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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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CASE REPORT

Almitrine for COVID-19 critically ill patients – a vascular therapy for a pulmonary vascular disease: Three case reports

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Author contributions: Huette P, Abou Arab O, Beyls C and Mahjoub Y conceived the study and drafted the manuscript; Jounieaux V, Guilbart M, Belhout M, Haye G and Dupont H participated in data acquisition and helped to draft the manuscript.

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Abstract

BACKGROUND

Several reports with clinical, histological and imaging data have observed the involvement of lung vascular function to explain the severe hypoxemia in coronavirus disease 2019 (COVID-19) patients. It has been hypothesized that an increased pulmonary blood flow associated with an impairment of hypoxic pulmonary vasoconstriction is responsible for an intrapulmonary shunt. COVID-19 may lead to refractory hypoxemia (PaO₂/FiO₂ ratio below 100 mmHg) despite mechanical ventilation and prone positioning. We hypothesized that the use of a pulmonary vasoconstrictor may help decrease the shunt and thus enhance oxygenation.

CASE SUMMARY

We report our experience with three patients with refractory hypoxemia treated with almitrine to enhance oxygenation. Low dose almitrine (Vectarion®; Servier, Suresnes, France) was started at an infusion rate of 4 μ g × kg/min on a central line. The PaO₂/FiO₂ ratio and total respiratory system compliance during almitrine infusion were measured. For the three patients, the PaO₂/FiO₂ ratio time-course showed a dramatic increase whereas total respiratory system compliance was unchanged. The three patients were discharged from the intensive care unit. The intensive care unit length of stay for patient 1, patient 2 and patient 3 was 30 d, 32 d and 31 d, respectively. Weaning from mechanical ventilation was performed 13 d, 18 d and 15 d after almitrine infusion for patient



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1, 2 and 3, respectively. We found no deleterious effects on the right ventricular function, which was similar to previous studies on almitrine safety.

CONCLUSION

Almitrine may be effective and safe to enhance oxygenation in coronavirus disease 2019 patients. Further controlled studies are required.

Key Words: COVID-19; Treatment; Acute vascular distress syndrome; Almitrine; Intensive care unit; Safety; Case report

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Core Tip: It has been hypothesized that increased pulmonary blood flow associated with impaired hypoxic vasoconstriction may lead to significant intrapulmonary shunt that plays a major role in coronavirus disease 2019 related severe hypoxia. In this report, three coronavirus disease 2019 patients with refractory hypoxemia were treated with continuous infusion of almitrine, a specific pulmonary vasoconstrictor. Almitrine infusion enhanced oxygenation of patients with severe coronavirus disease 2019 related acute respiratory distress syndrome without any change in pulmonary artery pressures and right ventricular function.

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INTRODUCTION

Several reports with clinical, histological and imaging data in coronavirus disease 2019 (COVID-19) have observed that the involvement of lung vascular function may explain the severe hypoxemia[1-5]. It has been hypothesized that an increased pulmonary blood flow is responsible for an intrapulmonary shunt with a decrease of ventilation/perfusion ratio[2,3]. Recently, three retrospective case series reported the use of almitrine, a pulmonary vasoconstrictor, in COVID-19 patients with inconsistent effects on oxygenation and outcome[6-8]. However, no data on key safety factors, such as right ventricular function or pulmonary artery pressure, were reported in these series. We report our experience with three patients with refractory hypoxemia treated with almitrine to enhance oxygenation. Complete hemodynamic assessment with transesophageal echocardiography and pulmonary artery catheter was performed.

CASE PRESENTATION

Chief complaints

Patients were admitted at Amiens University hospital intensive care unit for severe acute respiratory distress syndrome (ARDS) related to COVID-19. Severe acute respiratory syndrome coronavirus-2 infection was confirmed by real-time reverse transcription polymerase chain reaction on a sample from nasopharyngeal swab. Patient condition deteriorated rapidly leading to mechanical ventilation and refractory hypoxemia despite medical management.

History of present illness

Case 1: The patient was admitted to the hospital 7 d after onset of symptoms (dyspnea and headache). Initial treatment included lopinavir/ritonavir and high flow nasal oxygen for 2 d. Respiratory worsening lead to mechanical ventilation 2 d after hospital admission.



Case 2: The patient was admitted to the hospital 11 d after onset of symptoms (dyspnea and cough). Initial treatment included lopinavir/ritonavir. Respiratory worsening required mechanical ventilation 5 d after intensive care unit (ICU) admission.

Case 3: The patient was admitted to the hospital 5 d after symptoms onset (anosmia, dyspnea and cough). He was admitted to the ICU because of respiratory worsening 6 d after hospital admission. After 5 d with high flow nasal oxygen, respiratory worsening required mechanical ventilation. After 2 d of mechanical ventilation, the patient developed severe ARDS.

History of past illness

The patients' medical histories is presented in Table 1. The first patient was a 57-yearold female with a medical history of smoking and hypertension. The second patient was a 56-year-old female with a medical history of dyslipidemia and obesity (body mass index (BMI) = 39 kg/m^2). The third patient was a 53-year-old male with a history of obesity (BMI = 40 kg/m^2) and rheumatoid arthritis treated with steroids.

Personal and family history

The patients had no personal or family history.

Physical examination

Case 1: Prior to almitrine infusion, the plateau pressure was 28 cmH₂O and positive end expiratory pressure (PEEP) at 14 cmH₂O. Baseline pulmonary compliance was 32 mL/cmH₂O. Pulmonary artery catheter showed pulmonary vascular resistance at 5.9 Wood units and pulmonary artery occlusion pressure of 7 mmHg. Cardiac index (CI) was 2.6 L/min/m². Right ventricular (RV) fractional area change (FAC) was 45%. Speckle tracking based right ventricular two-dimensional strain was performed (Table 1 and Figure 1).

Case 2: Prior to almitrine infusion, the plateau pressure was 27 cmH₂O and PEEP at 14 cmH₂O. Baseline pulmonary compliance was 33 mL/cmH₂O. Pulmonary artery catheter showed pulmonary vascular resistance at 4.1 Wood units and pulmonary artery occlusion pressure of 9 mmHg. CI was 2.9 L/min/m². RV FAC was 42%.

Case 3: Prior to almitrine infusion, the plateau pressure was 29 cmH₂O and PEEP at 15 cmH₂O. Baseline pulmonary compliance was 31 mL/cmH₂O. Pulmonary artery catheter showed pulmonary vascular resistance at 3.3 Wood units and pulmonary artery occlusion pressure of 11 mmHg. CI was 2.9 L/min/m². RV FAC was 58%.

Laboratory examinations

Case 1: Prior to almitrine infusion, the PaO₂/FiO₂ ratio was 77 mmHg. Arterial blood gas sample showed PaCO₂ of 46.2 mmHg, pH at 7.4 and lactate at 1.8 mmol/L. Laboratory investigations revealed lymphopenia at 550/mm³ and high C reactive protein level at 65 mg/L.

Case 2: Prior to almitrine infusion, the PaO₂/FiO₂ ratio was 91 mmHg. Arterial blood gas sample showed PaCO₂ of 39.5 mmHg, pH at 7.4 and lactate at 1.9 mmol/L. Laboratory investigations revealed lymphopenia at 370/mm³ and high C reactive protein level at 95 mg/L.

Case 3: Prior to almitrine infusion, the PaO₂/FiO₂ ratio was 95 mmHg. Arterial blood gas sample showed PaCO₂ of 49 mmHg, pH at 7.3 and lactate at 1.4 mmol/L. Laboratory investigations did not reveal any other specificities.

Imaging examinations

Case 1: Chest computed tomography (CT) angiography showed ground-glass opacity with crazy paving and severe lobar involvement (> 75%). There was no pulmonary embolism.

Case 2: Chest CT angiography showed ground-glass opacity with crazy paving and moderate lobar involvement (50%-75%). There was no pulmonary embolism.

Case 3: Chest CT angiography showed ground-glass opacity with bilateral crazy paving, consolidation and limited lobar involvement (25%). There was no pulmonary embolism.



Huette P et al. Almitrine for COVID-19 critically ill patients

Table 1 Patients' characteristics prior and after almitrine infusion Variables Case 1 Case 2 Case 3 Age in yr 57 56 53 BMI in kg/m^2 39.0 40.1 38.9 Gender Female Female Male Medical history Smoking, hypertension, obesity Dyslipidemia, obesity Rheumatoid arthritis, obesity Medication use None Statin Steroids 5 7 Days from symptom onset to hospital 11 admission in d Days from hospital admission to ICU 2 6 6 admission in d High flow or low flow oxygen support 2 5 5 prior to mechanical ventilation in d 2 Mechanical ventilation prior to 2 1 almitrine infusion in d Chest CT scan GGO, crazy paving and severe GGO, crazy paving and moderate GGO, bilateral crazy paving, lobar involvement (> 75%), no lobar involvement (50%-75%), no consolidation, limited lobar pulmonary embolism pulmonary embolism involvement (25%), no pulmonary embolism Two sessions No Two sessions Respiratory management Prone positioning before almitrine Supine Supine Supine infusion/Position during almitrine infusion Hemodynamic parameters ICU admission HR as / min 66 115 61 SAP in mmHg/DAP in mmHg MAP 115/50 (71) 119/69 (85) 124/61 (82) in mmHg 90 90 SpO2, % Lactate in mmol/L 1.800 1.900 1.493 Norepinephrine infusion as µg × kg × 0.09 0.35 min SAPS II 68 40 56 SOFA 13 7 8 Respiratory parameters Baseline PaO₂/FiO₂ 77 91 95 PEEP in cmH₂O 15 14 14 Plateau pressure in cmH₂O 28 27 29 Compliance in mL/cmH2O 32 33 31 H1 PaO₂/FiO₂ 121 82 150 PEEP in cmH₂O 15 14 14 Plateau pressure in cmH2O 30 29 28 33 Compliance in mL/cmH₂O 29 28 H2 PaO₂/FiO₂ 163 330 135 PEEP in cmH₂O 14 14 15

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Baseline							
RV FAC, % 45 42 58							
RV outflow tract VTI in cm 19 13 19							
H2							
RV FAC, % 44 42 34							
RV outflow tract VTI in cm 16 15 24							
H12							
H12 RV FAC, % 48 34 42							

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Baseline						
RVGLS, %	13.5	25.3	14.8			
TMAD septal in mm	13.0	29.7	23.5			
H2						
RVGLS, %	13.3	24.7	22.7			
TMAD septal in mm	9.6	27.6	25.0			
H12						
RVGLS, %	16.9	25.0	18.7			
TMAD septal in mm	16	32	23			
ICU course						
Length of stay in d	30	32	31			
Mechanical ventilation duration in d	18	22	21			
Outcomes	Discharged from ICU	Discharged from ICU	Discharged from ICU			

BMI: Body mass index; CI: Cardiac index; CT: Computed tomography; DAP: Diastolic arterial pressure; FAC: Fractional area change; GGO: Ground-glass opacity; H1: 1 h after almitrine infusion; H2: 2 h after almitrine infusion; H12: 12 h after almitrine infusion; HR: Heart rate; ICU: Intensive care unit; MAP: Mean arterial pressure; NO: Nitric oxide; PAP: Pulmonary artery pressure; PAOP: Pulmonary artery occlusion pressure; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure; PVR: Pulmonary vascular resistance; RV: Right ventricle; RVGLS: Right ventricle global longitudinal strain; SAP: Systolic arterial pressure; SAPS II: Simplified acute physiology score; SOFA: Sepsis-related Organ Failure Assessment; STE: Speckle tracking echocardiography; TEE: Transesophageal echocardiography; TMAD: Tricuspid longitudinal annular displacement; VTI: Velocity time integral.

FINAL DIAGNOSIS

All three patients were admitted to the ICU for severe ARDS according to the Berlin definition with a PaO₂/FiO₂ ratio < 150. They were treated with protective ventilation (low tidal volume 6-7 mL/kg, PEEP for plateau pressure \leq 30 cmH₂O), neuromuscular blocking agents and inhaled nitric oxide (at 10 ppm). Despite medical management they presented persistent severe hypoxemia.

TREATMENT

The local institutional review board waived the need for written informed consent; data storage was authorized by national licensing authority (CNIL PI2020_843_0026). Patients and/or next of kin were informed of the study. We prospectively collected data from three consecutive patients with COVID-19 and severe ARDS who received almitrine infusion.

Study evaluation

Low dose of almitrine (Vectarion®; Servier, Suresnes, France) was started at an infusion rate of 4 μ g × kg × min⁻¹on a central line. The effect of almitrine infusion on respiratory parameters (blood gases, PaO₂/FiO₂ ratio, total respiratory system compliance) was evaluated. Pulmonary artery pressure (PAP), cardiac output and pulmonary vascular resistance (PVR) were monitored via a pulmonary artery catheter. RV FAC, RV global longitudinal strain and tricuspid longitudinal annular displacement were monitored via transesophageal echocardiography. Data were collected before and 1 h, 2 h and 12 h after almitrine infusion start.

Case 1: Almitrine infusion was started after 2 d of mechanical ventilation and sustained for 3 d.

Case 2: Almitrine was started at day 6 after ICU admission (5 d with high flow oxygen and 1 d under mechanical ventilation). Almitrine infusion was given for 3 d.

Case 3: Almitrine infusion was started after 2 d of mechanical ventilation. Almitrine infusion was given for 4 d.

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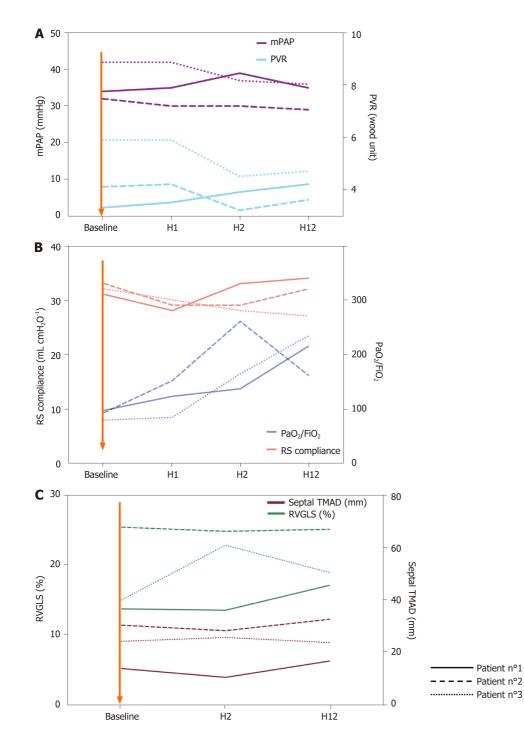


Figure 1 Evolution of pulmonary artery catheter, respiratory and echocardiographic parameters with almitrine infusion. A: Pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) during almitrine infusion; B: PaO2/FiO2 ratio and total respiratory system compliance (CRS) during almitrine infusion; C: Right ventricular fractional area change (FAC) and right ventricular (RV) global longitudinal strain (RVGLS) remained unchanged for patient 1 and patient 2 and improved for patient 3. Tricuspid longitudinal annular displacement (TMAD) remained unchanged for the three patients.

OUTCOME AND FOLLOW-UP

ICU course

The PaO_2/FiO_2 ratio and total respiratory system compliance during almitrine infusion are presented in Figure 1 and Table 1. For the three patients, PaO_2/FiO_2 ratio time-course showed a dramatic increase whereas total respiratory system compliance was unchanged. The three patients were discharged from the ICU. ICU length of stay for patient 1, patient 2 and patient 3 was 30 d, 32 d and 31 d, respectively. Weaning from mechanical ventilation was performed 13 d, 18 d and 15 d after almitrine infusion for patient 1, 2 and 3, respectively.

Safetv

Time-course of pulmonary artery catheter parameters and echocardiographic parameters during almitrine infusion are presented in Figure 1. PAP and PVR remained unchanged during almitrine infusion. Regarding RV function, RV FAC and RV global longitudinal strain remained unchanged for patient 1 and patient 2 and improved for patient 3. Tricuspid longitudinal annular displacement remained unchanged for the three patients. None of the patients needed extracorporeal membrane oxygenation therapy. Liver function test remained unchanged.

DISCUSSION

In this report, we found that almitrine infusion enhanced oxygenation of patients with severe COVID-19 related ARDS without any change in PAP and RV function. At baseline, the patients showed an increased PAP without pulmonary embolism and left ventricular dysfunction (normal pulmonary artery occlusion pressures and CI). Hence, we cannot discard the occurrence of at least a certain level of hypoxic pulmonary vasoconstriction that has been suggested by some authors[3].

In our patients, almitrine led to increased oxygenation without any changes in ventilatory parameters or right-side circulation. Hence, almitrine improved the ventilation/perfusion ratio by decreasing pulmonary flow. The lack of increase in PVR with almitrine is not in favor of an increase in hypoxic pulmonary vasoconstriction as encountered in typical ARDS. Recently, Ackermann et al[4] observed that the pulmonary histological pattern that distinguishes COVID-19 infected lungs from influenzae infected lung is the amount of new vessel growth in the COVID-19 lung. Moreover, Lang *et al*[1] studied lung perfusion by dual-energy chest CT scan for COVID-19 patients and found an increased perfusion of the lungs especially proximal to lung opacities. Increase of pulmonary vessels number is probably responsible of an intrapulmonary shunt with an increased ventilation/perfusion mismatch.

Almitrine acts as a selective pulmonary vessel vasoconstrictor that is able to decrease and redistribute pulmonary blood flow from shunt areas to pulmonary units with normal ventilation/pulmonary flow ratios[9]. We believe that the improvement in oxygenation with almitrine for our patients was related to a decrease in intrapulmonary shunt in both aerated and non-aerated lung regions^[2]. Inhaled nitric oxide is a selective pulmonary vasodilator, and intravenously administered almitrine is a selective pulmonary vasoconstrictor. The resulting effects of combining almitrine and inhaled nitric oxide are likely related to the respective vascular effect of each drug on aerated and non-aerated lung compartments and explain why additive respiratory effects were observed. Previous studies confirmed that when reinforcing hypoxic pulmonary vasoconstriction by small doses of almitrine, the nitric oxide-induced increase in arterial oxygenation can be markedly enhanced[10,11].

The major risk with short term use of almitrine is the increase of RV afterload by excessive vasoconstriction. Hence, we evaluated RV function with very sensitive and reproducible parameters: RV global longitudinal strain and tricuspid longitudinal annular displacement[12,13]. We found no deleterious effects on RV function, which was similar to previous studies on almitrine safety[14]. Recently, Barthélémy et al[6] tested almitrine for COVID-19 patients, but crucial data on RV function was not reported.

CONCLUSION

Despite a small sample size, almitrine seems to be effective and safe to enhance oxygenation for COVID-19 critically ill patients. Further controlled studies are required.

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