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.

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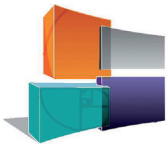

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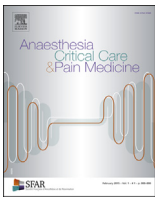

Letter to the Editor

Almitrine as a non-ventilatory strategy to improve intrapulmonary shunt in COVID-19 patients

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The SARS-CoV-2 acute lung infection can induce severe hypoxia, which seems related to intense pulmonary blood vessel dilatation and severe intrapulmonary oxygen shunt without major respiratory mechanics alteration [1]. Some non-ventilatory strategies have been proposed:

- ECMO is limited to trained centres, and cannot meet the vast COVID-19 pandemic demand;
- the prone positioning, supposed to facilitate alveolar recruitment and decrease the heterogeneity of compliance, appeared a good option [2] and improved PaO_2 was frequently observed;
- in the 90s', pharmacological strategies have been reported, especially almitrine bismesylate [3].

According to the French National agency for Drug Security (ANSM), only IV almitrine is indicated for hypoxic acute respiratory failure as a Drug of Major Therapeutic Interest. The hypothesis was that almitrine might restore oxygenation, even partially, both in supine or prone positioning in a case series of mechanically ventilated COVID-19 patients during their early phase.

1. Patients and measurements

The Research Program was approved by the Direction de la Recherche et de l'Innovation (DRI) (ref. 2020PI080), by the research Ethical Committee (Saisine 263) of the Centre Hospitalier Régional Universitaire (CHRU) de Nancy, France, and registered at ClinicalTrials.gov (NCT04380727). The relatives or patients were questioned about objections to use collected data for scientific purposes and/or potential publications. The statement and objection form were dated and recorded in the medical file.

Between March 16th and April 12th, 2020, COVID-19 patients referred to ICU with positive PCR testing received IV almitrine bismesylate (Vectarion®, Servier Laboratory, Neuilly, France) for acute hypoxia in acute respiratory failure. After baseline measurement in prone or supine positioning, a second measurement was carried out 45 min after 4 mcg/kg/min, followed by 12 mcg/kg/min almitrine infusion rate, to test a dose -effect response. Matched (on age, BMI, gender, and baseline PaO_2/FiO_2) controls COVID-19 patients were compared over similar delays (8 hours H8). Patients having an acute cor pulmonale (trans-thoracic 2D Echo–Doppler) or abnormal liver function tests or hyperlactatemia [4] were not included. Data were reported as median (interquartile) for continuous variables and as count (percentage) for categorical variables. Changes during almitrine infusion were assessed using a Friedman test followed by a post hoc Wilcoxon signed-ranks test if appropriate. A two-point comparison was performed using a Wilcoxon signed-ranks test: baseline *versus* the best PaO_2/FiO_2 obtained with 4 or 12 mcg/kg/min almitrine infusion (almitrine group), and baseline *versus* H8 (matched control group). Tests were 2-sided and a P-value < 0.05 was considered as statistically significant. Statistical analyses were performed using R version 3.6.0 for Mac OS (The R Foundation for Statistical Computing, Vienna, Austria).

2. Results

Seventeen patients were included (10 males, age = 70 [54–78] years, BMI = 29 [23–34]) having chronic metabolic and cardiovascular diseases. Haemoglobin was stable at 12.2 [8.9–13.8] g/dL. All patients were intubated just before or soon after ICU admission and ventilated at FiO_2 1. The length of stay in ICU was 18 [7–33] days. Four patients (24%) died in ICU.

The Fig. 1 showed individual data for $ScvO_2$ (not shown in control group) and PaO_2/FiO_2 in both groups, which significantly increased only in the almitrine group. Eight over 10 patients increased their PaO_2 with almitrine, with no clear relation with infusion rate. During this short perfusion time, no haemodynamic side effects were observed (Table 1) and lactate remained < 1.5 mmol/L. Only one of these severe patients underwent rescue ECMO (persistent $PaO_2/FiO_2 < 70$ mmHg).

3. Discussion

Intravenous almitrine was associated with almost a doubling of the PaO_2/FiO_2 ratio in the early phase of severe COVID-19 acute respiratory failure with no dose-effect relationship. $ScvO_2$ increased consistently, while neither Pra nor CI was altered. The individual increase in PaO_2 to almitrine infusion varied in amplitude between patients, on average 80 mmHg. Just like others, we have beforehand shown that almitrine may spectacularly improve PaO_2 by reducing intrapulmonary oxygen shunt [3,5]. Among other non-ventilatory methods to improve oxygenation, the prone positioning is leading with frequent and rapid increase in PaO_2/FiO_2 [2]. The combination of these conditions (prone and almitrine) could then be seen as a combination of gravitational and pharmacological effects to improve the intrapulmonary VA/Q mismatch. The increase of PaO_2/FiO_2 ratio in 80% of the patients confirmed the validity of this approach. The PaO_2

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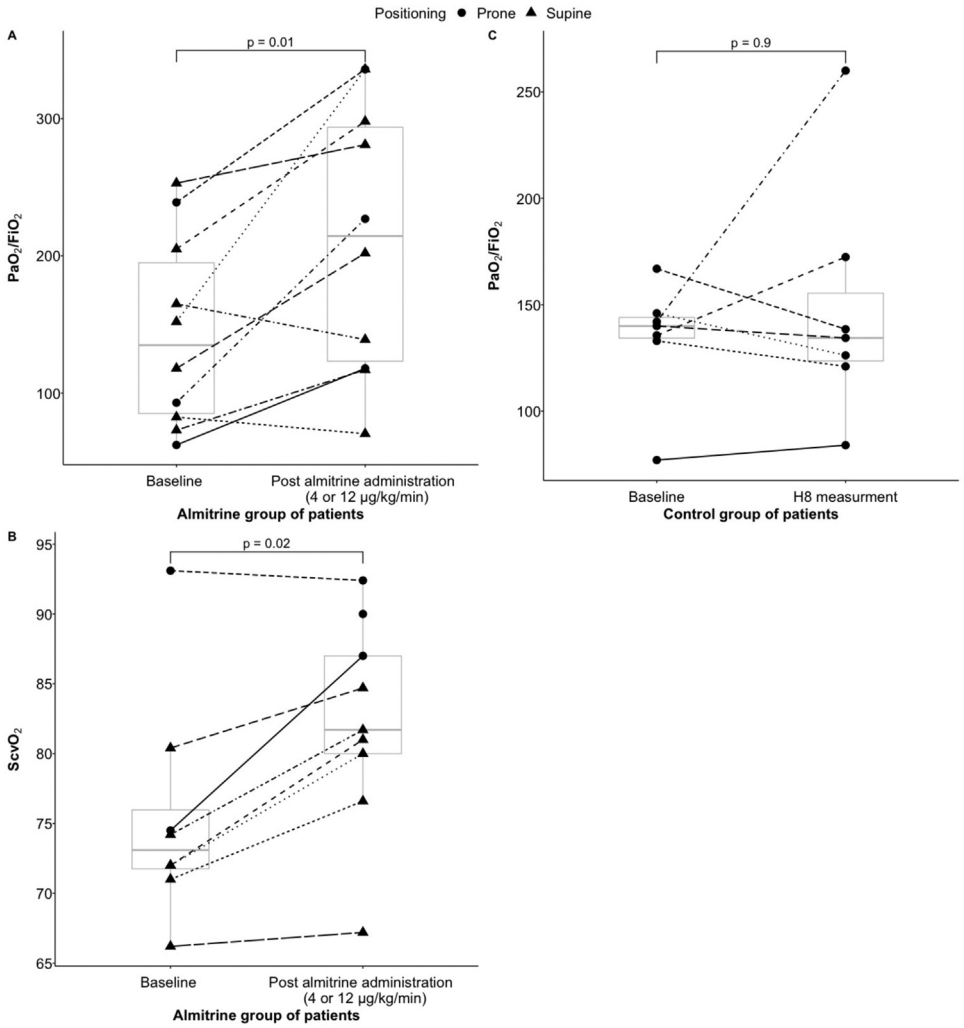

Fig. 1. Individual change of the PaO_2/FiO_2 ratio (A) and the $ScvO_2$ (B) between baseline and post-almitrine administration (best dose response in terms of PaO_2/FiO_2 ratio) in the almitrine group of patients (n = 10). Individual change of the PaO_2/FiO_2 ratio (C) in the matched-control group (n = 7) between baseline and H8. $ScvO_2$ measurements were not available for the control group. Shape of the individual point corresponds to the position of the patients (circle: prone positioning; triangle: supine positioning). Tukey boxplots on the background show correspondent median with 25th and 75thpercentiles (lower and upper hinges). Whiskers extend from the correspondent hinge to the largest or smaller value not further than 1.5*interquartile range.

Table 1
Haemodynamic, pulmonary gas exchange and mechanical ventilation parameters at baseline and after 4 and 12 µg/kg/min of almitrine.

Median (IQR)	Baseline	4 µg/kg/min	12 µg/kg/min	*P*
n	10	10	10	
FiO_2	1.00	1.00	1.00	NA
Positioning				
Prone	3	3	3	NA
Supine	7	7	7	
PaO_2 (mmHg)	135 (85, 195)	149 (91, 28)	215 (121, 275)	0.06
$PaCO_2$ (mmHg)	42 (40, 45)	42 (40, 45)	43 (37, 46)	0.45
pH	7.38 (7.36, 7.44)	7.40 (7.36, 7.42)	7.41 (7.36, 7.42)	0.70
HCO_3 (mmol/L)	25.1 (23.5, 28.2)	25.3 (24.1, 27.9)	24.8 (23.9, 27.6)	0.91
BE	1.4 (−1.4, 2.7)	1.1 (−0.3, 2.4)	−0.3 (−1.5, 2.5)	0.91
$ScvO_2$ (%)	73 (72, 76)	81 (79, 82)	85 (78, 87) *	0.03
Pra (mmHg)	8 (7, 9)	9 (8, 11)	9 (8, 11)	0.33
CI (L/min/m^2)	2.1 (1.9, 2.2)	2.2 (1.9, 2.3)	2.2 (1.9, 2.5)	0.42
Vt (mL)	425 (398, 465)	425 (398, 465)	425 (398, 465)	1
RR (/min)	23 (22, 24)	24 (22, 25)	24 (22, 25)	1
PEEP (cmH_2O)	10 (10, 11)	10 (8, 10)	10 (10, 10)	0.14
PIPressure (cmH_2O)	27 (26, 29)	27 (26, 30)	27 (26, 29)	1
Pplat (cmH_2O)	22 (19, 24)	22 (20, 24)	22 (20, 24)	1

BE: base excess; $ScvO_2$: central venous O_2 saturation; Pra: right atrial pressure; CI: cardiac index; CO: cardiac output; Vt: tidal volume; RR: respiratory rate; PEEP: positive end-expiratory pressure; PIPressure: peak inspiratory pressure; Pplat: plateau pressure; *: $P < 0.05$ *vs.* baseline value.

increase associated with almitrine infusion was concomitant with a significant increase in $ScvO_2$. This observation confirms the absence of tissue hypoperfusion with no large peripheral O_2 extraction, as suggested by the low lactate levels. This $ScvO_2$ increase provides a greater reserve for O_2 extraction in case of acute desaturation, and increased the level of dissolved O_2, the diffusible form of oxygen to the tissues.

The small size of the series would increase bias. The absence of a spontaneous PaO_2 improvement over 8 hours in matched controls reinforced the credence in an almitrine effect. In absence of a drug shortage, all of these patients would have received almitrine, and we were able to administer the drug for a longer period than 36 hours in only few patients. This precluded any conclusion about the potential benefit on mechanical ventilation duration and on the number of prone positioning. Following the same line of thinking, the almitrine test on arterial oxygenation cannot be proposed as either a prognostic test or a predicator of the prone position response.

In conclusion, in a case series of early hypoxemic COVID-19 pneumonia with acute respiratory failure, IV almitrine was associated with an improvement in arterial blood oxygenation both in prone or supine positioning in most patients, suggesting a partial recovery of the pulmonary vessels' contractility. This pharmacological intervention may offer an alternative and/or an additional strategy to the prone positioning in severe COVID-19 ARDS. It may help to support the lung function during a pandemic when the capacity to offer ECMO is very limited.

Contributions

MRL: supervision, data curation, methodology, validation, writing – original draft, writing – review & editing. Funding acquisition.

CL: data curation, visualisation.

MD: data curation, validation.

BC: visualisation, formal analysis, software, writing – review & editing.

DP: conceptualisation, formal analysis, visualisation, validation, methodology, writing – original draft, Writing – review & editing.

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Disclosure of interest

The authors declare that they have no competing interest.

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