CASE SERIES

Systemic Oxygen Utilization in Severe COVID-19 Respiratory Failure: A Case Series

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Highlights

- There are limited data on pulse oximetry oxygen saturation (SpO_2) targets in patients with COVID-19 respiratory failure
- Hyperoxia is common in critically ill patients and associated with worse outcomes
- Markers of systemic oxygen (O_2) utilization suggest that hyperoxia occurs in this disease
- Adjusting SpO_2 targets to systemic O_2 utilization may limit hyperoxia
- Limiting hyperoxia in COVID-19 respiratory failure may improve outcomes

Abstract

Background: Management of hypoxemia in patients with severe COVID-19 respiratory failure is based on the guideline recommendations for specific SpO_2 targets. However, limited data exist on systemic O_2 utilization. The objective of this study was to examine systemic O_2 utilization in a case series of patients with this disease.

Patients and methods: Between March 24, and April 9, 2020, 8 patients intubated for severe COVID-19 respiratory failure had near-simultaneous drawing of arterial blood gas (ABG), central venous blood gas (cVBG), and central venous oxygen saturation ($ScvO_2$) at a mean of 6.1 days into hospitalization. Three patients were managed with indirect cardiac output (CO) monitoring by FloTrac sensor and Vigileo monitor (Edwards Lifesciences, Irvine, CA). The oxygen extraction index (OEI; SaO_2-$ScvO_2/SaO_2$) and oxygen extraction fraction (OEF; CaO_2-$CvO_2/CaO_2 \times 100$) were calculated. Values for hyperoxia ($ScvO_2 \geq 90\%$), normoxia ($ScvO_2$ 71–89%), and hypoxia ($ScvO_2 \leq 70\%$) were based on the literature. Mean values were calculated.

Results: The mean partial pressure of oxygen (PaO_2) was 102 with a mean fraction of inspired O_2 (FiO_2) of 44%. One patient was hyperoxic with a reduced OEI (17%). Five patients were normoxic, but 2 had a reduced OEF (mean 15.9%). Two patients were hypoxic but had increased systemic O_2 utilization based on OEF or OEI.

Conclusion: In select patients with severe COVID-19 respiratory failure, O_2 delivery (DO_2) was found to exceed O_2 utilization. SpO_2 targets based on systemic O_2 utilization may help in reducing oxygen toxicity, especially in the absence of anaerobic metabolism. Further data are needed on the prevalence of systemic O_2 utilization in COVID-19.

Keywords: Acute respiratory distress syndrome, COVID-19, Hyperoxia, Hypoxia.

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23722

Introduction

Progressive hypoxemia remains a prominent feature in patients infected with COVID-19. In severe COVID-19 acute respiratory distress syndrome (ARDS), there are limited data on optimal SpO_2 targets.[1] Liberal use of O_2 therapy has been associated with increased mortality.[2] In contrast, reduced O_2 delivery (DO_2) may lead to anaerobic metabolism and cell death. Since a major focus in the management of COVID-19 ARDS patients is the treatment of hypoxemia, optimal SpO_2 targets may be best titrated towards systemic O_2 utilization. However, there are minimal data on systemic O_2 utilization in patients with severe COVID-19 respiratory failure.

Central venous O_2 saturation ($ScvO_2$) has been used as a surrogate marker for O_2 consumption (VO_2).[3] $ScvO_2$ measurements of hyperoxia ($ScvO_2 \geq 90\%$) and hypoxia ($ScvO_2 \leq 70\%$) have both been associated with increased mortality in patients with sepsis suggesting the importance of optimal O_2 balance.[4] In addition, derivation of the oxygen extraction index (OEI; SaO_2-$ScvO_2/SaO_2$) and oxygen extraction fraction (OEF; CaO_2-$CvO_2/CaO_2 \times 100$) can provide additional data on systemic O_2 utilization. Along with markers of anaerobic metabolism, $ScvO_2$, OEI, and OEF can provide a more complete picture of O_2 metabolism in critically ill patients. In this study, we examine systemic O_2 utilization in a case series of patients with severe COVID-19 respiratory failure.

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How to cite this article: Garg RK, Kimbrough T, Lodhi W, DaSilva I. Systemic Oxygen Utilization in Severe COVID-19 Respiratory Failure: A Case Series. Indian J Crit Care Med 2021;25(2):215–218.

Source of support: Nil

Conflict of interest: None

Material And Methods

This study was approved by the Rush University Medical Center (RUMC) institutional review board and ethics standards committee to perform this case series. Between March 24, and April 9, 2020, 8 patients with COVID-19 were managed in the intensive care unit (ICU) at RUMC. Sociodemographic, relevant past medical history, hemoglobin level, and ejection fraction (EF; %) on 2D echocardiography were collected for each patient. Patients were managed according to a set institutional protocol based on the guideline recommendations at that time.[1] Target SpO_2 was maintained at 92–96%. Mean arterial pressure was maintained greater than 65 mm Hg with norepinephrine as the first-line agent. Sedation was titrated to maintain adequate patient–ventilator synchrony with daily sedation holidays when possible. Neuromuscular blockade with cisatracurium was initiated in select patients who remained asynchronous with the ventilator despite adequate sedation. The amount of vasopressors and sedation was abstracted from each patient's flow sheet at the time of blood gas measurements. The presence or absence of continuous neuromuscular blockade was also recorded.

During these patients' hospitalization, ABGs were obtained for lactic acid, PaO_2, partial pressure CO_2 ($PaCO_2$), and SaO_2. Near-simultaneous cVBG was obtained to assess central venous partial pressure O_2 ($PcvO_2$), central venous partial pressure CO_2 ($PcvCO_2$), and $ScvO_2$. Per the clinician's discretion, 3 patients were placed on the FloTrac sensor and Vigileo monitor (Edwards Lifesciences, Irvine, CA) for indirect CO monitoring. This was the maximum device available in our ICU. CO data were used in the derivation of the OEF according to Fick equation. The distance from the tip of the internal jugular central venous line to the cavoatrial junction was measured based on the chest X-ray performed on the day closest to the blood gas drawings. All patients had their central venous catheter placed at or below 15 cm suggesting close approximation (~1%) between the $ScvO_2$ and mixed venous O_2 (SvO_2).[5] However, since pulmonary artery catheters were not utilized, SvO_2 was calculated to be 5% less than $ScvO_2$ based on the current guideline recommendations for septic shock.[6] $ScvO_2$ levels were categorized according to the outcome data as follows: hypoxia (≤70%), normoxia (71–89%), and hyperoxia (≥90%). The derived SvO_2 was used in the calculation of the OEI and OEF. Markers of anaerobic metabolism were assessed in each patient by examining arterial lactate levels and venoarterial carbon dioxide (CO_2) difference ($PcvCO_2$-$PaCO_2$).[7] Mean levels were calculated for each variable.

Results

Table 1 highlights the sociodemographic data and clinical data collected based on the patient's hospital day. The average age of the cohort was 55.3 years, 63% were men, and 50% were Hispanic. A majority of patients had a premorbid diagnosis of hypertension (75%) and diabetes (87.5%). All patients met the criteria for severe ARDS (PaO_2/FiO_2 < 100) on presentation and were intubated for hypoxemic respiratory failure. Mean hemoglobin was 10.6 mg/dL for the cohort. All patients had a normal EF on presentation. None of the patients were on more than one vasopressor for blood pressure maintenance. One patient (#5) was receiving continuous neuromuscular blockade with cisatracurium whereas the remainder were on sedative regimens (Table 1) for patient–ventilator synchrony. The distance of the tip of the central lines from the cavoatrial junction is outlined in Table 1. None of the patients were

Table 1: Sociodemographic and clinical data of cohort

Patient #	*#1*	*#2*	*#3*	*#4*	*#5*	*#6*	*#7*	*#8*
Days of MV	8	6	1	14	2	4	8	4
Gender	M	M	M	M	M	F	M	F
Race	White	Hispanic	Hispanic	Hispanic	Black	Black	Hispanic	Black
Age (years)	34	56	64	57	60	58	48	65
DM	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
HTN	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Hemoglobin (g/dL)	13.9	11.5	13.4	7.1	7.1	11.3	8.4	11.8
EF (%)	65	N/A	55	65–70	60–65	60–65	70–75	65–70
CO (L/min)	4.0	N/A	6.5	N/A	N/A	N/A	N/A	4.5
CV distance (cm)	−3.7 cm	−3.8 cm	−5.1 cm	0 cm	3.5 cm	−2.8 cm	−5.2 cm	−1.2 cm
Paralytics	No	No	No	No	Yes	No	No	No
Sedation	4 mg/hr HME	5 mg/hr ME 4 mg/hr MDZ	175 µg/hr FEN 50 µg/kg/hr PRF	0.6 µg/kg/hr DEX	250 µg/hr FEN 5 mg/hr MDZ	4 mg/hr HME 6 mg/hr MDZ	4 mg/hr HME 4 mg/hr MDZ	3 mg/hr HME 15 µg/kg/hr PRF
Norepinephrine (µg/min)	None	2	22.5	2	10	5	None	3

Abbreviations: N/A, not available; MV, mechanical ventilation; EF, ejection fraction; CO, cardiac output; CV distance, distance of central venous catheter from cavoatrial junction; DM, diabetes mellitus; HTN, hypertension; HME, hydroxymorphone; ME, morphine; MDZ, midazolam; FEN, fentanyl; PRF, propofol; DEX, dexamedetomidine

Table 2: Arterial and central venous blood gas data

Patient #	*#1*	*#2*	*#3*	*#4*	*#5*	*#6*	*#7*	*#8*	*Mean*
pH	7.44	7.42	7.34	7.45	7.44	7.35	7.39	7.41	7.41
HCO_3^- (mmol/L)	21	25	20	26	25	25	25	17	23
FiO_2 (%)	60	40	40	40	70	40	40	40	46
SpO_2 (%)	93	95	97	99	94	93	98	96	96
PaO_2 (mm Hg)	94	98	104	98	62	141	123	94	102
$PaCO_2$ (mm Hg)	35	42	37	38	38	46	42	35	39
SaO_2 (%)	96.6	96.1	97.2	96.3	89.4	98.4	98.5	95.7	96.0
$PcvO_2$ (mm Hg)	41	46	55	48	43	108	40	50	53.9
$PcvCO_2$ (mm Hg)	41	47	40	46	42	46	48	38	43.5

Abbreviations: HCO_3^-, serum bicarbonate; FiO_2, fraction of inspired O_2; SpO_2, pulse oximetry; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of CO_2; SaO_2, oxygen saturation; $PcvO_2$, partial pressure of central venous O_2; $PcvCO_2$, partial pressure of central venous CO_2

Table 3: Markers of oxygen utilization and anaerobic metabolism

Patient #	*#1*	*#2*	*#3*	*#4*	*#5*	*#6*	*#7*	*#8*	*Mean*
Systemic O_2 utilization									
$ScvO_2$ (%)	69.5	75.3	83.2	72.6	71.3	94.2	68.2	80.2	76.8
Estimated SvO_2 (%)	64.5	70.3	78.2	67.6	66.3	63.2	63.2	75.2	71.8
OEI	33.2	26.8	19.5	29.8	25.8	9.3	35.8	21.4	22.5
OEF	28.5	N/A	14.8	N/A	N/A	N/A	N/A	17	20.1
Anaerobic metabolism									
Arterial lactate (mmol/dL)	1.9	1.0	1.4	1.1	0.8	1.4	1.1	NR	1.2
Delta PCO_2	6	5	3	4	4	0	0	NR	1.1

Abbreviations and reference ranges: OEI, oxygen extraction index (ref: 20–25%); OEF, oxygen extraction fraction (ref: 22–30%); Arterial lactate (ref: >2 mmol/L); Delta PCO_2 (ref: >6 mm Hg)

suspected of being treated for cytokine release syndrome at the time of measurement.

Blood gas data for each patient are presented in Table 2. The mean days of mechanical ventilation before the ABG and cVBG were obtained was 6.1 days. At the time of sampling, the mean FiO_2 was 46%, SpO_2 was 96%, and PaO_2 was 102 mm Hg. The mean pH, pCO_2, and serum bicarbonate were within the reference range. Parameters for systemic O_2 utilization are presented in Table 3. The mean $ScvO_2$ was 76.8%. One patient (#6) was hyperoxic with a $ScvO_2$ = 94.2% and OEI below the reference range (9.3%). Two patients (#1 and #7) were hypoxic but had an elevated OEI (33.2 and 35.8%, respectively). Patient #1 also had an OEF at the upper limits of normal. The remaining patients were normoxic, but 2 patients had a reduced OEF (mean 15.9%). Their corresponding OEI were also reduced. None of the patients had evidence of anaerobic metabolism based on the arterial lactate levels or venoarterial CO_2 difference.

Discussion

Our results suggest that systemic O_2 utilization is abnormal in patients with severe COVID-19 respiratory failure when assessed using $ScvO_2$, OEI, and OEF. In one patient who was hyperoxic, the combination of elevated $ScvO_2$ and reduced OEI suggests excessive DO_2. In two patients who were hypoxic, the absence of anaerobic metabolism and elevated OEI suggests adequate DO_2. Although theoretically one could target a lower $ScvO_2$ to reduce DO_2, this may place the patient at risk for a metabolic crisis. However, in 2 normoxic patients, the presence of reduced OEF also suggests a relatively excessive DO_2, especially given the absence of anaerobic metabolism. These patients may potentially tolerate lower systemic DO_2. These data suggest that select patients with severe COVID-19 respiratory failure are at risk for DO_2 exceeding systemic O_2 utilization. This may place these patients at risk for O_2 toxicity and worse outcomes.

Current guidelines for oxygenation levels (SpO_2 > 88% or PaO_2 > 55) in patients with ARDS do not account for systemic O_2 levels.[8] In patients with COVID-19 respiratory failure, current guidelines recommend a SpO_2 goal of 92–96%.[1] Despite evidence that prolonged hyperoxia has been associated with an acute lung injury, excessive DO_2 remains common in mechanically ventilated patients.[9–11] In a recent meta-analysis, both time and duration of PaO_2 elevation has been associated with increased mortality in critically ill patients regardless of the presenting disease.[12] Therefore, matching DO_2 to O_2 utilization may be a significant factor in improving the outcomes in patients with a primary acute lung injury, such as that seen with COVID-19. Tolerance of lower SpO_2 targets in COVID-19 patients based on systemic O_2 utilization may allow for less-aggressive interventions to maintain SpO_2. Furthermore, in patients with "happy hypoxemia," tolerance of lower SpO_2 goals based on systemic O_2 utilization may be beneficial in reassessing intubation and preventing the secondary complications of mechanical ventilation.[13]

Outside the lungs, there is growing pathologic evidence of multiorgan involvement from severe acute respiratory syndrome coronavirus 2 (SARS-CoV2).[14] While ongoing research suggests that SARS-CoV2 may affect host mitochondrial function, there are limited data on its final influence on cellular metabolism.[15] Impairments in cellular function may lead to reduced VO_2 without necessarily causing anaerobic metabolism, especially in a deeply

sedated patient with reduced O_2 demands. Similar pathophysiology has been described in other models of sepsis with inhibition of the mitochondrial respiratory chain complex.[16] Therefore, by assessing the trends in VO_2 indirectly through $ScvO_2$, OEF, and OEI, we may be able to limit DO_2 and potentially delay the toxic effects of excessive systemic O_2.

Our results are preliminary with several limitations. Firstly, it involves a small cohort of heterogeneous patients from a single center. However, our data are only hypothesis generating and warrant further examination in a larger cohort of patients. Secondly, derivation of SvO_2 from $ScvO_2$ remains controversial and may have influenced our derivation of OEI and OEF.[17] $ScvO_2$ and SvO_2 are useful measurements of tissue oxygen extraction per physiologic principles.[17] While SvO_2 is considered more accurate than $ScvO_2$ given its anatomic location, the simplicity of measuring $ScvO_2$ from a properly placed central line provides the greatest advantage in critically ill patients. Finally, we do not have longitudinal data on systemic O_2 utilization to assess whether our results are consistent over time. The inability to perform repeated interval or continuous $ScvO_2$ monitoring would have been ideal in strengthening our results.

Conclusion

While only hypothesis generating, our preliminary data suggest that hyperoxia occurs in a subset of patients with severe COVID-19 respiratory failure. Given the association of worse outcomes with hyperoxia, $ScvO_2$, OEF, and OEI may be the useful parameters in optimizing DO_2. Further prospective data are needed on optimal systemic O_2 targets in patients with this deadly disease.

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