Annals of Clinical Case Reports

Case Series
Published: 19 Jan, 2021

Two Severe COVID-19 Cases of Successful Withdrawal from Mechanical Ventilatory Support Using Continuous Intravenous Morphine Sulfate

*Daiki Morikawa[1], Ayu Minoura[1], Goji Shimizu[1], Nobuhiko Shimozawa[1], Kenichirou Morisawa[1], Toru Yoshida[1], Lonny Ashworth[2] and Shigeki Fujitani[1]**

[1]Department of Emergency and Critical Care Medicine, St. Marianna University School of Medicine, Japan

[2]Department of Respiratory Care, Boise State University, USA

Abstract

Background: COVID-19 infection can develop into Acute Respiratory Distress Syndrome (ARDS). When using low tidal volume strategy, patients with COVID-19 ARDS have demonstrated a strong inspiratory effort. Morphine sulfate (morphine) is an effective and safe therapy for severe dyspnea in advanced lung disease. It is unclear whether morphine is effective for the acute phase of critically ill COVID-19 ARDS patients. We used continuous intravenous morphine for severe COVID-19 ARDS patients to ameliorate breathing effort and facilitate withdrawal of ventilator support.

Case Presentation: Case A: A 63-year-old male was admitted and COVID-19 Polymerase Chain Reaction (PCR) was positive. His respiratory status worsened leading to moderate ARDS, prompting oral intubation. Deterioration of his respiratory status necessitated the need for Veno-Venous Extracorporeal Membrane Oxygenation (V-V ECMO).

Case B: A 54-year-old male was admitted and COVID-19 PCR was positive. His respiratory status worsened leading to ARDS, necessitating oral intubation.

In both cases, we were unable to normalize a strong inspiratory effort despite increasing dosage of fentanyl, midazolam and propofol. We switched from these analgesics and sedative agents to morphine, leading to a reduction in the inspiratory effort. In both cases, respiratory status improved slowly.

Conclusion: Continuous intravenous morphine has the possibility of suppressing extreme inspiratory effort in ventilated COVID-19 ARDS patients, while still maintaining consciousness. This may prevent patient self-inflicted lung injury, which may be caused by high driving pressure. The pharmacologic benefits of morphine use for patients with a strong inspiratory effort from acute respiratory failure in COVID-19 ARDS patients should be considered.

OPEN ACCESS

Correspondence:
Shigeki Fujitani, Department of Emergency and Critical Care Medicine, St. Marianna University School of Medicine, 2-16-1,Sugao, Miyamae-ku, Kawasaki, Kanagawa, 2168511, Japan, Tel: +81-44-977-8111; E-mail: shigekifujitani@marianna-u.ac.jp

Received Date: *14 Dec 2020*
Accepted Date: *12 Jan 2021*
Published Date: *19 Jan 2021*

Citation:
Morikawa D, Minoura A, Shimizu G, Shimozawa N, Morisawa K, Yoshida T, et al. Two Severe COVID-19 Cases of Successful Withdrawal from Mechanical Ventilatory Support Using Continuous Intravenous Morphine Sulfate. Ann Clin Case Rep. 2021; 6: 1906.

ISSN: 2474-1655

Copyright *© 2021 Shigeki Fujitani. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

Introduction

Most cases of Coronavirus Disease 2019 or COVID-19 infection developed Acute Respiratory Distress Syndrome (ARDS). A key therapeutic strategy frequently used for treatment of COVID-19 ARDS, is lung protective ventilation, an approach that entails low tidal volumes and permissive hypercapnia. Unfortunately, low tidal volume mechanical ventilation may easily cause an increased "breathing effort". In the Seattle and Boston cohorts, prior to mechanical intubation, dyspnea was a very common presenting symptom in severe COVID-19 infection on presentation in 88% and 91% of patients, respectively [1].

Opioid are the drugs of choice for treating dyspnea refractory to disease-specific therapy in advanced disease [2]. Opiates have been shown to reduce sensations of breathlessness in patients with a variety of advanced lung diseases, including Chronic Obstructive Pulmonary Disease (COPD) and lung cancer [3]. Continuous intravenous morphine is an effective and safe therapy, without any serious adverse events, for patients with severe dyspnea in terminal, acute exacerbation of end-stage interstitial pneumonia [4]. It is unclear whether morphine is effective for the acute phase of critically ill ARDS patients and COVID-19 patients. We used continuous intravenous morphine for severe COVID-19 ARDS patients to ameliorate breathing effort and facilitate the withdrawal of ventilatory support.

Case Presentation

Case A

A 63-year-old male with past medical history of hypertension and obstructive sleep apnea syndrome on Non-Invasive Positive Pressure Ventilation (NIPPV), initially presented to an outside clinic due to fever and cough. A week after the clinic visit, he was admitted to another hospital due to shortness of breath. Initial workup demonstrated bilateral infiltrates on chest imaging and COVID-19 Polymerase Chain Reaction (PCR) was positive. His respiratory status worsened leading to moderate ARDS with partial pressure of arterial oxygen divided by fractional concentration of inspired oxygen (PaO_2/FiO_2) of 115 Torr, which needed prompted intubation. Three days later his respiratory status continued to worsen with PaO_2/FiO_2 ratio of 89 Torr and was transferred to our tertiary care facility.

He was managed with low tidal volume and high peep as standard ARDS management, muscle relaxation therapy and prone position therapy. The patient was treated with Favipiravir and prednisolone. The patient's respiratory status continued to deteriorate and, despite optimal ventilator settings, the PaO_2/FiO_2 did not exceed 80 Torr. Therefore, Veno-Venous Extracorporeal Membrane Oxygenation (V-V ECMO) was initiated on Hospital Day (HD) 8. Oxygenation improved gradually, but we were unable to normalize low minute ventilation, strong inspiratory effort and tachypnea despite increasing dosage of fentanyl, midazolam and propofol. His tidal volume was approximately 100 ml (Predicted Body Weight (PBW) 1.78 ml/kg) on the following ventilator settings: Pressure-targeted, Assist-Control (PC AC), FiO_2 0.4, inspiratory pressure 28 cmH2O, Positive End-Expiratory Pressure (PEEP) 14 cmH2O, peak airway pressure 42 cmH2O and respiratory frequency 38 per minute. We switched to a continuous intravenous of morphine from other analgesics and sedative agents, leading to ameliorate low minute ventilation. A tracheotomy was performed on HD26. V-V ECMO was successfully discontinued on HD36 and his respiratory status improved slowly. On HD55, he was taken off the ventilator, and his condition remained stable.

Case B

A 54-year-old male, with no significant past medical history, presented to our hospital due to difficulty breathing. Ten days prior to his visit, he initially presented to an outside clinic due to fever and cough. Initial workup at our hospital demonstrated bilateral infiltrates on chest imaging and COVID-19 PCR was positive. His respiratory status worsened leading to moderate ARDS with PaO_2/FiO_2 ratio of 115 Torr, prompting intubation. He was managed with low tidal volume and high peep as standard ARDS management, muscle relaxation therapy and prone position therapy. The patient was treated with Favipiravir and prednisolone. The patient's respiratory status continued to deteriorate despite optimal ventilator settings. It was felt that his respiratory condition needed V-V ECMO but we were not able to place V-V ECMO due to a right internal jugular venous thrombus. However, oxygenation improved gradually but we were unable to normalize low ventilation, strong respiratory effort and tachypnea despite increasing dosage of fentanyl, midazolam and propofol. His tidal volume was about 243 ml (PBW 3.57 ml/kg) with the following ventilator settings: PC AC, inspiratory pressure 17 cmH2O, PEEP 11 cmH2O, respiratory frequency 25 per minute, FiO_2

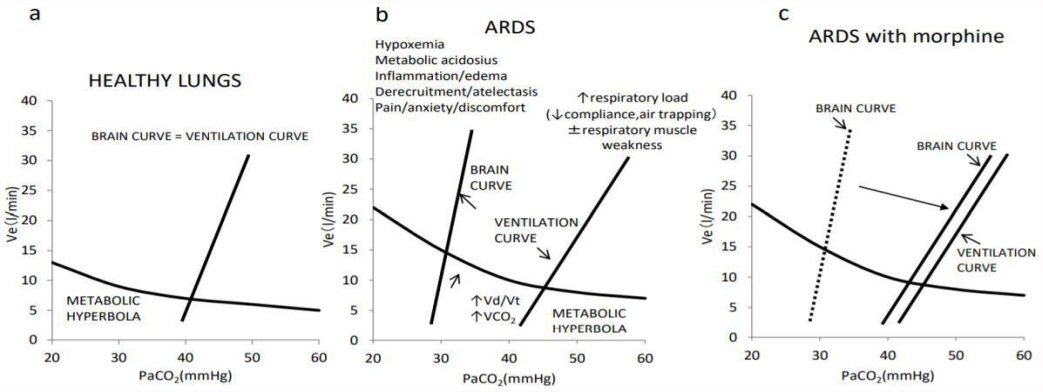


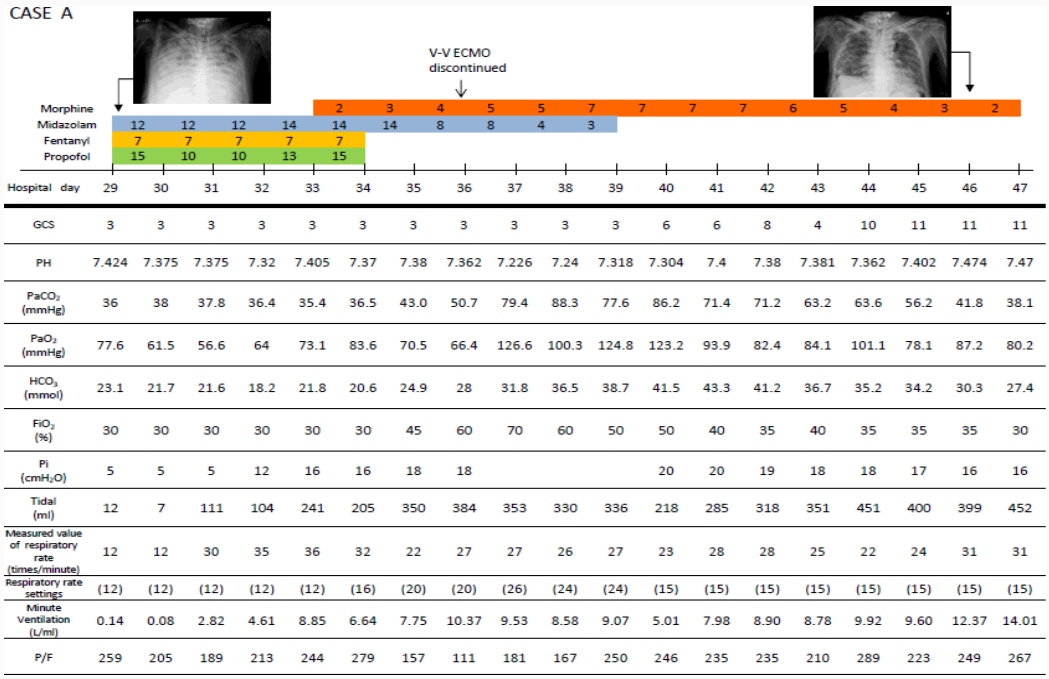
Figure 1: Metabolic hyperbola, brain and ventilation curves in health, ARDS and ARDS with morphine.

Metabolic hyperbola, brain and ventilation curves in health, ARDS and ARDS with morphine [6]. The metabolic hyperbola is the relationship between ventilation and the resultant $PaCO_2$ for a given level of metabolic CO_2 production and dead space. Increased dead space or CO_2 production will shift the hyperbola up. The ventilation curve describes the actual effect of changing $PaCO_2$ on resultant minute ventilation. ARDS can shift the ventilation curve to the right (lower minute ventilation despite higher $PaCO_2$) due to increased respiratory load and muscle weakness. Finally, the brain curve (also known as the "controller curve", "CO_2 sensitivity curve" or "ventilation gain curve") describes the minute ventilation theoretically requested by the neural respiratory drive for a given $PaCO_2$. During ARDS, this is shifted to the left (higher minute ventilation despite lower $PaCO_2$) due to multiple concomitant pathologic conditions, including acidosis, inflammation and others.

a. In health, brain and ventilation curves overlap and the ventilation response (i.e. the change in minute ventilation induced by a change in $PaCO_2$) reflects the neural respiratory drive. The metabolic hyperbola is obtained assuming a dead space of 0.3 and a metabolic CO_2 production (VCO_2) of 200 ml/min. Brain and ventilation curves are overlapping and are calculated assuming a $PaCO_2$ of 39.5 mmHg, a minute ventilation of 6.5 l/min, linearly increasing to 30 l/min at a $PaCO_2$ of 49 mmHg.

b. In ARDS, the metabolic hyperbola is shifted upward due to an increase of dead space (0.5) and VCO_2 (250 ml/min). The listed factors cause the brain and ventilation curves to be shifted in opposite directions and diverge. Please, note that a single ARDS patient will be characterized by both curves at the same time: the brain curve will correspond to the theoretical ventilation/$PaCO_2$ correlation desired by the neural respiratory drive, while the ventilation curve will be the actual ventilation/$PaCO_2$ correlation measured by spirometer and blood gas analysis. This divergence can cause higher driving pressure. Brain and ventilation curves are calculated assuming a minute ventilation of 6.5 l/min at 28 mmHg $PaCO_2$ (increasing to 30 l/min at 33 mmHg $PaCO_2$) and a minute ventilation of 5 l/min at 40 mmHg $PaCO_2$ (increasing to 25 l/min at 52 mmHg $PaCO_2$), respectively.

c. In ARDS with morphine, brain curve will be shifted to ventilation curve due to morphine effect. Morphine depresses respiratory drive by a direct effect on the responsiveness of brainstem respiratory centers to hypoxia and hypercapnia. Gap reduction between brain curve and ventilation curve can decrease higher driving pressure.



Hospital day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47
GCS	3	3	3	3	3	3	3	3	3	3	3	6	6	8	4	10	11	11	11
PH	7.424	7.375	7.375	7.32	7.405	7.37	7.38	7.362	7.226	7.24	7.318	7.304	7.4	7.38	7.381	7.362	7.402	7.474	7.47
$PaCO_2$ (mmHg)	36	38	37.8	36.4	35.4	36.5	43.0	50.7	79.4	88.3	77.6	86.2	71.4	71.2	63.2	63.6	56.2	41.8	38.1
PaO_2 (mmHg)	77.6	61.5	56.6	64	73.1	83.6	70.5	66.4	126.6	100.3	124.8	123.2	93.9	82.4	84.1	101.1	78.1	87.2	80.2
HCO_3 (mmol)	23.1	21.7	21.6	18.2	21.8	20.6	24.9	28	31.8	36.5	38.7	41.5	43.3	41.2	36.7	35.2	34.2	30.3	27.4
FiO_2 (%)	30	30	30	30	30	30	45	60	70	60	50	50	40	35	40	35	35	35	30
Pi (cmH_2O)	5	5	5	12	16	16	18	18				20	20	19	18	18	17	16	16
Tidal (ml)	12	7	111	104	241	205	350	384	353	330	336	218	285	318	351	451	400	399	452
Measured value of respiratory rate (times/minute)	12	12	30	35	36	32	22	27	27	26	27	23	28	28	25	22	24	31	31
Respiratory rate settings	(12)	(12)	(12)	(12)	(12)	(16)	(20)	(20)	(26)	(24)	(24)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)
Minute Ventilation (L/ml)	0.14	0.08	2.82	4.61	8.85	6.64	7.75	10.37	9.53	8.58	9.07	5.01	7.98	8.90	8.78	9.92	9.60	12.37	14.01
P/F	259	205	189	213	244	279	157	111	181	167	250	246	235	235	210	289	223	249	267

Figure 2: Clinical course of Case A related to morphine sulfate treatment.
GCS: Glasgow Coma Scale; Pi: Inspiratory Pressure; TV: Tidal Volume; P/F: PaO_2/FiO_2; V-V ECMO: Veno-Venous Extracorporeal Membrane Oxygenation
Morphine was started on HD 33. $PaCO_2$ was increased to 88.3 mmHg on HD 38 from 35.4 mmHg on HD 33 and pH was 7.24 on HD 38. Bicarbonate increased to 43.3 mmol on HD 41 from 21.8 mmol on HD 33. The pH on HD 41 was 7.4 and normalized. Tidal volume was resolved to 451 ml on HD 44 from 241 ml on HD 33. GCS was 3 before morphine use, which was supposed to be the effect of the use of sedation. GCS was gradually resolved to 11 after discontinuation of sedation.

Table 1: Transpulmonary pressure of Case A.

	Before initiation of morphine	After initiation of morphine	
Hospital day	32	42	48
Airway pressure (mmHg)	24/12	32/9	21/3
Esophageal pressure (mmHg)	1/20	15/8	15/1
Inspiratory Transpulmonary pressure (mmHg)	23	17	6
Expiratory Transpulmonary pressure (mmHg)	8	1	2
ΔTranspulmonary pressure (mmHg)	31	16	4

ΔTranspulmonary pressure (driving pressure) = Inspiratory Transpulmonary pressure
(Inspiratory Airway pressure – Inspiratory Esophageal pressure) – Expiratory Transpulmonary pressure (Expiratory Airway pressure – Expiratory Esophageal pressure).
ΔTranspulmonary pressure was resolved from 31 cm H_2O before morphine use to 4 cm H_2O after morphine use.

Table 2: Transpulmonary pressure of Case B.

	Before initiation of morphine	After initiation of morphine	
Hospital day	32	36	50
Airway pressure (mmHg)	27/8	19/4	19/8
Esophageal pressure (mmHg)	-1.5/9	-7/4	8/3
Inspiratory Transpulmonary pressure (mmHg)	-28.5	26	11
Expiratory Transpulmonary pressure (mmHg)	-1	0	5
ΔTranspulmonary pressure (mmHg)	29.5	26	6

ΔTranspulmonary pressure (driving pressure) = Inspiratory Transpulmonary pressure
(Inspiratory Airway pressure – Inspiratory Esophageal pressure) – Expiratory Transpulmonary pressure (Expiratory Airway pressure – Expiratory Esophageal pressure).
ΔTranspulmonary pressure was resolved from 29.5 cm H_2O before morphine use to 6 cm H_2O after morphine use.

0.7. He was switched to continuous intravenous morphine from other analgesics and sedative agents, leading to ameliorate low minute ventilation. A tracheotomy was performed on HD 52. His respiratory status improved slowly, and on HD 67, he was successfully withdrawn from the ventilator in stable condition.

Discussion

We herein report two cases of severe COVID-19 ARDS patients, treated with continuous intravenous morphine, who recovered from a difficult period of withdrawal of ventilatory support.

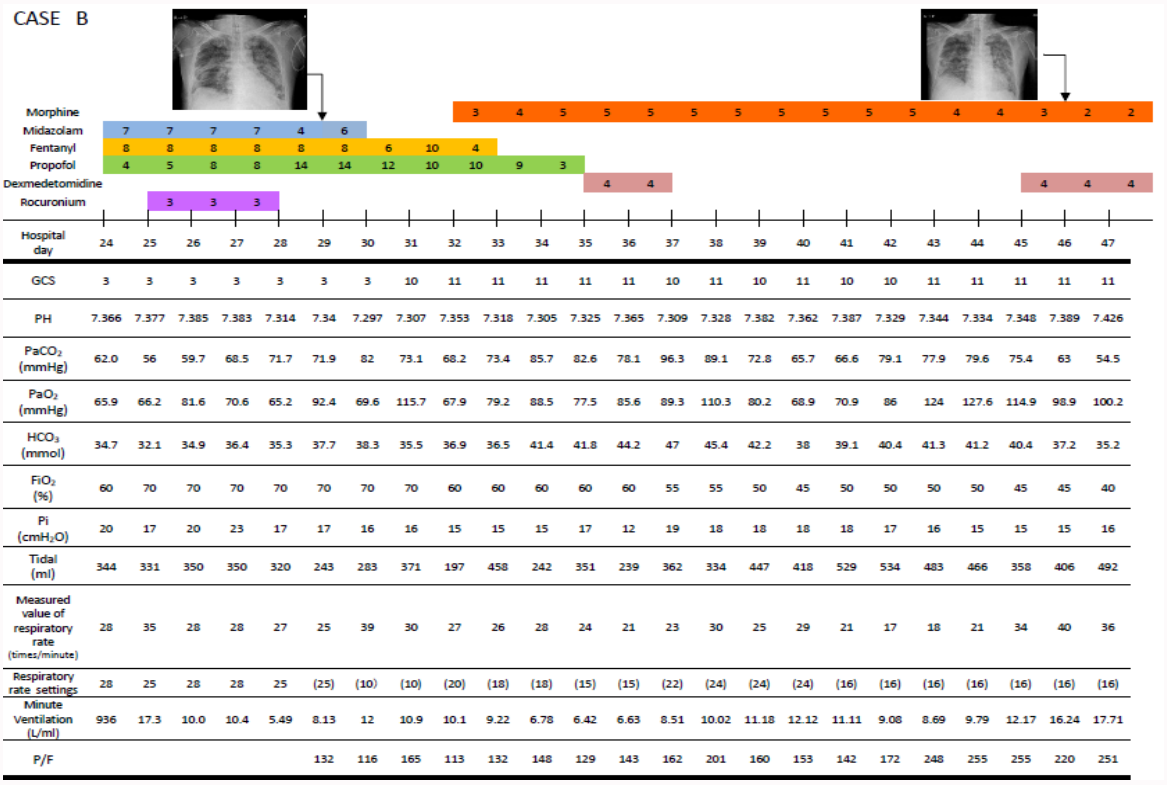


Figure 3: Clinical course of Case B related to morphine sulfate treatment.
GCS: Glasgow Coma Scale; Pi: Inspiratory Pressure; TV: Tidal Volume; P/F: PaO_2/FiO_2
Morphine was started from HD 32. $PaCO_2$ was increased to 96.3 mmHg on HD 37 from 68.2 mmHg on HD 32 and pH was 7.42 on HD 47. Bicarbonate increased to 41.3 mmol on HD 43 from 36.9 mmol on HD 32. The pH on HD 43 was normalized to 7.42. Tidal volume was resolved to 492 ml on HD 47 from 197 ml on HD 32. GCS was 3 before morphine use, which was supposed to be the effect of the use of sedation. GCS was gradually resolved to 11 after discontinuation of sedation.

Table 3: Clinical characteristics of Case A and Case B.

	Case A	Case B
Age	63	54
Sex	Male	Male
Past medical history	Hypertension OSAS	-
Current or past smoker L/D on admission	+	-
White blood cell count (×10^3/μL)	12,100	9,200
Lymphocyte count (×10^9/L)	774	782
Prothrombin time (%)	85	65
Lactate dehydrogenase (U/L)	588	718
Period from symptom onset to hospitalization (days)	10	12
Period from hospitalization to intubation (days)	1	1
Period from hospitalization to V-V ECMO installment (days)	9	-
SOFA on admission	5	3
SAPS II on admission	55	38
APACHE II on admission	24	8
Intubation period during hospitalization (days)	55	67
V-VVECMO installment period (days)	28	-
Duration of morphine sulfate (days)	14	36
Antiviral treatment for COVID-19	Favipiravir	Favipiravir
Use of steroid	prednisolone	prednisolone

OSAS: Obstructive Sleep Apnea Syndrome; L/D: Laboratory Data; VV-ECMO: Veno-Venous Extracorporeal Membrane Oxygenation; SOFA: Sequential Organ Failure Assessment Score; SAPS: Simplified Acute Physiology Score; APACHE: Acute Physiology and Chronic Health Evaluation, COVID-19: Coronavirus Disease 2019

The increased ventilatory drive, combined with constrained tidal volume as inspiratory capacity is diminished, intensifies the sensation of air hunger [5]. Excessive effort to breathe due to high respiratory drive may lead to Patient Self-Inflicted Lung Injury (P-SILI), even in the absence of mechanical ventilation [6].

Due to less effectiveness for air hunger and masked symptoms [1], other pharmacological interventions should be used for air hunger instead of neuromuscular blockade. Benzodiazepines are not effective for dyspnea [7]. Propofol is commonly used to sedate ventilated patients, but cannot maintain consciousness. Dexmedetomidine does not modify respiratory rate and gas exchanges in ICU patients [8].

Opioid are effective in relieving dyspnea by one or more different mechanisms [9]: Decreasing respiratory drive (associated decreased corollary discharge); altering central perception; altering activity of peripheral opioid receptors located in the lung and decreasing anxiety. With the decrease in respiratory output, there is a presumed corresponding decrease in corollary discharge from the brainstem to perceptual areas in the cerebral cortex [10]. In physiological studies, the response of the subject to raised $PaCO_2$ level is assessed by measuring the increase in minute ventilation [6] (Figure 1). In health, the brain curve coincides with the ventilation curve (Figure 1a). In ARDS, the position of the brain curve and the ventilation curve are altered in opposite directions (Figure 1b). This divergence can cause higher driving pressure. In ARDS with morphine, the brain curve will be shifted to the ventilation curve due to effect of morphine (Figure 1c). Gap reduction between brain curve and ventilation curve can decrease higher driving pressure.

Morphine sulfate has been used frequently for the treatment of refractory dyspnea. In opiate-naive healthy subjects, 5 mg of intravenous morphine provided profound relief of experimentally induced air hunger, and studies of opiate-relief of clinical dyspnea using even low doses of opioid similarly show relief from breathlessness [11].

In the two cases described, benzodiazepines, propofol, Dexmedetomidine and fentanyl were likely to have a less effect on a strong inspiratory effort. Neuromuscular blockade did reduce the tachypnea, but it could not be continued due to the need for increased analgesics and sedation, and side effects like disability of expectoration. Instead, continuous intravenous morphine was introduced, and it was expected to prolong the withdrawal of ventilatory support.

Possible mechanisms for effect of morphine for these two cases were that morphine acts through depression of ventilatory drive and ascending perceptual pathways, and suppressed tachypnea. In ARDS patients, low-volume lung-protective ventilation decreases tidal stretch receptor input and often increases respiratory drive (*via* elevated $PaCO_2$) [1]. Usually, central chemoreceptors, located in the ventral surface of the medulla oblongata, regulate the ventilatory response to stabilize CO_2; an increase in $PaCO_2$, by decreasing the pH of cerebrospinal fluid, leads to a linear increase in minute ventilation until steady state is achieved after a few minutes [12]. Therefore, usually the tendency of an elevated $PaCO_2$ was compensated by tachypnea, but in these two cases suppressed tachypnea caused hypercapnia due to decompensation by opiates (Figure 2 and 3). Hypercapnia caused respiratory acidemia and increased bicarbonate by compensation of renal function (Figure 2 and 3). Increased bicarbonate normalized pH (Figure 2 and 3). Although acidemia had caused hyperventilation, normalized pH decreased the need for ventilation and decreased breathing effort and tachypnea. Decreased breathing effort prevented further lung injury, decreased tachypnea and enabled deep breathing. Decreased tachypnea and profound breathing increased tidal volume (Figure 2 and 3). Finally increased tidal volume resulted in successful ventilator weaning. In other words, morphine prevented P-SILI, which was caused by high driving pressure.

In both cases (Figure 2 and 3), Glasgow Coma Scale (GCS) was gradually resolved after discontinuation of sedation. That improvement was because morphine use enabled a reduction in the other sedatives and analgesics and improved the patients' level of consciousness. In both cases (Figure 2 and 3), the spontaneous breathing was suppressed before the use of morphine because of the use of sedation and analgesics but patients had spontaneous breathing later after the morphine use owing to the discontinuation of other sedation and analgesics. Spontaneous breathing may offer multiple physiologic benefits in these patients, including decreased need for sedation, preserved diaphragm activity and improved cardiovascular function [6].

Transpulmonary pressure is useful to evaluate driving pressure. In both cases, driving pressure was suppressed after morphine use (Table 1 and 2).

In Case A, morphine had been used for 14 days and in Case B, it had been used for 36 days and successfully discontinued without any significant side effects or withdrawal symptoms in either case (Table 3).

Continuous intravenous morphine was able to decrease breathing effort and increase tidal volume while maintaining consciousness and spontaneous breathing.

Conclusion

Continuous intravenous morphine has the possibility of suppressing extreme breathing effort in ventilated COVID-19 ARDS patients. Morphine prevented P-SILI, which was caused by high driving pressure, while maintaining consciousness and spontaneous breathing. The pharmacologic benefits of morphine use for difficult to wean patients in COVID-19 ARDS patients, should be considered.

References

1. Worsham CM, Banzett RB, Schwartzstein RM. Air hunger and psychological trauma in ventilated COVID-19 patients: An urgent problem. Ann Am Thorac Soc. 2020;17(8):926-7.
2. Gallagher R. The use of opioids for dyspnea in advanced disease. CMAJ. 2011;183(10):1170.
3. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med. 2012;185(4):435-52.
4. Takeyasu M, Miyamoto A, Kato D, Takahashi Y, Ogawa K, Murase K, et al. Continuous intravenous morphine infusion for severe dyspnea in terminally ill interstitial pneumonia patients. Intern Med. 2016;55(7):725-9.
5. Soffler MI, Rose A, Hayes MM, Banzett R, Schwartzstein RM. Treatment of acute dyspnea with morphine to avert respiratory failure. Ann Am Thorac Soc. 2017;14(4):584-8.
6. Spinelli E, Mauri T, Beitler JR, Pesenti A, Brodie D. Respiratory drive in the acute respiratory distress syndrome: pathophysiology, monitoring, and therapeutic interventions. Intensive Care Med. 2020;46(4):606-18.
7. Simon ST, Higginson IJ, Booth S, Harding R, Weingärtner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant

and non-malignant diseases in adults. Cochrane Database Syst Rev. 2016;10(10):Cd007354.

8. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. Crit care. 2000;4(5):302-8.
9. Mahler DA, Selecky PA, Harrod CG, Benditt JO, Carrieri-Kohlman V, Curtis JR, et al. American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. Chest. 2010;137(3):674-91.
10. Mahler DA. Opioids for refractory dyspnea. Expert Rev Respir Med. 2013;7(2):123-34.
11. Ekström M, Bajwah S, Bland JM, Currow DC, Hussain J, Johnson MJ. One evidence base; three stories: Do opioids relieve chronic breathlessness? Thorax. 2018;73(1):88-90.
12. Smith CA, Rodman JR, Chenuel BJ, Henderson KS, Dempsey JA. Response time and sensitivity of the ventilatory response to CO2 in unanesthetized intact dogs: Central *vs.* peripheral chemoreceptors. J appl physiol (1985). 2006;100(1):13-9.