Rescue therapy with inhaled nitric oxide and almitrine in COVID-19 patients with severe acute respiratory distress syndrome

François Bagate1,2†, Samuel Tuffet1,2†, Paul Masi1,2, François Perier1,2, Keyvan Razazi1,2, Nicolas de Prost1,2, Guillaume Carteaux1,2, Didier Payen3 and Armand Mekontso Dessap1,2,4*

Abstract

Background: In COVID-19 patients with severe acute respiratory distress syndrome (ARDS), the relatively preserved respiratory system compliance despite severe hypoxemia, with specific pulmonary vascular dysfunction, suggests a possible hemodynamic mechanism for VA/Q mismatch, as hypoxic vasoconstriction alteration. This study aimed to evaluate the capacity of inhaled nitric oxide (iNO)–almitrine combination to restore oxygenation in severe COVID-19 ARDS (C-ARDS) patients.

Methods: We conducted a monocentric preliminary pilot study in intubated patients with severe C-ARDS. Respiratory mechanics was assessed after a prone session. Then, patients received iNO (10 ppm) alone and in association with almitrine (10 μg/kg/min) during 30 min in each step. Echocardiographic and blood gases measurements were performed at baseline, during iNO alone, and iNO–almitrine combination. The primary endpoint was the variation of oxygenation (PaO2/FiO2 ratio).

Results: Ten severe C-ARDS patients were assessed (7 males and 3 females), with a median age of 60 [52–72] years. Combination of iNO and almitrine outperformed iNO alone for oxygenation improvement. The median of PaO2/FiO2 ratio varied from 102 [89–134] mmHg at baseline, to 124 [108–146] mmHg after iNO (p = 0.13) and 180 [132–206] mmHg after iNO and almitrine (p < 0.01). We found no correlation between the increase in oxygenation caused by iNO–almitrine combination and that caused by proning.

Conclusion: In this pilot study of severe C-ARDS patients, iNO–almitrine combination was associated with rapid and significant improvement of oxygenation. These findings highlight the role of pulmonary vascular function in COVID-19 pathophysiology.

Keywords: iNO, Almitrine, COVID-19, ARDS

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is responsible for the coronavirus disease 2019 (COVID-19) pandemic is causing a massive influx of patients presenting with severe acute respiratory distress syndrome (ARDS) to intensive care units (ICUs) worldwide [1]. For the most severe cases, refractory ARDS may lead to a discussion regarding the use of extracorporeal membrane oxygenation (ECMO), an expensive and invasive life support resource, available in limited numbers in expert centers [2, 3]. Since the possibilities cannot fit with the large-scale outbreaks, alternative solutions should be proposed [4]. Some authors have hypothesized that potential relatively preserved respiratory system compliance (Crs)
despite severe hypoxemia in COVID-19 patients suggests a possible hemodynamic mechanism for ventilation/perfusion (VA/Q) mismatch as hypoxic vasoconstriction alteration [5]. The SARS-COV-2 uses angiotensin converting enzyme 2 (ACE2) receptor expressed by pneumocytes in the epithelial alveolar lining to infect the host, thereby causing lung injury, but the ACE2 receptor is also widely expressed on endothelial cells, including the heart, kidney, intestine and lung. The presence of viral elements within endothelial cells with an accumulation of inflammatory cells, suggest that SARS-CoV-2 infection may induce endotheliitis altering vascular reactivity [6] including the hypoxic vasoconstriction or other vasomotor control.

The combination of inhaled nitric oxide (iNO), a selective pulmonary vasodilator, and almitrine, a specific pulmonary vasoconstrictor, was proposed several decades ago as to improve VA/Q mismatch. It was spectacular in many ARDS patients with maintained vasodilation in ventilated zones receiving iNO and reduced perfusion in poorly or non-ventilated zones after almitrine treatment [7–9]. In the particular context of COVID-19, we hypothesized that iNO–almitrine combination could improve arterial oxygenation in severe COVID-19 ARDS (C-ARDS) by a redistribution of the pulmonary blood flow towards ventilated areas.

Methods
Patient selection
Intubated patients with laboratory-confirmed COVID-19, who met the criteria for ARDS (Berlin definition) [10] with persistent severe hypoxemia (PaO2/FiO2 < 150 mmHg), were prospectively included at the medical ICU of Henri Mondor University Hospital (Creteil, France). SARS-CoV-2 infection was confirmed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasal swabs or lower respiratory tract samples (bronchoalveolar lavage or endotraceal aspirate). Age lower than 18 years, acute cor pulmonale defined as septal dyskinesia with dilated endotracheal aspirate). Age lower than 18 years, acute cor pulmonale defined as septal dyskinesia with dilated endotracheal aspirate). Age lower than 18 years, acute cor pulmonale defined as septal dyskinesia with dilated endotracheal aspirate). The study was approved by the ethics committee of the French Intensive Care Society as a component of standard care, and patient consent was waived as per French law. Families were given information about the study.

Enrolled patients were sedated and received neuromuscular blockers to maintain a volume-control mechanical ventilation adapted to keep the tidal volume around 6 mL/kg of predicted body weight (PBW) and the PaCO2 below 50 mmHg. After hemodynamic and ventilatory optimization, prone positioning was tested because of persisting severe hypoxemia (PaO2/FiO2 < 150 mmHg). After a proning session lasting 16 to 18 h, the patients were put back to supine position and the iNO (10 ppm) alone followed by iNO associated with 10 mcg/kg/min of almitrine (Vectarin®, Servier, Suresnes, France) were tested. The FiO2 was settled at 1 to limit heterogeneity within patients and to look at the effect of the drugs on true Qs/Qt, eliminating mostly the low VA/Q zones. The effect on arterial oxygenation was evaluated at least after 30 min in each condition: supine baseline, iNO, and iNO plus almitrine. Because of the potential negative impact of right ventricle afterload increase during almitrine, the right ventricular function was assessed by echocardiography along with arterial blood gases at baseline, during iNO alone, and with iNO–almitrine combination. Patients who had a PaO2/FiO2 ratio that increased by at least 20% or by 20 mmHg as compared to the baseline situation were considered “responders” [12].

Respiratory mechanics
The assessment of respiratory mechanics included the following measurements. Plateau pressure and total PEEP were assessed during an end-inspiratory (0.3 s) and end-expiratory (1–2 s) occlusion maneuver, respectively. The driving pressure and the Crs were computed as the difference between plateau pressure and total PEEP and tidal volume divided by the difference between plateau pressure and total PEEP, respectively. The potential airway closure phenomenon was detected by measuring the airway opening pressure during a low flow (≤6 L/min) insufflation and potential for lung recruitment was assessed by the mean of the recruitment-to-inflation ratio (R/I ratio) computation, as previously described by Chen et al. [13]. A R/I ratio < 0.5 was used to characterize a poorly recruitable patient.

Echocardiography
Trained operators (competence in advanced critical care echocardiography) performed transthoracic echocardiography in the supine position at baseline, and during iNO and almitrine administration. They focused on global function (velocity–time integral of left ventricular outflow tract, cardiac index), and the right ventricle function as previously proposed [14]. Because of severe hypoxia, all patients had a detection of potential shunting across patent foramen ovale in four-chamber view after

Protocol
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injection of sterile-modified fluid gelatine solution (Plasmion, Fresenius-Kabi, Sevres, France) aerated with room air to generate microbubbles as previously proposed [15].

Other variables collected
The following data were collected at inclusion: age, gender, body mass index, past medical history, standard treatments, Charlson comorbidity index, Sequential Organ Failure Assessment (SOFA) score [16], Simplified Acute Physiologic Score (SAPS) II [17], and the need for vasopressors. In addition, the need for ECMO support, limitation of life-sustaining therapies and ICU mortality were collected during hospitalization.

Statistical analysis
Statistical analyses were performed with the JMP software (version 9; SAS Institute Inc, Cary, NC) and GraphPad Prism software (version 5; GraphPad Software Inc., La Jolla, CA, USA). The primary endpoint of this study was the variation of oxygenation (PaO₂/FiO₂). Data were presented as median with interquartile range or number with percentage. Multiple paired values were compared using Friedman test followed by paired Wilcoxon test with Benjamini–Hochberg correction. Spearman’s test was used to assess correlation. For all tests, a two-way \( p \)-value < 0.05 was considered statistically significant.

Results
Patients characteristics
As a pilot study, ten severe C-ARDS patients were assessed (seven males and three females), with a median age of 60 [52–72] years. Median time since endotracheal intubation was 7 [5–15] days, allowing to mix potential different hypoxic mechanisms. Clinical characteristics, comorbidities, standard treatments and organ failures at inclusion are presented in Table 1.

Prone session and respiratory mechanics
As shown in Additional file 1: Table S1, the gas exchange response of the last prone position the day before the protocol was favorable (increase in PaO₂/FiO₂ of at least 20% or 20 mmHg) in most (8/10, 80%) patients; overall, the PaO₂/FiO₂ ratio increased from 77 [62–114] mmHg (supine) to 137 [97–167] (prone), \( p < 0.01 \) (Additional file 1: Table S1). Respiratory mechanics in supine position after proning are reported in Additional file 2: Table S2. The median values of Crs and driving pressure were 28 [21–38] mL/cmH₂O, and 15 [12–16] mmHg, respectively. R/l ratio was <0.5 in 6/10 (60%) patients, indicating limited recruitability in a majority of patients.

Effect of iNO and almitrine
In supine position, patients were still severely hypoxic with median PaO₂ of 102 [89–134] mmHg at FiO₂ of 1 (Table 2). On supine position, only the addition of almitrine to iNO increased significantly PaO₂ from baseline (Fig. 1), with no significant changes in pulmonary blood flow and other hemodynamic and echocardiographic variables (Table 2). The median of PaO₂/FiO₂ ratio increased from 102 [89–134] mmHg at baseline, to 124 [108–146] mmHg after iNO (\( p = 0.13 \)) and 180 [132–206] mmHg after iNO and almitrine (\( p < 0.01 \)) (Table 2). PaO₂ increased by more than 50% in seven of ten patients with iNO–almitrine combination (Additional file 3: Figure S1). One non-responder had an intra-cardiac shunt related to patent foramen ovale.

Table 1 Clinical characteristics of ten patients with Coronavirus 19 severe acute respiratory distress syndrome

| Variables                             | Values |
|---------------------------------------|--------|
| Age (years)                           | 60 (52–72) |
| Female gender                         | 3 (30%) |
| Body mass index (kg/m²)               | 28.2 (22.0–37.4) |
| Comorbidities                         |        |
| Dyslipidemia                          | 2 (20%) |
| Current smoker                        | 2 (20%) |
| Arterial hypertension                 | 5 (50%) |
| Diabetes mellitus                     | 5 (50%) |
| Atrial fibrillation                   | 0      |
| Heart failure                         | 0      |
| Previous stroke                       | 0      |
| COPD                                  | 1 (10%) |
| Cirrhosis                             | 0      |
| Dialysis                              | 1 (10%) |
| Previous stroke                       | 0      |
| Standard treatments                   |        |
| Anticoagulant                         | 0      |
| Antiplatelet therapy                  | 0      |
| ACE inhibitors or ARB                 | 5 (50%) |
| Organ failure at admission            |        |
| Charlson comorbidity index            | 2 (0–2) |
| SAPS-II                               | 36 (32–46) |
| SOFA score                            | 6 (3–7) |
| PaO₂/FiO₂                             | 112 (92–144) |
| Neuromuscular-blocking agent use      | 7 (70%) |
| Shock                                 | 1 (10%) |

Values are expressed as median (interquartile range)

C-ARDS COVID-19 ARDS patients, ARDS: acute respiratory distress syndrome, COPD: chronic obstructive pulmonary disease, ACE: angiotensin-converting enzyme, ARB: angiotensin receptors blockers, SAPS II: Simplified Acute Physiology Score II, SOFA score: Sequential Organ Failure Assessment, PaO₂: arterial oxygen tension, FiO₂: fraction of inspired oxygen
The response to iNO + almitrine did not correlate with the benefit on $\text{PaO}_2$ induced by prone positioning ($\rho = -0.09, p = 0.80$). Similarly, the baseline respiratory mechanics were not associated with the iNO–almitrine response (Additional file 4: Table S3).

**Outcomes**

Although the study was not designed to evaluate the impact on outcome, it is important to report that six out of ten patients had a refractory hypoxemia ($\text{PaO}_2/\text{FiO}_2 < 80$ mmHg), which could not be treated by almitrine due to the shortage of drug reserve. One patient benefited from ECMO support with a favorable final outcome, the five remaining could not be treated by ECMO and died during ICU stay.

**Discussion**

The main findings of this pilot study were as follows: i) only the combination of iNO and almitrine improved the arterial oxygenation in severe C-ARDS patients; ii)
the response to iNO–almitrine was not associated to the prone positioning effect and to the baseline respiratory mechanics variables.

In vitro studies suggested a direct antiviral effect of iNO on the SARS-CoV replication cycle [18, 19]. During the first SARS-CoV outbreak in 2004, a pilot study reported the efficacy of iNO in a limited series of severe patients, with reversal of pulmonary hypertension, improved hypoxemia and shortened duration of mechanical ventilation [20]. Some authors suggested that iNO could be used as a rescue therapy during the current pandemic [21, 22], inasmuch as COVID-19 is characterized by major pulmonary vascular dysfunction with endothelialitis, and thrombosis [23, 24]. In our case series, iNO alone had a negligible effect on oxygenation. In addition, in the absence of RV dysfunction, iNO did not change the RV 2D echocardiographic measures. These results confirm the adequate exclusion of patients with pulmonary hypertension and/or RV dysfunction, to safely use almitrine. Ongoing randomized controlled trial testing iNO will probably shed light on its usefulness in a broader population of patients with C-ARDS [25].

Some authors have hypothesized that in some patients with C-ARDS (especially those with low elastance–“L type”), hypoxemia was not completely explained by pulmonary shunt resulting from diffuse alveolar damage [26]. The respiratory mechanics of our selected patients did not fully match with the proposed “L type”, described byGattinoni et al. [26], but was in accordance with a recent larger cohort of critically ill adults with COVID-19 [27]. The frequency of vascular and perfusion abnormalities [28] and pulmonary embolism incidence seems higher in COVID-19 pneumonia as compared to classical ARDS [29]. There is also a specific pulmonary procoagulant pattern [30], causing alveolar capillary microthrombi, as revealed by post-mortem studies [31, 32]. More interestingly, Ackermann et al. reported [31] the presence of intussusive angiogenesis. These anomalies may alter hypoxic pulmonary vasoconstriction, a possible mechanism for VA/Q mismatch and hypoxemia during C-ARDS. Addition of almitrine to iNO in patients with C-ARDS has the potential for restoring vascular homeostasis, in particular hypoxic pulmonary vasoconstriction [28].

The first reported study on almitrine in severe hypoxia in COVID-19 patients [33] showed a highly significant increase in P/F ratio with almitrine, independently from the dose used (4 or 12 mcg/kg/min). Because the level of PvO\textsubscript{2} entering the pulmonary circulation is a major controller of hypoxic pulmonary vasoconstriction [34], they measured the SvO\textsubscript{2}, that increased significantly. Recently, Barthélémy et al. [35] described the effect of almitrine in 19 critically ill COVID-19 patients. In this study, almitrine (2 μg/kg/min) globally increased oxygenation within 6 h of infusion start. However, the studied population was heterogeneous, and the effect of prone position was not reported. Another study reported the effect of iNO (10 to 20 ppm in 10 patients), almitrine (0.5 mg/kg over 30 min in 13 patients), or both (7 patients). Surprisingly, the authors failed to observe any oxygenation improvement, with all patients investigated in prone position [36]. Taken together, previous reports and our study suggest a beneficial effect mainly during almitrine infusion in C-ARDS in the supine position.

In our study, since pulmonary blood did not change, it is reasonable to consider that the drugs combination creates pulmonary resistance gradient favoring the perfusion of ventilated areas reducing the VA/Q mismatch [37]. These data are consistent with previous larger studies in non-COVID ARDS [7, 8, 38]. Moreover, a recent preliminary study in non-COVID ARDS patients with veno-venous ECMO support, might renew the interest for almitrine [39]. The role of iNO and almitrine in the therapeutic arsenal of ARDS is not yet completely clear, but it is reasonable to consider iNO and almitrine as potential rescue therapies that might be applied in case of persisting severe hypoxemia despite prone positioning and before considering ECMO [11].

Our study suffers from several limitations. First, it is a pilot study on a small cohort, with no control group of ARDS not resulting from COVID-19, making the results only exploratory. However, our C-ARDS patients were homogeneous in terms of severity and selection. Second, because of limited drug availability, we did not evaluate the prolonged effect of this therapeutic combination. Thus, full interpretation on efficacy and tolerance is not possible. We did not observe adverse events on this short duration of administration. At least for a short duration, almitrine did not cause hyperlactatemia, hemodynamic instability (by favoring acute cor pulmonale), or hepatic disturbances [40]. Third, we could not standardize the timing of evaluation referring to prone position. A potential impact of additive effects of prone position and iNO-almitrine on arterial oxygenation cannot be ruled out [36]. Fourth, ventilation in FiO\textsubscript{2} 1 may theoretically increase the alveolar partial pressure in oxygen and inhibit or at least decrease hypoxic pulmonary vasoconstriction in non- or hypo-ventilated areas. However, an FiO\textsubscript{2} of 1 was used for the following reasons: i) the level of hypoxia for almost all patients necessitated very high FiO\textsubscript{2} close to 1; ii) the FiO\textsubscript{2} of 1 allows measuring hypoxia mainly related to true Qs/Qt and not low VA/Q zones. It is then more rigorous to compare the results of modification of true shunt instead of global venous admixture containing also low VA/Q; iii) the gas equation used to
calculate the P/F ratio may introduce large bias as previously shown.

**Conclusion**
In this small series of severe C-ARDS patients, the iNO–almitrine combination was associated with rapid and significant improvement of oxygenation, which was not observed with iNO alone. These findings highlight the role of pulmonary vascular vasoreactivity in COVID-19, which could partially be corrected by almitrine. This may help to avoid the ECMO or delay the time at which ECMO can be initiated. This aspect could only be evaluated in a randomized clinical trial in presence or not of almitrine. More work is warranted to test whether the prolonged use of these medicines could alter the long-term outcome of such patients.

**Supplementary information**

**Supplementary information** accompanies this paper at https://doi.org/10.1186/s13613-020-00769-2.

**Additional file 1: Table S1.** Blood gas before and after the last proning session in ten patients with severe acute respiratory distress syndrome secondary to coronavirus disease 2019.

**Additional file 2: Figure S1.** Correlations between respiratory mechanics and oxygenation response to the combination of inhaled nitric oxide and almitrine in ten patients with severe acute respiratory distress syndrome secondary to coronavirus disease 2019.

**Additional file 3: Table S2.** Respiratory mechanics in supine position in ten patients with severe acute respiratory distress syndrome secondary to coronavirus disease 2019.

**Additional file 4: Table S3.** Correlations between respiratory mechanics and oxygenation response to the combination of inhaled nitric oxide and almitrine in ten patients with severe acute respiratory distress syndrome secondary to coronavirus disease 2019.

**Abbreviations**

Crs: Respiratory system compliance; ARDS: Acute respiratory distress syndrome; iNO: Nitric oxide; C-ARDS: COVID-19 ARDS; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; ACE2: Angiotensin converting enzyme 2; ICU: Intensive care units; ECMO: Extracorporeal membrane oxygenation; Crs: Respiratory system compliance; VA/Q: Ventilation/perfusion; PBW: Predicted body weight; PaO2/FiO2: Arterial oxygen tension to fraction of inspired oxygen ratio; RT-PCR: Real-time reverse transcriptase-polymerase chain reaction; PEEP: Positive end-expiratory pressure; SOFA: Sequential Organ Failure Assessment; SPAS II: Simplified Acute Physiologic Score II; LV: Left ventricle; RV: Right ventricle; PaCO2: Partial pressure of arterial carbon dioxide; SaO2: Arterial oxygen saturation; VR: Ventilatory ratio; VCO2: Carbon dioxide production.

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**Authors’ contributions**

FB, ST and AMD designed the study and wrote the manuscript. FB, PM and FP collected the data. KR, NdP, GC and DP designed the study. All authors read and approved the final manuscript.

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**Availability of data and materials**

All data generated and analyzed during the study are included in the published article and can be shared upon request. All authors helped to revise the draft of the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

The study was approved by the institutional ethics committee of the French Intensive Care Society as a component of standard care and patient consent was waived as per French law. Information about the study was given to families.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Author details**

1. AP-HP, Hôpitaux Universitaires Henri-Mondor, Service de Médecine Intensive Réanimation, 51, avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France. 2. Univ Paris Est Créteil, CARMAS, 94010 Créteil, France. 3. UFR de Médecine Villemin, Université Paris 7 Paris Cité Sorbonne, Paris, France. 4. Univ Paris Est Créteil, INSERM, IMRR, 94 010 Créteil, France.

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