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INTERMEDIATE

CASE REPORT: CLINICAL CASE

Acute Cor Pulmonale in COVID-19-Related ARDS

Improvement With Almitrine Infusion

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ABSTRACT

Coronavirus disease-19 (COVID-19)-related severe acute respiratory distress syndrome can lead to acute cor pulmonale. We report a case of acute cor pulmonale secondary to severe COVID-19 acute respiratory distress syndrome diagnosed with transesophageal echocardiography. Almitrine infusion allowed rapid enhancement of right ventricular function as well as improvement in oxygenation. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:1311–4)

HISTORY OF PRESENTATION

A 57-year-old woman was admitted at the Amiens University Hospital intensive care unit for severe acute respiratory distress syndrome (ARDS) 12 days following onset of cough, dyspnea, and fever. Real-time reverse transcriptase polymerase chain reaction of nasopharyngeal swab was positive for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Chest computed tomography (CT) scan revealed peripheral ground glass-like opacities with superimposed interlobular and intralobular septal thickening (crazy paving). The patient's condition deteriorated rapidly, leading to mechanical ventilation with lung-protective settings, prone positioning, deep sedation, neuromuscular blockade, and inhaled nitric oxide at 10 ppm. Despite these measures, she remained hypoxemic with a partial pressure of oxygen (Pa_{O_2})-to-fraction of inspired oxygen (Fi_{O_2}) ratio of 70. After starting mechanical ventilation and sedation, mean arterial pressure dropped to 60 mm Hg. Norepinephrine was administered at the dose of 0.3 $\mu g/kg/min^{-1}$ to achieve a mean arterial pressure target higher than 65 mm Hg. Blood pressure rapidly reached 115/50 (71) mm Hg. For patients in severe ARDS associated with hemodynamic impairment, local guidelines recommend close monitoring with a pulmonary artery catheter and transesophageal echocardiography (TEE). A pulmonary artery catheter and TEE revealed acute cor pulmonale (ACP) with pulmonary hypertension.

LEARNING OBJECTIVES

- To diagnose ACP in patients with SARS-CoV-2-related ARDS.
- To appreciate potential role of almitrine in improving oxygenation and RV function.
- To understand SARS-CoV-2-related atypical type of ARDS.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

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ABBREVIATIONS AND ACRONYMS

ACE2 = angiotensin-converting enzyme 2

ACP = acute cor pulmonale

ARDS = acute respiratory distress syndrome

CI = cardiac index

COVID-19 = coronavirus disease-19

CT = computed tomography

Fio_2 = fraction of inspired oxygen

Pao_2 = partial pressure of oxygen

RV = right ventricle

RVSWI = right ventricular stroke work index

SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

TEE = transesophageal echocardiography

PAST MEDICAL HISTORY

Medical history included only an overweight with a body mass index of 38.9 kg/m^2.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included pulmonary embolism and right ventricular (RV) infarction, which were discounted later due to the CT pulmonary angiogram not showing pulmonary embolism and normal electrocardiography and normal high-sensitivity troponin. D-dimer was 3.69 μg/ml^{-1}.

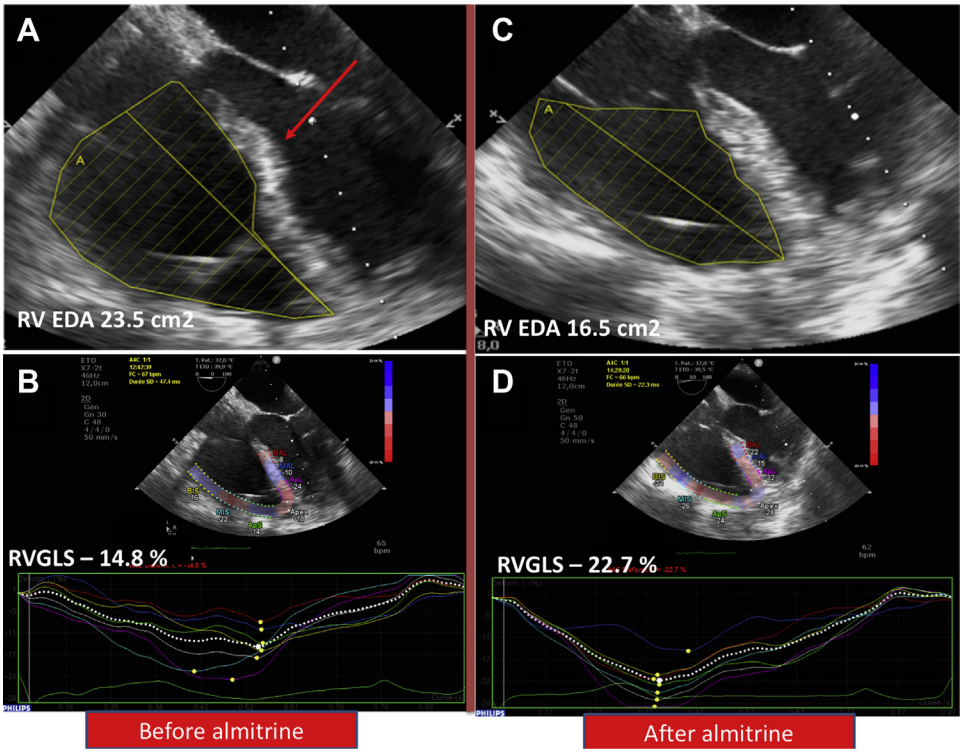
INVESTIGATIONS

Prior to commencing almitrine, arterial blood gas sample showed a Pao_2 of 63 mm Hg, $Paco_2$ of 46.6 mm Hg, pH at 7.4, Pao_2/Fio_2 ratio of 70, and lactate at 2.3 mmol/l^{-1}. Pulmonary artery catheter showed pulmonary artery pressure of 57/32 (42) mm Hg with pulmonary vascular resistance at 5.9 WU and pulmonary artery occlusion pressure of 7 mm Hg. RV stroke work index (RVSWI) was 19.7 g/m/beat/m^2 (normal range 8 to 10 g/m/beat/m^2). TEE showed an ACP: the RV-to-left ventricular area ratio was of 1:1 with septal dyskinesia (Figure 1A). In 2-dimensional conventional TEE, tricuspid annular plane systolic excursion was 22 mm, tricuspid lateral annulus systolic velocity (S'-wave) was 15.2 cm/s^{-1}, and RV fractional area change was 43%. Speckle tracking-based RV 2-dimensional strain was performed (Figure 1B). The RV global longitudinal strain was -14.8% and RV free wall longitudinal strain was -17.3% (RV global longitudinal strain normal value <-20%). Left ventricular ejection fraction was 65% without any valvular disease. Cardiac index (CI) was 2.6 l/min^{-1}/m^{-2}.

MANAGEMENT

Severe and prolonged hypoxemia can lead to organ dysfunction. Thus, the need for venovenous extracorporeal membrane oxygenation to improve

FIGURE 1 Transesophageal Echocardiography Before and After Almitrine Infusion



(A) Two-dimensional image before almitrine infusion showing dilated right ventricle (RV) with an RV-to-left ventricular area ratio of 1:1 with septal dyskinesia **(red arrow)**. **(B)** Speckle tracking-based RV 2-dimensional strain showing impaired RV global longitudinal strain (RVGLS) of -14.8% (normal value: <-20%). **(C)** Two-dimensional image after almitrine infusion showing RV-to-left ventricular area ratio of 0.75 and normal septal shape. **(D)** Speckle tracking-based RV 2-dimensional strain showing improvement of RVGLS to -22.7%. EDA = end-diastolic area.

oxygenation was considered for this patient with a very low Pao_2/Fio_2 ratio of 70. As inhibition of hypoxic vasoconstriction was considered as a key point to explain severe hypoxemia related to coronavirus disease-2019 (COVID-19), the decision was made to test almitrine treatment before starting extracorporeal membrane oxygenation (2). However, because almitrine may increase RV afterload in a patient who already has an ACP, close RV monitoring was performed. A low dose of almitrine was given at an infusion rate of 4 μg/kg/min via a central venous catheter. Complete hemodynamic, echocardiographic, and biological assessment was repeated at 1, 2, and 12 h following almitrine initiation (**Table 1**). TEE video loops before and after almitrine infusion are shown in Videos 1 and 2. Oxygenation improved significantly in the few hours following almitrine treatment (**Table 2**). TEE showed an improvement of RV function: RV dilatation decreased (ratio at 0.75) and septal dyskinesia disappeared (**Figure 1C**). Moreover, RV global longitudinal strain improved from -14.8% to -22.7% (**Figure 1D**). Twelve hours following almitrine infusion, RVSWI decreased from 19.7 to 17.5 g/m/beat/m^2.

TABLE 1 Pulmonary Artery Catheter Parameters Before and After Almitrine Infusion

	Before	H1	H2	H12
Mean PAP, mm Hg	42	42	37	36
Systolic PAP, mm Hg	57	65	52	50
PAOP, mm Hg	7	8	8	6
Diastolic PAP, mm Hg	32	29	30	28
CI, $l/min^{-1}/m^{-2}$	2.6	2.6	3.9	3
PVR, Wood units	5.9	5.9	3.4	4.5

CI = cardiac index; H1 = 1 h following almitrine infusion; H2 = 2 h following almitrine infusion; H12 = 12 h following almitrine infusion; PAOP = pulmonary arterial occlusion pressure; PAP = pulmonary artery pressure; PEEP = positive end-expiratory pressure; PVR = pulmonary vascular resistance.

DISCUSSION

The clinical spectrum of SARS-CoV-2-related cardiovascular complication includes myocarditis, pericarditis, vasoplegia, RV failure, and acute coronary syndromes (1,2).

In this case, we highlight the RV dysfunction related to SARS-CoV-2 infection. Pathophysiology of cardiovascular dysfunction related to SARS-CoV-2 remains unclear. One explanation is the recognition of human angiotensin-converting enzyme 2 (ACE2) by SARS-CoV-2. ACE2 is used by the virus as a functional receptor to enter the cell (3). Moreover, ACE2 receptor is not only present in lung alveolar cells but also in many extra pulmonary tissues especially heart, and vascular endothelium. Hence, direct viral effect on the heart and vessels may lead to RV dysfunction. Another explanation is the impact of ARDS and mechanical ventilation on the RV. ACP is a well-known complication of ARDS despite a protective ventilation, with an incidence of 25%. Hence, ACP may be related to a high driving pressure, leading to an increased RV afterload (4). Moreover, the patient was on norepinephrine, which may increase RV afterload. Another explanation is that hypoxia could lead to RV dysfunction in its own right (5).

SARS-CoV-2-related ARDS seems to be a nontypical ARDS, as several patients had a preserved lung mechanics with high compliance despite severe hypoxemia. Some authors have hypothesized that SARS-CoV-2-related hypoxemia is due the impairment of hypoxic pulmonary vasoconstriction and dysregulation of pulmonary blood flow, leading to an intrapulmonary shunt responsible for the severe hypoxemia (6). In a recently published report on a critically ill patient with SARS-CoV-2 infection, the authors used dual-energy chest CT. They found "considerable" pulmonary vessels dilatation and increased pulmonary blood flow surrounding areas of consolidation (7).

Almitrine, a selective pulmonary vessel vasoconstrictor, was shown to increase arterial oxygenation via redistribution of pulmonary blood flow from shunt areas to pulmonary units, with normal ventilation-to-perfusion ratio (8). Moreover, previous studies in the 1990s showed that at a low dose, the deleterious effect on pulmonary vascular resistance was negligible, especially when associated with nitric oxide (9). Hence, we hypothesized that almitrine use in the case of SARS-CoV-2 atypical ARDS might be useful.

In the present case, almitrine infusion was associated with RV function improvement and decrease in

TABLE 2 Respiratory Parameters Before and After Almitrine Infusion

	Before	H1	H2	H12
RR/min	30	30	30	30
PEEP, cm H_2O	12	12	12	12
Tidal volume, ml	420	420	420	420
Plateau pressure, cm H_2O	31	30	29	28
Respiratory system compliance, $ml/cm\ H_2O^{-1}$)	22	23	24	26
Driving pressure	19	18	18	18
Pao_2, mm Hg	63	67	130	170
Fio_2	90	80	60	60
Pao_2/Fio_2 ratio	70	84	216	283

Fio_2 = fraction of inspired oxygen; Pao_2 = partial pressure of oxygen; RR = respiratory rate; other abbreviations as in Table 1.

pulmonary vascular resistance. This is probably due not only to a better oxygenation, but also to a better distribution of pulmonary vascular flow to aerated lung areas. Before almitrine infusion, we observed a high RVSWI with a normal-to-low range of CI, suggesting a hemodynamic disconnection between the RV and left ventricle. The reduction in RV afterload by almitrine infusion resulted in an improvement in this disconnection (decreased RVSWI and improved CI).

As almitrine infusion could induce reversible lactic acidosis and hepatic dysfunction (10), careful monitoring of lactate and screening test for hepatic function were performed. We did not observe those side effects.

To our knowledge, this is first report of almitrine use for SARS-CoV-2-related ARDS showing an improvement in oxygenation. Nevertheless, monitoring of pulmonary artery pressure and RV function are important for safe use of almitrine. Before clinical use, well-conducted studies with sufficient sample sizes are needed to demonstrate the efficacy of almitrine in SARS-CoV-2-associated severe ARDS. A randomized controlled trial is underway to address this issue and will investigate the efficacy of intravenous almitrine in reducing the need for mechanical ventilation in patients with hypoxemic acute respiratory failure due to COVID-19-related pneumonia (NCT04357457).

FOLLOW-UP

Almitrine was administered to the patient for 4 days, resulting in consistent improvement in oxygenation and ventilator parameters. RV function remained stable. Weaning from mechanical ventilation occurred on day 16. The patient was discharged from the intensive care unit on day 26.

CONCLUSIONS

ACP may occur in patients suffering from SARS-CoV-2-related ARDS. Echocardiography is the main tool to diagnose ACP in this context. In the present case, almitrine infusion was effective in improving oxygenation and RV function.

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REFERENCES

1. Creel-Bulos C, Hockstein M, Amin N, Melhem S, Truong A, Sharifpour M. Acute cor pulmonale in critically ill patients with COVID-19. N Engl J Med 2020;382:e70.

2. Augoustides JG. Cardiovascular consequences and considerations of coronavirus infection – perspectives for the cardiothoracic anesthesiologist and intensivist during the coronavirus crisis. J Cardiothorac Vasc Anesth 2020;34:1713–6.

3. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94. e00127-20.

4. Mekontso Dessap A, Boissier F, Charron C, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. Intensive Care Med 2016;42:862–70.

5. Netzer NC, Strohl KP, Högel J, Gatterer H, Schilz R. Right ventricle dimensions and function in response to acute hypoxia in healthy human subjects. Acta Physiol (Oxf) 2017;219: 478–85.

6. Gattinoni L, Coppola S, Cressoni M, Busana M, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;201: 1299–300.

7. 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 [E-pub ahead of print].

8. Roch A, Hraiech S, Dizier S, Papazian L. Pharmacological interventions in acute respiratory distress syndrome. Ann Intensive Care 2013; 3:20.

9. Gallart L, Lu Q, Puybasset L, Umamaheswara Rao GS, Coriat P, Rouby JJ. Intravenous almitrine combined with inhaled nitric oxide for acute respiratory distress syndrome. The NO Almitrine Study Group. Am J Respir Crit Care Med 1998;158: 1770–7.

10. B'chir A, Mebazaa A, Losser MR, Romieu M, Payen D. Intravenous almitrine bismesylate reversibly induces lactic acidosis and hepatic dysfunction in patients with acute lung injury. Anesthesiology 1998;89:823–30.

KEY WORDS acute cor pulmonale, almitrine, ARDS, COVID-19, SARS-CoV-2

APPENDIX For supplemental videos, please see the online version of this paper.