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Personalized Evaluation of Oxygen and Carbon Dioxide Exchange in COVID-19 Patients with Regard to Energy Homeostasis

Authors: Bayram Yilmaz[1,*], Sibel Temur[2], Sina Ercan[3], Seha Akduman[4], Ecem Gücü[5], Cihan Suleyman Erdogan[1], Ayberk Yenikale[4] and Mustafa Ozilgen[6]

Affiliations:

[1]Yeditepe University, Faculty of Medicine, Department of Physiology, Istanbul, 34755, Turkey

[2]Yeditepe University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Istanbul, 34755, Turkey

[3]Yeditepe University, Faculty of Medicine, Department of Thoracic Surgery, Istanbul, 34755, Turkey

[4]Yeditepe University, Faculty of Medicine, Department of Pulmonology, Istanbul, 34755, Turkey

[5] Yeditepe University, Faculty of Engineering, Department of Biomedical Engineering, Istanbul, 34755, Turkey

[6]Yeditepe University, Faculty of Engineering, Department of Food Engineering, Istanbul, 34755, Turkey

*** Correspondence to:** Prof. Dr. Bayram Yilmaz

Address: Yeditepe University, Faculty of Medicine, Department of Physiology, Kayisdagi Cad., 34755, Istanbul, Turkey

e-mail: byilmaz@yeditepe.edu.tr

Phone: +90 216 578 06 75

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Abstract

The COVID-19 does not proceed the same way in every patient. It may interfere with both oxygen (O_2) and carbon dioxide (CO_2) exchange in the alveoli; therefore, prevent ATP generation; subsequently, restrict energy supply for the life processes of the patient. Data sets representing the course of the COVID-19 in four patients, where the disease followed dissimilar paths were reassessed after the end of the treatment, by focusing on the respiratory and metabolic energy related parameters (FiO_2, PaO_2, SaO_2, $PaCO_2$) and the other parameters such as HCO_3, lactate, body temperature, C-reactive protein (CRP) and blood urea nitrogen levels. The valuable treatment data pertinent to each individual showed that each of them needed a personal treatment method. Group based statistical analyses may cause loss of the valuable medical information, if some of the dissimilar treatment details is considered as outliers. NIH has very recently reported that, there is no sufficient data yet to recommend either for or against the use of extracorporeal membrane oxygenation (ECMO) in the treatment of the COVID-19 patients. However, the results of this study suggest that ECMO may be useful for removal of the CO_2 from some of the COVID-19 patients; therefore, will be helpful if used in their treatment.

Keywords

COVID-19; ECMO; Energy metabolism; Extracorporeal methods; Oxygen and carbon dioxide exchange; Pneumonia

- Clinical Trial Registration clinical trial registration numbers of each patient: 503716, 348701, 79444, 499839

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INTRODUCTION

COVID-19 does not proceed the same way in every patient (Gusev, et al., 2021). At its initial stages a patient may suffer from a fever, cough, shortness of breath or trouble breathing, fatigue, chills, sometimes with shaking, body aches, headache, and a sore throat, congestion or a runny nose, loss of taste and smell, nausea or vomiting and diarrhea. More than 8 in 10 cases are mild and the symptoms may end within a few days (Shah, et al., 2020, WHO, 2020). On the other hand, 13.8% of the cases were severe, with dyspnea and pneumonia. In addition, 4.7% of the cases were critical and the symptoms included respiratory failure, septic shock and multi-organ failure, and about 2% of reported cases were fatal (WHO, 2020) (**Figure 1**). For some people infection may get more severe. About 5 to 8 days after the beginning of the symptoms, they have shortness of breath (known as dyspnea) and the acute respiratory distress syndrome (ARDS) begins. The end results of COVID-19 mechanisms interfere with oxygen (O_2) and carbon dioxide (CO_2) exchange in the alveoli; therefore, prevent ATP generation; subsequently, restrict energy supply for the life processes of the patient (Abassi, et al., 2020). Allocation of the energy of the nutrients for the physiological functions such as cardiovascular, nervous, endocrine, reproductive, gastrointestinal, and renal systems has been previously reported (Kutlu, et al., 2010, Marazuela, et al., 2020, Semerciöz, et al., 2020). Human body is a highly aerobic; therefore, sufficient O_2 needs to be provided to tissues to meet their demand (Gherardi, et al., 2020, Kabakus, et al., 2002, Kutlu, et al., 2004). In cells, about 10% of the ATP is produced in the cytoplasm via anaerobic metabolism, and the remaining 90% is produced in the mitochondria via aerobic metabolism (Genc, et al., 2013, Genc, et al., 2013, Nelson and Cox, 2017). In COVID-19 patients, due to the inefficient O_2 uptake,

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energy supply efficiency of the mitochondria decreases (Ozilgen and Yilmaz, 2020, Yilmaz, et al., 2020). COVID-19 causes inflammation in the pulmonary tissue (Dhont, et al., 2020) that results in reduced O_2 and CO_2 exchange through the respiratory membrane; therefore, prevents aerobic metabolism of the patients to run at full capacity. ARDS can cause increased breathing and heart rate, dizziness and sweating. It can damage the tissues and capillary blood vessels in the alveoli. Inflammatory process involving lung tissue reduces O_2 and CO_2 exchange in the alveoli (**Figure 2**). Thus, the patients suffer from the consequences of the lack of energy supply to the tissues (Yilmaz, et al., 2020). This is accompanied with failure of aerobic respiration, which supports production of more than 90 % of the ATP in the body (**Figure 3**). That means that the blood may not supply the organs and the patients may start experience liver or kidney damage and heart problems. There may be dangerous blood clots in the legs, lungs and arteries of the patients and some of these clots may cause a stroke. Cytokines are small pro-inflammatory signaling proteins within the range of 5-20 kDa of mass. They normally serve as a part of the immune response of a body to infection. Their uncontrolled release in very large quantities is called a cytokine storm or hyper-cytokinemia. In some diseases, including COVID-19 diseases, in the case of extreme level of inflammation, hyper-cytokinemia may lead to multisystem organ failure and death (Liu, et al., 2016, Wong, et al., 2017).

In case of restricted O_2 supply, lactic acid may accumulate in the tissues, and experienced as pain by the patients (Lesnak and Sluka, 2019). P_{O2} and P_{CO2} and lactate levels in the blood of the patients are among the parameters monitored in intensive care units (ICU). In the present study, wellbeing and recovery of the patients were assessed with a mathematical model based on these parameters. Partial pressure of the atmospheric O_2 is

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approximately 159 mmHg which decreases to 149 mmHg when it is warmed and humidified in the upper respiratory tract upon inhalation (Hall and Hall, 2020, Leiby, et al., 2020, Teppema and Dahan, 2010). Under physiological conditions, alveolar PO_2 is 104 mmHg, and vapor pressure is approximately 47 mmHg. In the brain, PO_2 may range from 20-25 mmHg at rest and low altitude and reach up to 48 mmHg at high altitudes or intense physical activity; P_{O2} may range from 50-55 mmHg in the liver and 7.5 to 31 mmHg in the muscle tissue (Ortiz-Prado, et al., 2019).

COVID-19, as explained here does not proceed the same way in every patient. The critically diseased patients, who are central to this study constitute approximately 4.7% of the total cases. They were critically ill and with symptoms including respiratory failure, septic shock and multi-organ failure, and about 2% of the total reported cases ended with death (WHO, 2020) (**Figure 1**). Trancossi et al. (Trancossi, et al., 2021) anticipated that studies on heat and mass transfer and thermodynamics, may help to prevent spread of Coronaviruses. Odish et al. (Odish, et al., 2021) argued that from April 2020 to January 2021, mobile ECMO was provided to 22 patients in 13 facilities across four southern California counties. The survival to hospital discharge of patients with COVID-19 who received mobile extracorporeal membrane oxygenation (ECMO) was 52.4% (11 of 21) compared with 45.2% (14 of 31) for similar patients cannulated in-house. No significant patient or transportation complications occurred during mobile ECMO. Neither the ECMO nor transport teams experienced unprotected exposures to or infections with severe ARDS. In the present study we analyzed the physiological measurements of four dissimilar patients and hypothesize that, after following the O_2 and the CO_2 partial

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pressures in the circulatory systems of the patients, medical practitioners may decide to use ECMO, without need for statistical support for the benefit of the treatment method.

MATERIAL & METHODS

In the present study 4 patients, with whom the COVID-19 has followed a significantly different path were selected retrospectively to analyze respiratory and metabolic energy related parameters (FiO_2 (%), PaO_2 (mmHg), SaO_2 (%), $PaCO_2$ (mmHg), HCO_3 (mmol/L), Lactate (mmol/L), enhancement of the mitochondrial energy in the ICU (%)), body temperature, C-reactive protein (CRP) and blood urea nitrogen (mg/dL) levels in four dissimilar patients treated for COVID-19 at Yeditepe University Kozyatagi Hospital in Istanbul, Turkey. The treatment protocols employed at the Yeditepe University Hospital were coordinated with those employed worldwide.

The present study was carried out with the data collected with four patients at the Yeditepe University Kozyatagi Hospital in Istanbul, Turkey. The patients, when admitted to the hospital were interviewed first about their medical history, and then by referring to the e-nabiz data base of the Ministry of Health, it was checked if there was anything else needed to be considered in their treatment. Their APACHE, Glasgow Coma and sofa scores were determined immediately at the admission to the hospital and then updated every day. In the data sheets of each patient the age, gender, height and weight, complaints at the admission to the hospital, his/her drug use history and previous surgeries were recorded. Physiological parameters, including, but not limited with arterial partial pressures of O_2 (PaO_2) and CO_2 ($PaCO_2$); O_2 saturation in the arteries (SaO_2) and additionally H_2CO_3, blood urea and lactate levels, hemoglobin, white blood cell, lymphocyte, carbon reactive protein, blood urea, nitrogen, creatine, sodium, potassium

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and albumin levels are measured daily. These measurements were repeated more than once, when needed. Summary of the variation of the daily-measured physiological parameters are presented in patients are summarized in Tables 1-4 for each patient. The other physiological parameters are referred to support the discussion, when needed. Liquid balance, including uptake, release and retention, and also nutrient supply data were recorded daily. Some of the cases, observed with the patients who stayed in the ICU for a very short period were referred to as "*mild*"; on the other hand, there were more serious cases, where the patients had pneumonia and stayed in the ICU up to 47 days. CRP is an annular ring-shaped, pentameric protein found in blood plasma, its circulating concentration rises in response to inflammation (Sproston and Ashworth, 2018). When metabolism of a patient is highjacked by a disease, healthy tissue is degraded and converted into a diseased tissue (Ongel, et al., 2020). CRP may increase in this process; therefore, the CRP was regarded as a measure of the inflammation. Ethical approval and institutional permission were obtained from the Ministry of Health of Turkey and Yeditepe University Medical Directorate, respectively, for this retrospective study. In our studies, Drager, Model Evita 2 Dura ventilator (US), non-rebreather face O_2 mask with reservoir (Plasti-Med, Istanbul) and GGN (Turkey), nasal high flow device (Model HF 2920) is used.

Patients:

Patient 1 was a 47-year-old male (weight: 116 kg and height: 1.78 m) who had type II diabetes mellitus and hypertension. He had no previous history of medical treatment. He was admitted to the hospital with high fever and fatigue and transferred to the intensive care unit on the fourth day of admission because of dyspnea, hypoxemia, and

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hemodynamic instability. His Acute Physiology and Chronic Health Evaluation (APACHE) score was 13, Sofa score was 2, and his Glasgow Coma Score was 15. He recovered after staying 15 days in ICU and then transferred to the ward.

Patient 2 was a 47-year-old female (Wight: 125 kg and height 1.65 m) who had a history of hypertension, rheumatoid arthritis, asthma and gastric ulcer in her medical history. She had also undergone right ovarian cyst rupture, cholecystectomy, and knee arthroscopy and umbilical hernia surgeries. She was admitted to the ICU in the 5th day of her hospitalization because of hypoxemia and dyspnea. Her APACHE score was 11, Sofa score was 2 and her Glasgow Coma Score was 15. She stayed in the ICU for 3 days, then transferred back to the ward.

Patient 3 was a 50-year-old male (Weight: 80 kg and height: 1.69 m) who had a history of hypertension. He did not have a genetically inherited disease in the family, no history of previous surgery. He was admitted to the hospital with difficulty in breathing and transferred to ICU after four days of admission. His APACHE score was 20, Sofa score was 2, his Glasgow Coma Score was 15. He developed pneumonia and stayed in the ICU for 38 days before he was and transferred to the ward.

Patient 4 was a 48-year-old male (Weight: 81 kg and height: 1.69 m) who had type II diabetes mellitus, chronic obstructive pulmonary disease (COPD) and cardiac failure. His APACHE score was 5, Sofa score was 2, and his Glasgow Coma Score was 15. He was admitted to the hospital with difficulty in breathing and transferred to ICU immediately. He stayed in the ICU for 47 days, and then transferred to the ward.

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Patients, who need respiratory support, were applied O_2 according to SaO_2 value with invasive or noninvasive mechanical ventilation in the ICU. The treatment protocols were based on clinical and laboratory evaluations. Observing a major positive change in the wellbeing of each patient. Energy requirements of all patients were supplied with enteral nutrition as 30 kcal/kg/day with Novasource or Novasource Diabetic® (Nestle, Turkey).

Mortality expectation of the patients was evaluated based on their APACHE and Sofa scores. The APACHE score describes the worst physiological derangement noted during the first 24 hours after admission to an intensive care unit and gives an estimate of the hospital survival as based on organ insufficiency. The maximum theoretically possible APACHE score is 71, although it does not exceed 55 in practice (Zimmerman and Kramer, 2008). The sequential organ failure assessment, SOFA score, is used to track a patient's status during the stay in an intensive care unit to determine the level or rate of failure of his/her organ functions based on cardiovascular, coagulation, hepatic, neurological, renal and respiratory parameters (Marshall, 2001). The Glasgow Coma Scale is a neurological scale which aims to give a reliable and objective way of recording the state of a person's consciousness for initial as well as subsequent assessments (Teasdale and Jennett, 1974). While Glasgow Coma Scale of 8 – 9 refers to a severe state, a score equal or larger than 13 describes a mild deterioration.

RESULTS and DISCUSSION

Arterial P_{O2} indicates how efficiently the patient's body is exchanging O_2 and CO_2. When the arterial blood P_{O2} decreases down to 95% or lower than that of its normal value, it may indicate a deterioration of the exchange of O_2 and in COVID-19 patient. Arterial P_{O2} values presented in Table 1 indicate such a deterioration at the first day, when Patient 1

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was admitted to the ICU. Table 1 also shows that the patient responded to the mechanical ventilation treatment positively and the arterial blood saturation reached to normal levels in the following days. Appearance of 0.5 to 2.7 mmol/L of lactate in the blood of the Patient 1 reflects the inefficiency of O_2 transport. Blood urea nitrogen level of a healthy person ranges between 6 to 20 mg/dL, however, this measurement in patient 1 varied between 14 to 50 mg/dL, approximately 2.5 folds of those of the healthy people (Table 1). Yilmaz et al. (Yilmaz, et al., 2020) and Özilgen and Yilmaz (Ozilgen and Yilmaz, 2020) argued that when a disease initiates changes in the metabolism of a patient, the energy needed for its expansion is initially obtained from the nutrients. In later stages of the disease, the body starts catabolism and utilizes its own resources for energy and building blocks. Increase of the lactic acid level in blood may be an outcome of the catabolic stage.

O_2 supply to a patient during the treatment in ICU seems like manipulating the parameters of equation (1):

$$N_{O2} = K_{O2} (P_{O2,\ alveoli} - P_{O2,\ artery}) \qquad \text{(eq. 1)}$$

where, N_{O2} is the O2 transport through the alveoli, K_{O2} is the mass transfer coefficient, $P_{O2,\ alveoli}$ and $P_{O2,\ artery}$ are the partial pressures of O_2 in the alveoli and the artery. The term ($P_{O2,\ alveoli}$-$P_{O2,\ artery}$) is the driving force of the O_2 transport from the alveoli to the pulmonary artery. Equation (1) is empirical in nature, and there are numerous alternatives of it available in the literature (Ozilgen, 2011). The empirical equation presented here rather than the more sophisticated expressions in the literature to describe O_2 transport in the lungs is preferred, not to lose the focus of the treatment in mathematical complexity.

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Inflammation of the respiratory membrane creates an additional barrier to O_2 transport, as a result parameter K_{O2} decreases. In order to maintain N_{O2} constant the driving force ($P_{O2,\ alveoli}$-$P_{O2,\ artery}$) needs to be increased and this is the major strategy of the treatment in the ICU. Prior to the admission to the ICU, the patient was subjected to Fi_{O2} of 20.9%. Table 1 explains in detail, how the driving force ($P_{O2,\ alveoli}$-$P_{O2,\ artery}$) was increased in the ICU by manipulating $P_{O2,\ alveoli}$.

The slowest step of a process is called the "*rate determining step*", the overall rate of a process cannot be faster than that of the rate determining step (Ozilgen, 2011). In the COVID-19, inspired air passes through the upper respiratory tract with relatively no difficulty, but encounters with an obstacle at the alveolar membrane (Cao and Li, 2020). Therefore, O2 transport at this step determines the amount of O_2 available for metabolism. Enhancement of the mitochondrial energy in the ICU was calculated as:

$$\%\ \text{improvement} = ([(FiO_2\text{-}20.9)/20.9]x100) - 10 \qquad \text{(eq. 2)}$$

Where FiO_2 is the percentage of O_2 in air supplied to the patient, 20.9 is the percentage of O2 in room air and 10 is the percentage of ATP generation in the cytoplasm, via glycolysis. Table 1 shows that at the first day of the Patient 1's stay at the ICU, his mitochondrial energy was increased by 369%.

The mechanical ventilation is addressing the needs of Patient 1, who was experiencing O_2 deficiency; however, Patient 4 appeared to experience difficulty in diffusion of CO_2 from the pulmonary artery to alveoli. Similarly, as Equation (1), CO_2 transport may be expressed as:

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$$N_{CO2} = K_{CO2} (P_{CO2,\ at\ the\ alveoli} - P_{CO2,\ at\ the\ pulmonary\ artery}) \quad \text{(eq. 3)}$$

where, N_{CO2} is the is the CO_2 transport trough the alveoli, K_{CO2} is the mass transfer coefficient, $P_{CO2,\ alveoli}$ and $P_{CO2,\ at\ the\ pulmonary\ artery}$ are the partial pressures of CO_2 in the alveoli and in the pulmonary artery. The term ($P_{CO2,\ at\ the\ alveoli} - P_{CO2,\ at\ the\ pulmonary\ artery}$) is the driving force of the CO_2 transport from the pulmonary capillaries to the alveoli. The mechanical ventilation helped the Patient 1 to recover, but it did not help to improve CO_2 transport in the case of Patient 4.

The hemoglobin level of Patient 1 varied between 12 and 13.7 g/dL with an average of 12.9 g/dL and the hematocrit level of Patient 1 was between 36.8 and 42%, with the average of 39.6%. In a healthy adult man, hemoglobin levels range between 14 to 18 gm/dL and hematocrit levels is between 45% and 52%. Apparently Patient 1 experienced hemoglobin and red blood cell deficiency and this appears as an additional compromise in O2-limited metabolic energy generation. Hemoglobin level of Patient 2 was initially 13.6 g/dL it became 12 g/dL the next day. Normal range for hematocrit is approximately 35.5 to 44.9% for women. Her levels of hematocrit were 41.6 the first day, then became 36.8 g/dL the next day. Hemoglobin level of Patient 3 was initially 13.8 g/dL, it varied between 13.7 and 7.8 and in the following days. His hematocrit levels were initially 42.2, until the 14th day in the ICU; then it first decreased down to 23.9, and then increased until the 32nd day up to 30.9 and fluctuated between 27.5 and 29.5 until the 37th day in the ICU. Levels of hemoglobin and hematocrit of Patient 3 were substantially lower than those of the healthy men of similar age, implying that he experienced hemoglobin and red blood cell deficiency and this again appears as an additional preventive factor in O_2-limited metabolic energy generation. Blood urea nitrogen (BUN) level of a healthy

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person ranges between 6 to 20 mg/dL. BUN level of Patient 1 was 9 mg/dL when he was first admitted to the ICU, the measurements increased by the 6th day to 29 mg/L and decreased down to 21 mg/dL by the 32nd day in the ICU. Although the blood lactate level of Patient 3 exceeded that of a healthy person at some points, it was very close to those of the healthy men in some days, implying that the major issue with Patient 3 was not about O_2 supply, but with CO_2 removal. In three of the four patients the mechanical ventilation was highly successful to improve the O_2 levels and adjust the CO_2 levels in the circulation. However, a totally different case was observed with Patient 3. His metabolism could not exhale CO_2 probably because of the severe inflammation in the alveoli, thus his arterial PCO_2 levels increased, as described in Table 3. Partial pressure of venous CO_2 exceeded that of arterial O_2 on the 12th day in the ICU, and remained the same, with fluctuations, until the 28th day. Inflammation must had been treated within this period, so his arterial PO_2 exceeded that of CO_2, during the rest of the treatment. Such an observation was also made for Patient 4 on the 20th day of ICU stay, in response to the treatment, his arterial PO_2 exceeded that of arterial CO_2 the next day and remained the same during the rest of the treatment.

It has been reported that COVID-19 affects metabolism and the endocrine system (Marazuela, et al., 2020, Wastnedge, et al., 2020, Yilmaz, et al., 2020). Summary of the energy metabolism is depicted in **Figure 3**. Usually, 2 moles of ATP and 2 moles of pyruvate are produced, when 1 mole of glucose enters into glycolytic pathway. When there is sufficient O_2 available in the tissues, then pyruvate enters into the TCA cycle and the electron transport chain and 30 moles more ATP is produced. However, when sufficient amount of O_2 is not available in the tissues, a fraction of the pyruvate

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is converted into lactic acid (Lesnak and Sluka, 2019). Increased acidity, i.e., increased H^+ concentration, in the blood and other body tissues is called metabolic acidosis. In addition to accumulation of lactic acid, increased concentrations of CO_2 in the blood may also cause respiratory acidosis, as in the case of Patient 3. The normal pH level of the blood is 7.4±0.05, any pH level below 7.35 indicates acidosis. Blood pH level of Patient 3 was 7.40, the first day when he was admitted to the ICU, and then it went down to 7.35, on the third day, became 7.3 on the 5^{th} day, around 7.5 for the next days, and then became 7.23 on the 9^{th} day, and remained in the physiological range when the arterial CO_2 levels were higher than those of the arterial O_2 levels, implying that the buffering effect of the blood of the person did not prevent acidosis in the tissues. CO_2 molecules are transported in the blood from the tissues to the lungs either by dissolving in the blood or by binding to hemoglobin, or carried as a bicarbonate ion (Hall and Hall, 2020). About 5 to 7 percent of all CO_2 is dissolved in the plasma. About 10% of the CO_2 can bind to plasma proteins or can enter red blood cells and bind to hemoglobin. When CO_2 binds to hemoglobin, a molecule, carbaminohemoglobin is formed which is a reversible reaction. Therefore, when it reaches the lungs, the CO_2 can freely dissociate from the hemoglobin and be expelled from the body. About 85% of CO_2 molecules are carried as part of the bicarbonate buffer system. When CO_2 diffuses into the red blood cells, an enzyme carbonic anhydrase, converts it quickly into an unstable intermediary carbonic acid. This intermediary molecule dissociates immediately into bicarbonate and hydrogen ions. Excessive release of H^+ may alter pH of the blood; therefore, hemoglobin binds some of the free H^+ ions and thus limits the variation of the pH of the blood. A detailed description of O_2 and CO_2 in the blood is provided by Berg et al. (Berg, et al., 2002). Du

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et al. (Du, et al., 2013), while performing a retrospective analysis with 172 patients treated for septic shock and reported that combination of central venous O_2 saturation and central venous-to-arterial partial pressure difference of CO_2 difference may predict recovery of critically ill patients from septic shock. In patients with more than 70% central venous O_2 saturation mortality was lower if venous-to-arterial partial pressure difference of CO_2 difference was less than 6 mm Hg.

The problem, experienced by COVID-19 patients is not unique, while some patients have difficulty with the O_2 transport from the alveoli to the pulmonary vein, the other patients may have a more pronounced problem with transferring CO_2 from the pulmonary vein to the alveoli. The mechanical ventilation technology (Kollisch-Singule, et al., 2020), which is commonly employed in the treatment of the COVID-19 patients today, addresses the needs of the patients who are experiencing difficulty with oxygenation. However, it does not address the needs of the patients who experience difficulty with eliminating CO_2. A different technology as described by Sukel (2020) (Sukel, 2018), which removes CO_2 from blood to help patient persistent to high respiratory rate with mechanical ventilation. Details of the equipment which may be used in such treatment modalities are described in detail in the literature (Barrett, et al., 2020, Burki, et al., 2013, Ercan, et al., 2020). It has been reported very recently that there are insufficient data to recommend either for or against the use of extracorporeal membrane oxygenation in patients with COVID-19 (NIH, 2020). Barbaro et al (Barbaro, et al., 2020), after analyzing the data for 1,035 patients with COVID-19 who received ECMO support by considering the end results only reported that the mortality rate was 38%, but the data were not reported in that study; therefore, it is difficult to decide whether survival of the remaining 62% was a

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success or not. The results of this study, which is based on the data obtained with four dissimilar patients, suggest that O_2 supply and the CO_2 removal are totally different issues, ECMO may be useful for a short period for removal of CO_2 from the arteries of the patients, when it reaches to high levels. Indeed, beneficial effects of ECMO has been further discussed in a recent report (Huang, et al., 2021).

In the present study, we evaluated treatment of four dissimilar patients individually, and found that every individual may follow a different path during the COVID-19. Physiological data collected during the treatment of four dissimilar patients implicate differences in the course of the disease. These variances point different requirements, such as removal of CO_2 with extracorporeal methods in the treatment. Experience obtained with such dissimilar patients may shorten the treatment period and the time spent in the ICU, help prevent the hospital acquired diseases and save the lives of some patients.

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Tables

Table 1. Respiration and inflammation related parameters of the Patient 1.

	Respiration and metabolic energy related parameters								Inflammation related parameters		
Days in the ICU	Respiratory support	FiO_2 (%)	PaO_2 (mmHg)	SaO_2 (%)	$PaCO_2$ (mmHg)	HCO_3 (mmol/L)	Lactate (mmol/L)	Enhancement of the mitochondrial energy in the ICU (%)	CRP (mg/L)	Body temperature (°C)	Blood urea nitrogen (mg/dL)
1	IMVS	100	86.9	84	56	28	0.5	369	246	38.7	14
2	IMVS	80	76.4	96.3	62.1	28.9	0.6	272	277	38.1	14
3	IMVS	60	117	95.4	45.9	32.7	1.2	177	116	37.1	29
4	IMVS	60	61.2	92.6	38.5	35.3	1.6	177	47.3	37.3	28
5	IMVS	60	63.4	93.8	39.1	34.3	1.4	177	24.9	37.5	28
6	IMVS	70	67.9	94.4	37.2	32.9	1.7	225	13.3	37.4	32
7	IMVS	70	87	96.9	35.8	30.3	2.4	225	8.5	36.8	50
8	IMVS	70	90	97.2	40	31	2.4	225	5.4	36.7	50
9	IMVS	70	64	93.1	38	30.6	2.4	225	3.4	36.9	46
10	OMWR	70	73	95.3	33	27.3	2.2	225	2.5	36.5	42

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11	OMWR	70	64	93.4	35	28	1.6	225	1.6	36.7	35
12	OMWR	60	66	94.2	35	28.4	1.7	177	1.3	36.6	29
13	OMWR	60	68	94.9	31	26.8	2.7	177	0.9	36.6	28
14	OMWR	60	67	94.8	36	29	1.1	177	7.3	36.8	23
15	OMWR	45	83	96.9	36	28.8	1.1	105	4.0	36.6	24

IMVS: Invasive mechanical ventilation support

NIMV: Noninvasive mechanical ventilation support

OMWR: Oxygen mask with reservoir

NS: No support

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Table 2. Respiration and inflammation related parameters of the Patient 2.

	Respiration and metabolic energy related parameters								Inflammation related parameters		
Days in the ICU	Respiratory support	FiO_2 (%)	PaO_2 (mmHg)	SaO_2 (%)	$PaCO_2$ (mmHg)	HCO_3 (mmol/L)	Lactate (mmol/L)	Enhancement of the mitochondrial energy in the ICU (%)	CRP (mg/L)	Body Temperature (°C)	Blood urea nitrogen (mg/dL)
1	NC	45		95				105			
2	NC	45	65	92.6	45	29.8	0.6	105		36.8	
3	NC	45	73	95	50	31.9	0.7	105	29.1	36.8	17

NC: Nasal Cannula

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Table 3. Respiration and inflammation related parameters of the Patient 3.

	Respiration and metabolic energy related parameters								Inflammation related parameters		
Days in the ICU	Respiratory support	FiO_2 (%)	PaO_2 (mmHg)	SaO_2 (%)	$PaCO_2$ (mmHg)	HCO_3 (mmol/L)	Lactate (mmol/L)	Enhancement of the mitochondrial energy in the ICU (%)	CRP (mg/L)	Body Temperature (°C)	Blood urea nitrogen (mg/dL)
1	OMWR	60	122	99	41.1	25.1	0.9	177	122	37.7	9
2	NIMV	100	92.7	93	40.1	25.5	0.8	368	149	38.1	10
4	IMVS	80	98	98	65	31.9	0.5	272	272	37.0	20
6	IMVS	70	54.5	92.5	50.7	39	1.2	225	58.2	37.2	29
8	IMVS	80	68.5	94	57.4	40	1.6	273	13.1	36.8	24
10	IMVS	80	108	98	85	39	1.6	273	12	38.8	26
12	IMVS	70	63.8	93.8	80	50	1.5	225	5.3	38.2	27
14	IMVS	70	60	94.5	44.6	42.1	2.5	225	2.5	38.3	26
16	IMVS	75	67	95	45	35.4	2	249		39	
18	IMVS	75	59	93	47.5	33.5	1.9	249	1.7	38.5	21
20	IMVS	75	59	92	55	34.8	1.5	249	0.8	38.2	22
22	IMVS	70	57	91.6	59	37	1.8	225	0.9	37.6	21

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24	IMVS	60	62.1	92	76.7	43.1	1.2	177	0.9	38.4	21
26	IMVS	60	63	93	73.3	43	1.1	177		36.8	
28	IMVS	65	47.3	85.8	67.9	43.8	1	201		37.6	
30	IMVS	60	77.6	97.5	61.9	42.5	0.6	177	13.1	36.8	21
32	IMVS	65	75.8	96.1	63.4	39.8	1	201	2.7	36.6	21
34	IMVS	60	64.9	93.3	60	35.9	1.5	177	3.2	36.8	
36	EB	53	63.2	93.4	48.8	35.3	1	143		36.6	
37	EB	53	55.3	91.7	41.1	32.9	0.9	143		36.6	

IMVS: Invasive mechanical ventilation support

NIMV: Noninvasive mechanical ventilation support

OMWR: Oxygen mask with reservoir, NS: No support, EB: Easy breath

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Table 4. Respiration and inflammation related parameters of the Patient 4.

	Respiration and metabolic energy related parameters								Inflammation related parameters		
Days in the ICU	Respiratory support	FiO_2 (%)	PaO_2 (mmHg)	SaO_2 (%)	$PaCO_2$ (mmHg)	HCO_3 (mmol/L)	Lactate (mmol/L)	Enhancement of the mitochondrial energy in the ICU (%)	CRP (mg/L)	Body Temperature (°C)	Blood urea nitrogen (mg/dL)
1	OMWR	45		100				105.3		36.6	
2	NC	37	65.8	97	38.4	25.5	0.6	67.0		37.0	
3	NC	37	48	87.3	35.3	26.3	0.5	67.0	75.7	36.6	21
5	OMWR	53	54	89.8	37	25.8	0.6	143.6	73.8	37.8	39
7	NC	43	63.3	94	35	26.1	0.6	95.7	83.3	37.3	32
9	NC	43	22.8	97	48	29.8	0.8	95.7	121	36.9	19
10	NC	43	35.7	99	45	29.6	0.8	95.7	109	37.7	16
12	SFM	53	65.5	93.9	43.7	29.9	0.8	143.6	148	38.4	16
14	IMVS	60	68.7	93.1	55.9	28.3	0.7	177.1	302	36.6	27
16	IMVS	60	83.3	97	47.2	31.1	0.7	177.1	504.4	38.3	52
18	IMVS	60	68.7	93.4	53.3	29.6	0.9	177.1	489.5	37.8	59
19	IMVS	80	68.1	94.6	46.1	29.7	1.0	272.8	421.9	37.5	66

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20	IMVS	90	60.7	86.5	70	26.6	0.6	320.6	437.8	37.5	79
21	IMVS	50	94.6	97.5	48.5	27.4	1	129.2	398.4	38.2	81
23	IMVS	60	84	96.3	43.7	34.5	1.1	177.1	263	38.2	102
25	IMVS	50	79.9	96.4	51	41	1.2	129.2	254.7	38.3	88
26	IMVS	60	81.4	95.6	61.3	38.2	0.6	177.1	225.4	39.2	89
28	IMVS	40	109	98.7	64.3	38.7	1.3	81.4	254	37.8	109
30	IMVS	50	63.4	94.1	55.6	41	1.2	129.2	189	37.8	65
32	IMVS	50	79.2	98	58.6	40.8	1.5	129.2	254.7	37.8	51
34	IMVS	60	82	96	55.7	40.7	0.8	177.1	117.3	38.2	44
35	IMVS	50	101	97.8	63.5	40	0.8	129.2	126.8	37	39
36	IMVS	50	109	97.7	65.9	41.1	0.9	129.2	109.6	37	41
38	IMVS	50	103	98	51.8	41.9	1	129.2	58	37.1	32
40	NC	53	84.8	96.9	55.5	40.3	0.6	143.6	25.1	36.8	21
42	NC	53	166	99	52.2	38.2	0.6	143.6	23.7	37.2	21
44	NC	53	110	98	51.6	33.9	0.6	143.6	80	37.2	21
46	SFM	53	99.7	98	56	35.1	0.4	143.6	51.3	36.2	18
47	SFM	53	98.4	115	55.7	34.9	0.5	143.6	31.6	36.2	19

IMVS: Invasive mechanical ventilation support

NIMV: Noninvasive mechanical ventilation support

OMWR: Oxygen mask with reservoir

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SFM: Simple Face Mask

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Figures

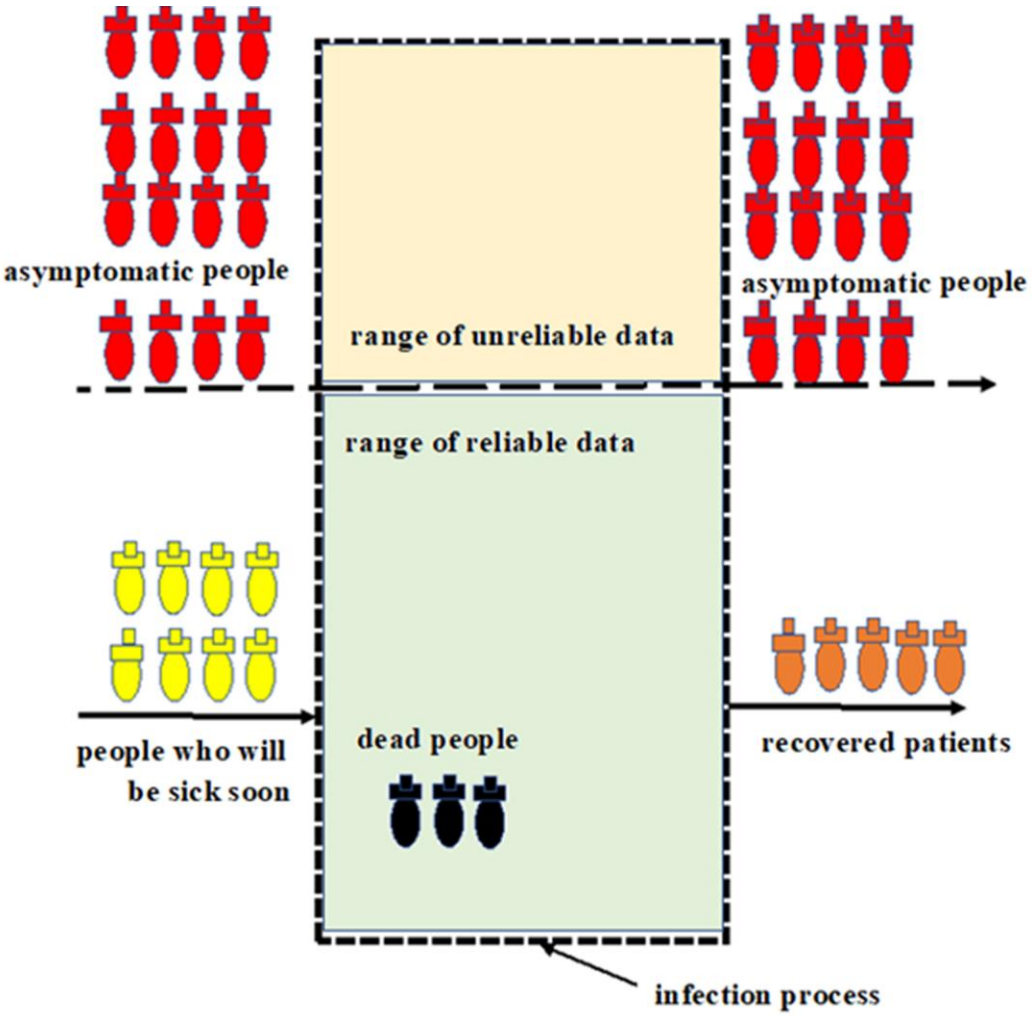

Figure 1. COVID -19 disease do not affect everybody the same way.

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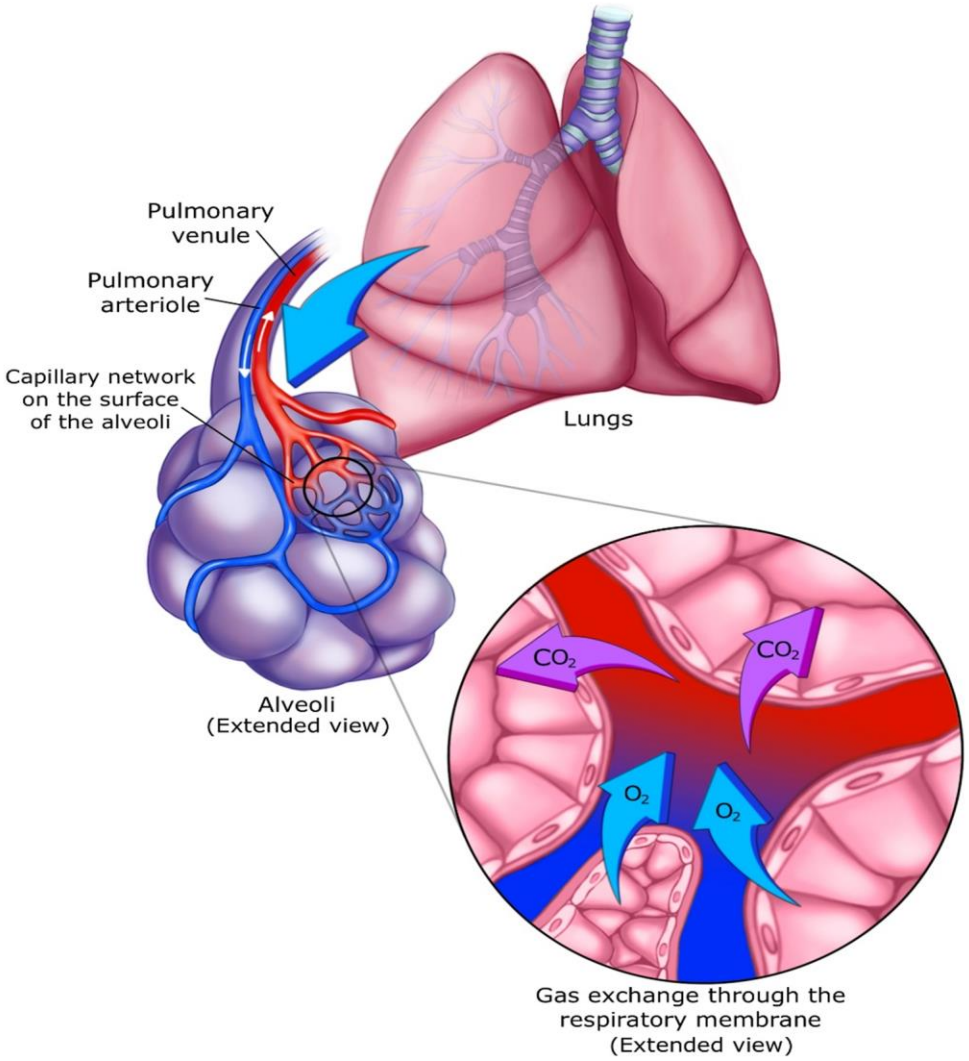

Figure 2. COVID-19 causes inflammation in the lung tissue that decreases gas exchange between the alveoli and pulmonary capillary network.

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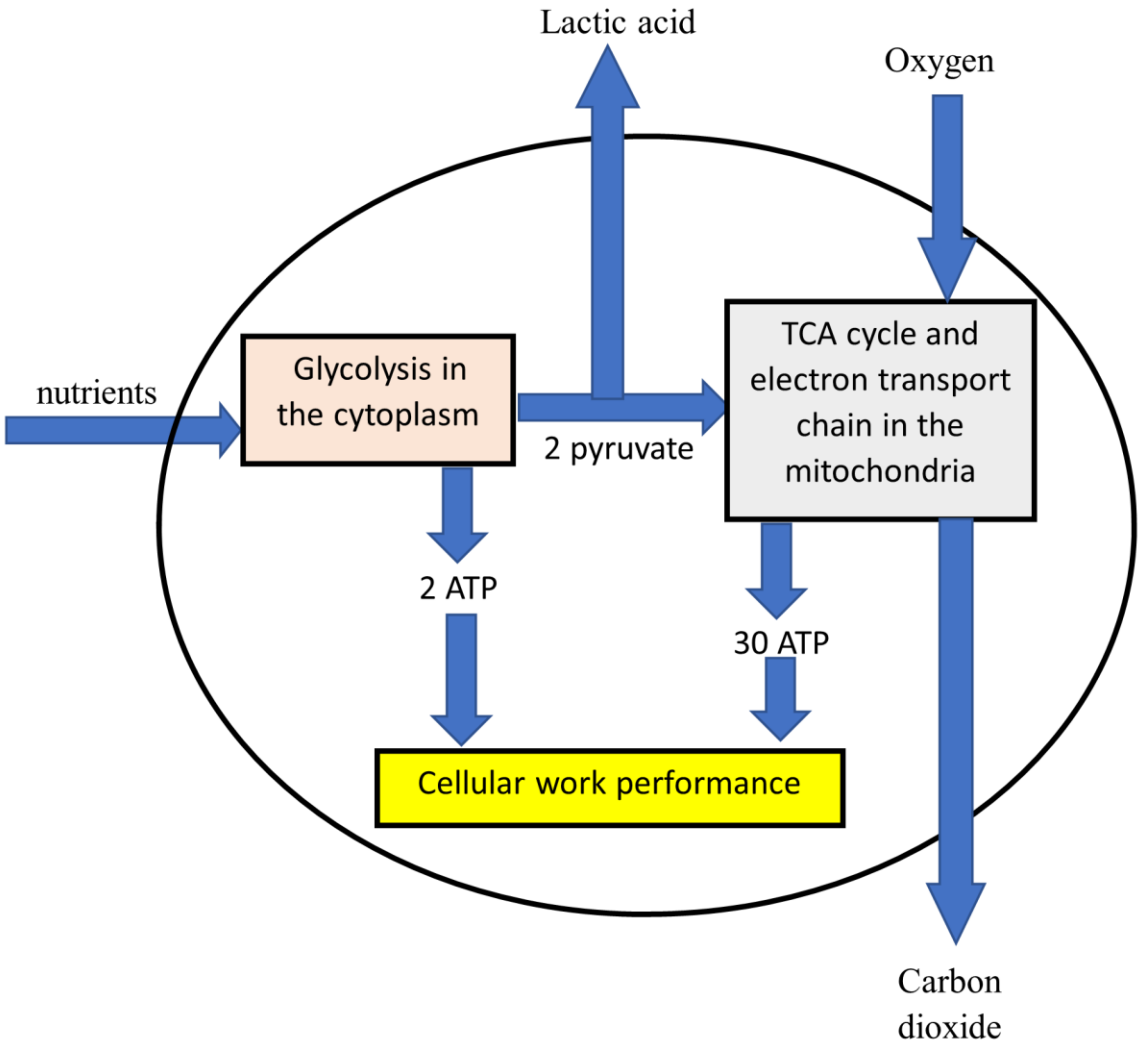

Figure 3. Schematic description of ATP, CO_2, and lactic acid generation in the cells.

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