HPV appears as a factor influencing the response to almitrine (13), the dose-response was not tested in our study. Finally, prospective studies should be carried out to evaluate the interest of almitrine on mortality, to specify the dose-response, and the appropriate timing for its use. Almitrine could be used earlier: 1) to reduce the need or the duration of MV and 2) to offer an alternative and/or an additional strategy to prone positioning or VV-ECMO.

CONCLUSIONS

Almitrine infusion improves oxygenation in patients with SARS-CoV-2-induced ARDS without side effects. Sixty-six percent of patients were responders with a median Pao_2/Fio_2 ratio improvement of 67%. Pending prospective studies, we believe these findings may incite intensivists to assess the response to almitrine in a multistep clinical approach to manage severe hypoxemia in COVID-19 patients.

ACKNOWLEDGMENT

(laurent.robriquet@chru-lille.fr), Anahita Rouze (anahita.rouze@chru-lille.fr), Arthur Simonnet (arthur.simonet@chru-lille.fr), Sophie Six (sophie.six@chru-lille.fr), and Guillaume Degouy (guillaume.degouy@chru-lille.fr) from Pôle de Réanimation, CHU Lille, University of Lille, Lille, France, and Eric Kipnis (eric.kipnis@chru-lille.fr) from Réanimation Chirurgicale, CHU Lille, University of Lille, Lille, France.

1 Pôle de Réanimation, CHU Lille, University of Lille, Lille, France.

2 Réanimation Chirurgicale, CHU Lille, University of Lille, Lille, France.

3 Pôle de réanimation, Lille Inflammation Research International Center (LIRIC), CHU Lille, Inserm U995, University of Lille, Lille, France.

4 Pôle de réanimation, CNRS, UMR 8576 - Unité de Glycobiologie Structurale et Fonctionnelle, CHU Lille, Inserm U1285, University of Lille, Lille, France.

REFERENCES

1. Gattinoni L, Chiumello D, Caironi P, et al: COVID-19 pneumonia: Different respiratory treatments for different phenotypes? *Intensive Care Med* 2020; 46:1099–1102

2. Lang M, Som A, Mendoza DP, et al: Hypoxaemia related to COVID-19: Vascular and perfusion abnormalities on dual-energy CT. *Lancet Infect Dis* 2020 Apr 30. [online ahead of print]

3. Reyes A, Roca J, Rodriguez-Roisin R, et al: Effect of almitrine on ventilation-perfusion distribution in adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 137:1062–1067

4. Paven D, Muret J, Beloucif S, et al: Inhaled nitric oxide, almitrine infusion, or their coadministration as a treatment of severe hypoxemic focal lung lesions. *Anesthesiology* 1998; 89:1157–1165

5. Combes A, Hajage D, Capellier G, et al; EOLIA Trial Group, REVA, and ECMONet: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378:1965–1975

6. Roch A, Papazian L, Bregeon F, et al: High or low doses of almitrine bismesylate in ARDS patients responding to inhaled NO and receiving norepinephrine? *Intensive Care Med* 2001; 27:1737–1743

7. Vieillard-Baron A, Prin S, Chergui K, et al: Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. *Am J Respir Crit Care Med* 2002; 166:1310–1319

8. B'chir A, Mebazaa A, Losser MR, et al: Intravenous almitrine bismesylate reversibly induces lactic acidosis and hepatic dysfunction in patients with acute lung injury. *Anesthesiology* 1998; 89:823–830

9. Losser MR, Lapoix C, Delannoy M, et al: Almitrine as a non-ventilatory strategy to improve intrapulmonary shunt in COVID-19 patients. *Anaesth Crit Care Pain Med* 2020; 39:467–469

10. Barthélémy R, Blot PL, Tiepolo A, et al: Efficacy of almitrine in the treatment of hypoxemia in SARS-CoV-2 acute respiratory distress syndrome. *Chest* 2020 Jun 6. [online ahead of print]

11. Sylvester JT, Shimoda LA, Aaronson PI, et al: Hypoxic pulmonary vasoconstriction. *Physiol Rev* 2012; 92:154

12. Santamarina MG, Boisier D, Contreras R, et al: COVID-19: A hypothesis regarding the ventilation-perfusion mismatch. *Crit Care* 2020; 24:395

13. Gallart L, Lu Q, Puybasset L, et al: Intravenous almitrine combined with inhaled nitric oxide for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; 158:1770–1777

14. Varga Z, Flammer AJ, Steiger P, et al: Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; 395:1417–1418

15. Kleinsasser A, Pircher I, Treml B, et al: Recombinant angiotensin-converting enzyme 2 suppresses pulmonary vasoconstriction in acute hypoxia. *Wilderness Environ Med* 2012; 23:24–30

16. Mahmudpour M, Roozbeh J, Keshavarz M, et al: COVID-19 cytokine storm: The anger of inflammation. *Cytokine* 2020; 133:155151

17. Wysocki M, Delclaux C, Roupie E, et al: Additive effect on gas exchange of inhaled nitric oxide and intravenous almitrine bismesylate in the adult respiratory distress syndrome. *Intensive Care Med* 1994; 20:254–259

18. Michard F, Wolff MA, Herman B, et al: Right ventricular response to high-dose almitrine infusion in patients with severe hypoxemia related to acute respiratory distress syndrome. *Crit Care Med* 2001; 29:32–36

19. Poissy J, Goutay J, Caplan M, et al; Lille ICU Haemostasis COVID-19 Group: Pulmonary embolism in patients with COVID-19: Awareness of an increased prevalence. *Circulation* 2020; 142:184–186