Proning versus Respiratory Pharmacotherapeutics in Hospitalized COVID-19 Patients

by

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Abstract

The purpose of this research and literature review is to compare the use of prone positioning and respiratory pharmacotherapeutics within hospitalized COVID-19 patients and the outcomes associated with each. A literature review was performed using the databases PubMed, Clinical Key, DynaMed, and CINAHL. A variety of key terms were used when searching. Studies chosen were retrospective reviews, a cross sectional study, an interventional study, and a pilot study. Articles within the last three years were utilized after exclusion criteria was applied. A total of thirteen articles were included within this project. The research shows that pulmonary vasodilators such as inhaled nitric oxide (iNO), epoprostenol (iEpo), and Iloprost did improve oxygenation within COVID-19 patients. Nitric oxide was seen to have the greatest impacts but is not a first line choice due to cost and potential adverse effects. The PF ratio is defined by a patient's oxygen in the arterial blood (PaO2) to the fraction of oxygen in the inspired air (FiO2) and was used as a marker for treatment and severity of disease throughout the literature. The research also showed the addition of prone positioning to the use of pulmonary vasodilators increased oxygenation and subsequently increased the PF ratios of the patients. iNO with prone positioning was seen to have the largest increase in PF ratios throughout the studies. Prone positioning was associated most with an adverse effect of pressure ulcers, with most being on the head and face. The most common adverse effect with the use of iEpo was noted to be bleeding which was not life threatening. iNO was noted to have bleeding and methemoglobinemia as the most common adverse effects. Overall, further research needs to be performed with larger patient populations and more control over various factors that could influence the patient's prognosis.

Keywords: COVID-19, pulmonary vasodilators, nitric oxide, epoprostenol, iloprost, and prone positioning

Introduction

Coronavirus disease-2019 (COVID-19) originated in Wuhan, Hubei Province, China in late 2019. This is a highly contagious viral disease that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a RNA virus which can adapt to new hosts and have genetic evolution with the development of mutations over time creating mutant variants all with different characteristics (Cascella et al., 2022). According to the National Institute of Allergy and Infectious Disease (2022), research suggests that SARS-CoV originated in bats; however, the SARS-CoV-2 origin has not been identified. Scientific evidence has suggested that SARS-CoV-2 has likely been a result of viral evolution within nature and spread to humans or through an unidentified animal host. Under a microscope these viruses have a crown-like appearance due to spiked glycoproteins which is how they earned their name from the Latin root *coronam* meaning crown. The primary mode of transmission is via exposure to respiratory droplets from a close contact or droplet transmission from presymptomatic, asymptomatic, or symptomatic people. Additionally, research has also shown that this virus is able to live on surfaces for up to 72 hours. However, the risk of transmission from surfaces was found to be quite low (Cascella et al., 2022). This virus rapidly spread throughout the world invading 223 countries, and the World Health Organization (WHO) declared a global pandemic on March 11, 2020.

The COVID-19 pandemic overwhelmed communities and health systems with the rapid transmission seen worldwide. The median time of incubation was estimated to be around 5 days with the majority of individuals becoming symptomatic by 11.5 days post infection. The most common symptoms caused by COVID-19 are fever, cough, shortness of breath, sore throat, loss

of taste and smell, and headache. Less common symptoms include chest pain, hemoptysis, sputum production, rhinorrhea, nausea, malaise, myalgias, and diarrhea.

Statement of the Problem

A total of over six million deaths globally have been attributed to the COVID-19 pandemic with over 593 million cases worldwide (Cascella et al., 2022). People of all ages are at risk of contracting COVID-19; however, individuals over the age of 60 along with people who have underlying medical comorbidities have an increased risk of developing a severe COVID-19 infection. Examples of underlying comorbidities include obesity, cardiovascular disease, chronic kidney disease, diabetes, chronic lung diseases, smoking, cancer, organ, or hematopoietic stem cell transplant. These patients were seen to have a six times greater likelihood of requiring hospitalization compared to patients who did not have pre-existing medical conditions (Cascella et al., 2022).

Acute respiratory distress syndrome (ARDS) within COVID-19 patients is characterized by a new onset of severe respiratory failure or worsening of an already identified respiratory status. This diagnosis requires a set of clinical criteria including chest imaging such as a chest x-ray or CT scan that demonstrates bilateral opacities of greater than 50% that cannot be fully explained by effusions, lobar, or lung collapse (Cascella et al., 2022). The Berlin definition classifies ARDS into three categories (mild, moderate, and severe) based on degree of hypoxia with the reference parameter being the PF ratio. The PF ratio is defined by a patient's oxygen in the arterial blood (PaO2) to the fraction of oxygen in the inspired air.

The treatment and management of COVID-19 has evolved since the pandemic first started. There are a multitude of studies with different treatment options including prone positioning and pulmonary vasodilators. Prone positioning is initially utilized on a typical ARDS

patient to improve oxygenation. A patient will go from lying on their back (supine position) to lying on their stomach (prone position). This normally occurs in intervals of 12-16 hours per day. Inhaled pulmonary vasodilators such as inhaled epoprostenol (iEpo) and inhaled nitric oxide (iNO) have been studied within this patient population to see if they provide any benefit with and without prone positioning.

Research Questions

In hospitalized COVID-19 patients, are there better outcomes with the use of proning or respiratory pharmacotherapeutics? Is it safe to use prone positioning and respiratory pharmacotherapeutics for hospitalized COVID-19 patients? What are the adverse effects associated with these treatments?

Methodology

A literature review was performed using databases such as PubMed, Clinical Key, DynaMed, and CINAHL. Clinical Key and PubMed were the primary databases used. Keyword and search terms used to define a set of literature for the study included: “prone positioning, proning, COVID-19, adverse effects, adverse events, inhaled pulmonary vasodilator, pharmacotherapeutics, nitric oxide, inhaled epoprostenol, safety, side effects”. The pearl growing method was also utilized within the literature. The literature was further searched regarding inhaled pulmonary vasodilators with the specific use of nitric oxide and prostaglandin analogues in COVID-19 with and without subsequent use of prone positioning. Article types that were excluded include: meta-analyses, systematic reviews, and patient testimonies. Articles using patients under the age of 18 or non-human subjects were excluded. Articles within the last three years were utilized.

Literature Review

Respiratory pharmacotherapeutics in hospitalized COVID-19 patients

Degrado et al. (2020) conducted a retrospective single center study evaluating the efficacy of iEpo and iNO in patients with COVID-19 ARDS. Patients were included if they were intubated and on mechanical ventilation, admitted to the ICU, and received either iEpo or iNO while mechanically ventilated. Patients needed to receive at least one hour of iEpo or iNO and have results from an arterial blood gas (ABG) within the first six hours of treatment. Patients were excluded if they received ECMO prior to starting iEpo or iNO, if they did not have a baseline ABG, if baseline ABG was greater than six hours prior to starting iEpo or iNO, or if neuromuscular blockade/prone positioning was started between the baseline ABG and ABG after starting inhaled pulmonary vasodilators. The institutions recommended dose range for iNO is 1-80 ppm and iEpo is 0.01-0.05 mcg/kg/min based on IBW. iEpo is their first line pulmonary vasodilator. If patients do not respond to iEpo (less than 10% improvement in PF ratio) then iNO is considered once iEpo is stopped. iNO would be started at 20ppm and titrated up to 80ppm if a 10% increase is not seen. A patient is deemed a “responder” if a 10% increase is seen in their PF ratio. ABGs are recommended at baseline and 2 hours after iEpo or iNO is started. Baseline demographics and past medical history were gathered on ICU admission. Ninety-three patients were screened and received pulmonary vasodilators. Forty-seven patients were excluded for the criterion mentioned above. Eight more patients were then excluded due to neuromuscular blockade/prone positioning between ABGs. Thirty-eight remained and were included for this study. The mean age of patients was 61 years with 14 patients being female (36.8%). Median BMI was 30.8 kg/m^2 and most common comorbidities were hypertension and diabetes mellitus. All 38 patients received iEpo as their first pulmonary vasodilator and eleven transitioned to iNO.

Median time from intubation to iEpo was 158 hours. Median change in PF ratio was 0 (-12.8-31.6) mmHg. Sixteen of the 38 patients (42.1%) were deemed responders and 11 patients (28.9%) had an increase of at least 10% in the PaO2. The 16 responders to iEpo had a median change in PF ratio of 34.1 (24.3-53.9) mmHg. Median starting dose of iNO in the 11 patients trialed was 20 ppm (20-30 ppm). Seven patients (64%) had their dose increased to 80 ppm. Median change in PF ratio was 11 (3.6-24.8) mmHg. Seven patients were deemed responders and the median increase in their PF ratio was 23.2 (16.5-28.2) mmHg. iEpo was continued in responders for 77.7 hours and 26.2 hours in non-responders. iNO was continued in responders for 58.3 hours and 35.9 hours in non-responders. Overall, 41% of patients in this study were deemed responders to iEpo. Both iNO and iEpo demonstrated improvements with oxygenation but did not improve mortality outcomes.

A strength of this study was the screening process that occurred, including comorbidities as well as ventilator settings and mechanics. A limitation of the study was the patients were not on or administered corticosteroids and had an increased number of failed attempts at proning before initiating inhaled pulmonary vasodilators. Another limitation was the lack of protocols; instead, the study had recommendations, but treatment and weaning were ultimately at the discretion of the individual physician.

Kataria et al. (2022) conducted a retrospective single-center study of adult patients that were admitted to the ICU. This study was conducted from June to December of 2020. All patients were diagnosed with COVID-19. Patients had to be over the age of 18, requiring oxygen through a high flow nasal cannula (HFNC) with a flow $\geq$ 50 L/min and FiO2 $\geq$ 80%, and treated with corticosteroids. Patients were excluded if they had a do not intubate advanced directive, taken off HFNC and placed on bilevel positive airway pressure (BIPAP), received nitric oxide,

or had pulmonary hypertension in their past medical history. One hundred forty-seven patients were initially screened; however, only 60 met this criterion and were included. These 60 patients were split into a control group and a treatment group. Each group consisted of 30 patients. The treatment group received aerosolized epoprostenol (aEPO) for at least one hour after reaching the oxygen/flow threshold described above. The treatment group members were then assessed to be responders to treatment or not. A patient was a responder if there was a sustainable (> four hours) 10% reduction in FiO2 requirements from baseline, while also maintaining SpO2 > 92% within the first 24 hours of treatment. A patient was a non-responder if the criterion mentioned for improvement were not fulfilled or worsened. The institution did have a policy for aEPO to be initiated at a dose between 10 and 50 ng/kg/min. The dose is based on ideal body weight (IBW) and can be titrated by 10 ng/kg/min every 30 minutes to maintain SpO2 ≥ 92%. Initial dosing and following titrations were at the discretion of the provider within the range given in the policy. The epoprostenol was all prepared in the institution's Department of Pharmacy in a 60 mL syringe to a final concentration of 30,000 ng/mL (1.5 mg/50 mL). The patient population of this study was evenly split between males and females. The median age was 62.5 years old and median BMI of 34.3kg/m^2. Both groups had similar severity of illness which was based on predicted mortality, expected length of stay, and admission comorbidities. The most common admission comorbidities were hypertension and diabetes between the two groups. The main outcome of this study was the rate of patients requiring invasive mechanical ventilation. There were several secondary outcomes measured in the study. These were time to mechanical ventilation, 28-day mortality and ICU, and hospital lengths of stay. Management strategies were also assessed between the groups. The groups had one difference with the patients in the treatment group receiving diuretics (63% vs 33%, p= 0.02). The main outcome of mechanical

ventilation was not statistically notable between groups. However, only 70% of patients in the treatment group required mechanical ventilation compared to 90% of patients in the control group. The time from HFNC initiation to intubation was considerably different between the groups. An observed prolonged time (3.4 days) to intubation was seen with the treatment group. The responders had decreased FiO2 requirements (90% to 75%) 24 hours after receiving aEPO compared to 100% FiO2 requirements of non-responders. The responders had a lower rate of mechanical ventilation (50% vs 88%, p= 0.025) and mortality (21% vs 63%, p= 0.024) compared to non-responders.

This study was effective in looking at a combination of therapies in non-intubated COVID-19 patients. It also can provide insight on the use/strategies of aEPO in COVID-19 patients and who could likely respond. A limitation of this study was the small sample size. Another limitation was that safety outcomes such as hypotension, bleeding rates, and rebound hypoxemia were not assessed.

Matthews et al. (2022) conducted a retrospective analysis of prospectively collected data of adult patients with confirmed COVID-19 infection who were admitted to the ICU. The hospital is a large teaching hospital and a tertiary care center for pulmonary hypertension. Due to this, they readily have access to nitric oxide delivery systems and nebulized prostaglandins. Data was analyzed from March 2020 to February 2021. The hospital had a standard of care for all COVID-19 patients in the ICU which included a trial of non-invasive ventilation that was followed by mechanical ventilation if the patient deteriorated further. Corticosteroids (dexamethasone) and IL-6 inhibitors (tocilizumab/sarilumab) were used as their local guidelines permitted. After initiation of mechanical ventilation, all patients would undergo a minimum of three proning cycles unless it was contraindicated. The proning cycles consisted of 16 hours

prone and eight hours supine. These patients also received a neuromuscular blocker and ventilation was titrated for a target PaO2 of 8 kPa allowing for permissive hypercapnia. Departmental guidelines were developed for the use of inhaled pulmonary vasodilators (IPVD) in patients with severe refractory hypoxemia (PaO2 < 13.3 kPa). IPVD would be considered if patients had a PF ratio < 13.3 kPa despite other rescue therapies (proning, PEEP titrations on the ventilator, and APRV ventilation modes). Inhaled nitric oxide (iNO) was started at a dose of 20 ppm and titrated to their response up to 40 ppm. If there was improvement in oxygenation, the iNO was weaned down and Iloprost nebulizers were started. Iloprost was started at doses of 10 mcg every four hours and increased in 10 mcg increments up to a maximum of 30 mcg every four hours. After 48 hours, if no improvement was seen the Iloprost nebulizers were stopped. The main outcomes were changes in the percentage of the PF ratio and Alveolar-arterial (A-a) gradient at 2, 6, 12, 24, 48, and 72 hours after IPVD therapy. Secondary outcomes evaluated were differences in patient characteristics, therapies received, and changes in PF ratio and A-a gradient in survivors versus non-survivors who all received IPVD. Another assessment done was looking at the number of patients who had an improvement in their PF ratio of 10%, 20%, and 50% to see if different percentage increments were corresponding to improved survival. Two hundred forty-one patients did not receive any IPVD, and eight patients received less than 24 hours of IPVD therapy. Fifty-nine patients received IPVD. Of those, nine received iNO, 11 received Iloprost, and 39 received a combination of both iNO and Iloprost. Between patients who received IPVD and those who did not, there were no significant differences noted in demographic and clinical variables such as age, gender, BMI, ethnicity, or baseline co-morbidities. The median PF ratio at the start of IPVD therapy was 11.33 kPa (9.93-12.91). Median time from ICU admission to receiving IPVD was six days. At 48 hours from the start of

IPVD, three patients of the 59 had died (5.1%) and one was transferred to a regional ECMO center. When assessed at 72 hours post IPVD, most patients showed an improvement in oxygenation (median increase in PF ratio of 33.9%). The increase occurred more quickly in iNO treated patients compared to Iloprost, with a max improvement seen at 12 and 72 hours. The highest percentage of change was seen in patients only receiving iNO (65.1% at 12 hours). This data from patients only receiving iNO was from a small number of patients. Patients receiving IPVD had a lower PF ratio (14.37 vs. 16.37 kPa, $p= 0.002$) and a higher APACHE-II score (17 vs. 13, $p= 0.028$) at admission. APACHE-II scores were used for illness severity meaning a high score indicates a patient's illness is more severe. Thirty-three (55.9%) patients in the IPVD group survived to ICU discharge, whereas 81.9% of the non-IPVD group survived until discharge ($p< 0.001$). The non-survivors had a median reduction in the PF ratio of 4.1% from baseline at 72 hours. Twenty-seven patients (45.8%) and 38 patients (69.1%) were seen to have an increment of 10% in the PF ratio at two and 72 hours. Similar changes were seen for a 20% incremental response. The 50% increment in PF ratio was lower at 10.2% and 43.6% at two and 72 hours. Increments of the PF ratio of 10% ($p= 0.006$), 20% ($p= 0.001$), and 50% ($p< 0.001$) at 48 hours from starting IPVD were associated with increased ICU survival.

The strengths of this study are the accuracy of the data collected and the protocols that were implemented throughout. Another strength would be this is potentially the first study to report the combined use of iNO and Iloprost in COVID-19 ICU patients. A weakness would be the smaller sample size and not evaluating ventilator variables such as PEEP, tidal volumes, compliance, and dead space.

Niss et al. (2022) conducted a retrospective observational study within a multicenter single health system. One hospital is a tertiary care medical center while the other is a

community hospital. This study was conducted on adults that received inhaled epoprostenol (iEpo) during their hospital stay from January 2016 to February 2021. It was associated with diagnosed acute respiratory distress syndrome (ARDS) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated ARDS. Laboratory confirmation was used to confirm COVID-19. Data was collected regarding gas exchange and ventilation before initiation of iEpo and included ventilator mode, PEEP, tidal volume, PaO2, SpO2, and FiO2 settings. All of those mentioned except tidal volume were then collected again at six hours after initiation of iEpo. The PF ratio was calculated for each individual patient prior to and within six hours after initiation. The SpO2: FiO2 was calculated at these times as well. An arterial blood gas (ABG) was drawn to determine the PF ratio and was drawn within three hours to starting iEpo. The PF ratio after initiation was determined from another ABG drawn within six hours. The physician's discretion was used to determine when to initiate iEpo. Flolan was the formulation of iEpo that was used. The hospitals used a fixed-dose guideline for administration. All patients were started on a continuous nebulizer with a 20,000-ng/mL solution that was delivered at eight mL/hour to the inspiratory limb of the ventilator. The main outcome was to determine different variables that could be associated with a positive response to iEpo. The positive response was defined as a 10% improvement of the PF ratio within six hours of starting iEpo. Secondary outcomes were a change in baseline PF and SpO2:FiO2 within six hours of starting iEpo. Three hundred thirty-one patients were included with most of this population being white men with severe ARDS. SARS-CoV-2 was the most common etiologies of ARDS (n=111, 33.5%) with pneumonia making up the second most common cause (n=108, 32.6%). It was found that as the baseline PF ratio increased it was less likely to see a positive response to iEpo ($p< 0.001$). SARS-CoV-2 ARDS was significantly associated with decreased likelihood to have a positive response (p=

0.007). Other variables such as prone positioning and neuromuscular blockade were also not associated with a positive response. Two hundred twenty-six patients (68.3%) were seen to have a positive response within six hours of starting iEpo and, more specifically, SARS-CoV-2 ARDS had a 59.5% response rate. The median PF ratio increase was from 72 to 89 ($p< 0.001$). Non-SARS-CoV-2 ARDS patients were seen to have a response rate of 72.7% and a median PF ratio increase from 71 to 99 ($p< 0.001$). Within the entire study population, the median PF increased from 71 to 95 ($p< 0.001$). The median SpO2: FiO2 increased from 94 to 120 ($p< 0.001$) after starting iEpo. The median duration of iEpo therapy was found to be 80 hours for the entire study population. Non-SARS-CoV-2 ARDS had a median duration of therapy of 73.5 hours and SARS-CoV-2 ARDS patients had a median duration of 96 hours. It was deduced from the data that SARS-CoV-2 ARDS patients had a smaller change in PF ratio with iEpo than non-SARS-CoV-2 patients and were less likely to have a positive response to iEpo.

A strength of this study was the large sample size that included COVID-19 patients. A limitation of the study was the single health system design and not looking at further variables such as patient co-morbidities or severity of their illnesses.

Safaee Fakhr et al. (2021) conducted an interventional study in 29 spontaneously breathing, non-intubated, hospitalized COVID-19 adult patients. This study evaluated the efficacy of breathing nitric oxide (NO) at 160 ppm, two times daily for 30 minutes each time. These patients were included if they had a confirmed PCR COVID-19 test and presence of COVID-19 symptoms such as tachypnea (respiratory rate ≥ 24 breaths/minute) and cough. Patients that were pregnant, on long term oxygen, have DNR or DNI advance directives, or comfort measures were excluded. Median age of patients was 50 with a predominant race being Caucasian. The most common co-morbidity was hypertension with diabetes being second. Six

different outcome variables were assessed during this study. This includes the incidence of intubation and placement on mechanical ventilation within 28 days after the study, the 28-day mortality and number of days to recovery, hospital length of stay, readmission rate to the hospital, a negative PCR to COVID-19 28 days after NO therapy, vital signs, and selected inflammatory markers. Pulmonary involvement was assessed with chest x-rays before NO therapy. A face mask was developed by the study team to deliver high volumes of NO. Inhaled NO was given at 160 ppm for 30 minutes two times daily for up to a max of 14 days. If hospital discharge, negative PCR for COVID-19, or lack of respiratory symptoms for three consecutive days occurred before the 14 days therapy was then discontinued. The median time between onset of symptoms to confirmed diagnosis of COVID-19 was six [IQR 3-10] days. The total number of treatments given to the 29 patients was 217 with a median number of treatments per patient being six [range 1-27]. Upon enrollment, 13 patients required additional oxygen (median two [(IQR 1.5-3.5] L/min), and 24 patients (82%) had abnormal chest x-rays. At hospital admission 16 (55%) of patients had pulmonary opacities which were considered “classic” findings of COVID-19. During NO therapy, patients experiencing tachypnea had a decreased respiratory rate. This demonstrated a role that NO gas can help relieve respiratory distress. Patients who experienced pre-treatment hypoxemia improved during NO therapy. NO is a selective pulmonary vasodilator and improvement of hypoxemia is likely due to increased ventilation to perfusion matching. The respiratory rate was noted to decrease by one breath/min each day of treatment. One patient required intubation out of the 29 in this study due to worsening pulmonary disease. No deaths were seen. No hospital readmissions were seen after the use of inhaled NO therapy, which was a significant finding compared to other literature reviewed. This study was effective in showing

that NO can decrease readmission rates and respiratory rate while also improving hypoxemia in COVID-19 patients.

A strength of this study was that it was one of the first to look at iNO within non-intubated COVID-19 patients and at higher doses than previously studied. Another strength would be the demographic and clinic characteristics that were documented (age, gender, race, ethnicity, and comorbidities). A limitation of this study is the small sample size and the need for a randomized clinical trial to further investigate the role of high dosed iNO within non-intubated COVID-19 patients.

Respiratory pharmacotherapeutics with proning in hospitalized COVID-19 patients

Bagate et al. (2020) conducted a monocentric pilot study with intubated patients that had severe COVID-19 associated ARDS (C-ARDS) and had persistent hypoxemia. Each patient had a laboratory confirmed PCR test and were in the ICU. Patients that were younger than 18, had acute cor pulmonale, a pulmonary embolism, hyperlactatemia (> 2 mmol/L), hepatic insufficiency, or on ECMO support were excluded from this study. Patients involved in this study were sedated and received a neuromuscular blocker to maintain a tidal volume of six mL/kg of predicted body weight on volume-controlled ventilation and a PaCO2 below 50 mmHg. Prone positioning was optimized due to persistent severe hypoxemia (PF ratio < 150 mmHg). Each proning session would be 16 or 18 hours before supination would occur. Inhaled nitric oxide (iNO) would then be placed on the patients starting at 10 ppm followed by iNO associated with almitrine at 10 mcg/kg/min. Almitrine, a selective pulmonary vasoconstrictor, was proposed several decades ago to be given with iNO to improve V/Q mismatch. The FiO2 was kept at 100% for every patient throughout the study. The effect on arterial oxygenation was calculated after 30 minutes in each of the three steps. Supine baseline, iNO alone, and iNO plus

almitrine together were these steps. An echocardiogram was also done with ABGs for those three steps. The echo was done to assess right ventricular function since a side effect of almitrine is an increase in right ventricular afterload. Patients were deemed "responders" if their PF ratio increased by at least 20% or by 20 mmHg compared to baseline. Ten patients were included in this study with seven being male and three being female. The median age was 60 [52-72] years old. The median time to intubation was seven [5-15] days. The two most common co-morbidities were diabetes mellitus and hypertension. It was noted that the gas exchange response was favorable with the last prone positioning (increased PF ratio by 20% or 20 mmHg) in 80% (8/10) patients. The overall PF ratio increased from 77 [62-114] mmHg supine to 137 [97-167] prone ($p< 0.01$). In the supine position, patients were found to still be hypoxic with the median PaO2 being 102 [89-134]. During supination, the only treatment that increased the PaO2 significantly was when almitrine was added to the iNO. No changes were noted to pulmonary blood flow, hemodynamics, or echocardiographic variables. The median PF ratio increased from 102 [89-134] mmHg at baseline to 124 [108-146] mmHg after iNO only ($p=0.13$) and after iNO plus almitrine it increased to 180 [132-206] mmHg ($p< 0.01$). Seven out of ten patients had more than a 50% increase in PaO2 with iNO and almitrine together. There was one patient who was a non-responder that had an intra-cardiac shunt that was related to a patent foramen ovale. The response to the combination of iNO and almitrine was seen to not correlate with the benefit proning produced on PaO2 ($p= -0.09$, $p=0.80$). Six patients out of the ten had refractory hypoxemia (PF ratio < 80 mmHg). This could not be treated with almitrine since there was a shortage of the drug reserve at the time. One of those six benefited from ECMO and had a favorable outcome. The five remaining did not qualify for ECMO and therefore died during their ICU stay.

This study had many limitations with the first being the incredibly small cohort size. The drug shortage contributed to not being able to evaluate prolonged effect, and it also left five patients without treatment. Strengths of the study were the inclusion/exclusion criteria, collection of other variables (age, gender, BMI, past medical history, and standard treatments received), and the need for ECMO and mortality rate were collected during hospitalization.

Bell et al. (2022) conducted a retrospective observational study with mechanically ventilated COVID-19 patients and the effectiveness of prone positioning. The study was conducted from two tertiary care centers in a single health system from March 2020 to July 2021. Both hospitals share the same guidelines for COVID-19 patients. All patients were diagnosed with COVID-19, mechanically ventilated, and underwent prone positioning. The average age of patients was 57 ± 13, with 65% of the patients being male and 52% of those being African American. Median BMI of patients was 31. Hypertension, diabetes mellitus, and COPD were the most common comorbidities found. The main outcome of this study was a change in oxygenation that was measured by the PaO_2/FiO_2, also known as the PF ratio. This was calculated by using an arterial blood gas (ABG) at four separate time points. The first time point was immediately before switching to the prone position and had a mean of 115 mmHg. The second was immediately after prone positioning with a mean of 114 mmHg. The third was immediately before returning to supine position with a mean of 140 mmHg. The fourth was immediately after returning to supine position with a mean of 137 mmHg. One hundred twenty-five patients underwent prone positioning a total of 309 times. The median duration was 23 hours IQR (14 – 49). This study defined a patient to be a “prone responder” if the PF ratio improved by 10% while prone. The study defined a patient to be a “sustained responder” if the PF ratio improved 10% after returning to the supine position. There were 176 (57%) prone responders

and 173 (56%) sustained responders. The average sustained response seen was an improvement in PaO2/FiO2 of 19% (115 mmHg to 137 mmHg). Prone responders were found to be in the prone position longer (24 v. 17 hr, $p<0.01$), had lower initial PF ratios (105 v. 128, $p<0.01$), and lower initial pCO_2 (46 v. 49 mmHg, $p=0.01$). The prone responders were also found to be more likely to be on inhaled epoprostenol (iEpo) (35 v. 23%, $p=0.02$). Initial ventilator parameters or lab data were not found to be associated with proning responsiveness. It was found that individuals with a lower PF ratio and on inhaled epoprostenol will respond to prone position more favorably. Bell et al. (2022) wrote, "Regarding iEpo, we speculate that improved ventilation in the prone position may lead to better drug distribution" (p. 887). This study was effective in showing that mechanically ventilated patients infected with COVID-19 generally had continuous improvements in oxygenation with proning, and the use of inhaled epoprostenol made improvements with prone positioning more likely.

A weakness of this study was that although each hospital shared the same guidelines it was still under the clinician's discretion. Therefore, the use of proning was not protocolized. The time from intubation/initiation of mechanical ventilation to proning varied from patient to patient. Ventilator modes also varied and were not consistent throughout the entire study with "most" patients being on assist control with volume cycling and the rest being on APRV or PCV. Another weakness is they did not have a matched cohort that did not receive prone positioning to compare to (Bell et al., 2022).

Berrill (2021) conducted a retrospective analysis of the evaluation of oxygenation in proning sessions of mechanically ventilated COVID-19 patients in the ICU. Thirty-four patients were included in this study from March 2020 to May 2020. A total of 131 proning sessions occurred. Thirty-three out of thirty-four patients had confirmed COVID-19. The one patient had

a negative swab originally but was admitted to the ICU for high clinical suspicion of COVID-19. This patient died before another swab could be obtained. Patients were included if they were proned for > three hours while being mechanically ventilated and had survived > 24 hours from admission. ABG measurements and ventilator settings were recorded within three hours of proning initiation or termination. The median age of patients was 58.5, median BMI was 31, and the most common co-morbidity was hypertension with diabetes coming in second. Patients were proned within two days of admission with an average proning duration of 16.5 hours. Patients were proned for a median of four separate occasions. Each patient during the first proning session was on a ventilator mode of PRVC or APRV being treated with a tidal volume of 6-8 mL/kg IBW. The median tidal volume during this first session was 7.86 mL/kg. The median PF ratio during the first session was 87.8 mmHg. Eighty-one percent or 72/89 proning sessions had an improvement in the PF ratio. The median PF ratio overall at the start was 99.8 mmHg and at the end was 151.9 mmHg. This resulted in a median increased change of 43.5 or 43.6% ($p < 0.0001$). Proning also resulted in a significant reduction in FiO2 over the course of the study. A relative decrease of 25% ($p < 0.0001$) in FiO2 was seen. Arterial oxygenation was noted to significantly increase in the majority of patients within this study.

A strength of this study is the screening and documentation of patient characteristics (age, BMI, comorbid conditions), documentation of proning characteristics (time to first prone, number of cycles, duration of hours), documentation of ventilator settings, and documentation of ABG values. A limitation, however, would be the relatively smaller sample size with only having 34 patients included in the study in a short time frame.

Imtiaz et al. (2022) conducted a retrospective study looking at the use of inhaled epoprostenol (iEpo) in mechanically ventilated COVID-19 ARDS patients. This was conducted

from three different hospitals all within the same health system from April 2020 to May 2020. Patients were included if they had a confirmed positive PCR COVID-19 test. They were excluded if there was not a documented ABG within 12 hours before starting iEpo, were under 18, or were pregnant. Important comorbidities, ventilator settings, and ABGs were collected before starting iEpo. The most common comorbidities of the patients included in the study were hypertension, obesity, and diabetes mellitus. COVID-19 treatments such as hydroxychloroquine, tocilizumab, convalescent plasma, remdesivir, and corticosteroids were also utilized. iEpo is becoming more popular due to its lower cost and reduced toxicities when compared to iNO. iEpo is a potent vasodilator, but it also has anti-inflammatory and antiplatelet aggregation properties that can be beneficial in COVID-19 patients. These three hospitals did not have any form of dosing protocols for iEpo and therefore initiation and dosing were at the discretion of the provider. One hospital utilized starting doses of 30,000 ng/mL with a flow rate of 50 ng/kg/mL and a weaning rate of 10 ng/kg/mL. The other two hospitals started at 20,000 ng/mL with a fixed flow rate of 9 mL/hr and a weaning rate of 50% of the previous concentration depending on clinical improvement. Parameters that were monitored included vital signs and ABGs (PaO2, PF ratio). Eighteen patients in the ICU with COVID-19 and being managed with iEpo were identified; however, only 15 met the inclusion criterion above. Primary outcomes of this study were a change in PF ratio following iEpo administration, clinical improvement (10% increase in PF ratio), hospital mortality rate, time to the first wean of mechanical ventilation (decrease in FiO2 or PEEP), the time to extubation, and total days of iEpo therapy. The mean (SD) age of patients in this study was 57.2 (13.7). Eleven out of 15 patients were male (73.3%). The mean BMI was 33 (10.9) kg/m^2 and 13 out of 15 (86.7%) were on vasopressors. Nine patients at the time of starting iEpo were receiving renal replacement therapy and eight of the nine had end-

stage renal disease. The one patient remaining had an acute kidney injury. Twelve patients or 80% received hydroxychloroquine, four (26.7%) received tocilizumab, 13 (86.7%) received glucocorticoids, five (33.3%) received remdesivir, and three (20%) received convalescent plasma. Eleven (73.3%) patients were started on prone positioning before iEpo administration while six (40%) other patients were chemically paralyzed. The ABG before starting iEpo showed a mean FiO2 of 91.3% and a PF ratio of 95.9 mmHg. After starting iEpo the mean ABG was drawn at 204 minutes. The mean PF ratio was 119 mmHg after the first administration of iEpo. This was not a significant increase from baseline ($p= 0.279$). The mean increase in PF ratio was 26.4 mmHg during the first ABG draw. Ten patients had at least a 10% increase in PF ratio just from initiation which did indicate a positive response to therapy. The number of patients requiring to be proned decreased to seven (46.7%), and patients needing to be paralyzed decreased to three (20%). The second ABG after starting iEpo was from 13 patients and occurred at an average of 20.3 hours. The average PF ratio at this time was 131.8 mmHg. Nine patients were considered to have severe COVID-19 ARDS before starting iEpo. The PF ratio improved from 66.1 mmHg to 95.7 mmHg on a subsequent ABG ($p=0.317$). Patients who were not proning when starting iEpo had an improvement in their PF ratio following administration of iEpo of 36.1 mmHg. This can be compared to an improvement of 26.5 mmHg in the patients that were proning before the start of iEpo ($p=0.06$). After iEpo, the average time until ventilator weaning occurred was 6.8 hours with the median duration being 5.3 hours. Four patients (26.7%) would progress to extubation with an average of 9.9 days after being intubated. Two patients needed to be transferred to another facility for ECMO. Mortality was seen in 10 patients. The patients in this study showed a mean improvement of 37.3% in the PF ratio within 48 hours of receiving iEpo (95.9 to 131.7 mmHg).

A strength of this study was the documentation of patient characteristics (age, sex, BMI, comorbidities), COVID-19 treatments received prior to starting iEpo, and ventilator parameters including ABG values. A limitation would be the small sample size of only 15 patients within three hospitals and the lack of protocols for dosing iEpo.

Li et al. (2020) conducted a retrospective study looking at the effects of iEpo and prone positioning in intubated COVID-19 patients. This was conducted from March 2020 to the end of May 2020. Adult patients who received iEpo and prone positioning (PP) with a confirmed COVID-19 PCR test were included. Patients were excluded if iEpo was started at an outside facility or after PP was stopped, if iEpo was started during ECMO or CPR, or if iEpo was started and the patients PF ratio was greater than 150 mmHg. The iEpo was prepared within the hospital and placed in 50 mL syringes that would be delivered by a continuous nebulizer. The initial starting dose was 50 ng/kg/min of the patients predicted body weight. This dose was maintained for at least 24 hours. The weaning of iEpo was at the discretion of the provider and was titrated down by 10 ng/kg/min every 30-60 minutes depending on how the patient's oxygenation was. PP would be started if the PF ratio could not be maintained around 150 mmHg with a PEEP of 10 or more and FiO2 of 60%. A patient would remain proned for at least 16 hours at a time. A patient's position (supine or prone) was documented when iEpo was started as well as the number of PP sessions before and after iEpo initiation. The PF ratio was calculated and compared within two hours before and after either iEpo or PP or both in combination together. A positive response was considered when a greater than 20% improvement in the PF ratio was seen. Three hundred thirty-six patients had confirmed COVID-19. Among those, 234 were intubated and 57 patients received iEpo and PP while mechanically ventilated. Fourteen patients were excluded due to criterion stated above. This study had 43 patients in total that were eligible.

The mean age was 55.1 (13.8 SD) with 27 patients being male. The main ethnicities were Hispanic/Latino (54%) and African American (33%). The day of iEpo being started the median (IQR) SOFA score was nine (8-11) with duration from COVID-19 confirmation until the start of iEpo was nine days (4-14 days). Mechanical ventilation was used for 68 hours (5.3-203.3 hr) upon starting iEpo. Before treatment was started a baseline PF ratio was obtained. The median PF ratio was 86.6 (28.9) mmHg with a PEEP of 16 cmH2O (12-18 cmH2O) and FiO2 of 100% (80-100%). Twenty-two patients had a median number of three (1-5) PP sessions before starting iEpo. Nine patients (41%) experienced a response to PP before starting iEpo, however, there was not a significant difference in PF ratio between before and after initiating PP (91.7 [31.8] vs 98.0 [31.9] mmHg; n=21; p=0.570) for these patients. iEpo was started for this group of 22 patients at a mean time of 5.4 hours (1.8-17.9 hr) after being proned. A significant improvement in PF ratio was noted (83.3 [23.5] vs 106.9 [53.4] mmHg; n=20; p=0.034). Out of the nine patients that experienced a positive response to PP, four patients showed continuous improvements in oxygenation when iEpo was added to PP. The thirteen other patients who did not respond to PP alone had four that responded when iEpo was added. Six out of 22 patients had iEpo used during their first PP, four (67%) responded to PP, and three (75%) continued responding when iEpo was added. Two patients did not respond to the first PP responded once the combination of iEpo and PP was used. Seven patients had iEpo started while they were in the supine position. Oxygenation did not have a significant change before or after iEpo. Six patients had a higher PF ratio with the addition of PP after the iEpo was started (85.3 [21.1] vs 141.7 [90] mmHg; p=0.046). Within those seven patients, two responded to iEpo alone, and one continued to respond with the addition of PP. Out of the five that did not respond to iEpo alone, four of these patients responded once PP was added to the iEpo. The 29 patients mentioned above that

received PP or iEpo alone before the combination did not have a significant change in PF ratio before or after PP or iEpo (89.1 [30.6] vs 97.6 [30.2] mmHg; n=24; p=0.393). Combination therapy in these patients yielded a higher PF ratio (89.1 [30.6] vs 113.3 [66.7] mmHg; p=0.042). Fourteen patients had iEpo started within 51 minutes; therefore, only combination effects were evaluated. The combined use of PP and iEpo within these patients significantly improved their PF ratios (78.9 [27.0] vs 150.2 [56.2] mmHg; p=0.005). When comparing oxygenation from baseline (supine) position to the combination of iEpo and PP, 27 patients had a 20% or greater improvement. Responders had fewer PP sessions before starting combination therapy (1 [0-4] vs 3 [1.3-3.8]; p= 0.054). Responders also had a higher percentage of patients who had never been proned before (44 vs 6%; p=0.022). Additionally, responders had a lower mortality rate than the non-responders (52 vs 81%; p= 0.025). This study was effective in showing that the combined use of iEpo and PP improved PF ratios and oxygenation in patients intubated who were diagnosed with COVID-19.

A strength of this study was the extensive inclusion/exclusion criteria, patient demographics that were documented (age, gender, ethnicity), ventilator parameters included (PEEP, compliance), and documentation of the patients' 28 day outcome (mortality, ECMO, discharged from hospital alive). A limitation of this study is there was a lack of a proper control group. Likewise, the study only included a small sample size. Different comorbidities as well as ventilator settings were not considered either.

Sonti et al. (2021) performed a retrospective observational study with patients who had COVID-19 and were mechanically ventilated for hypoxemic respiratory failure and receiving inhaled epoprostenol (iEpo). This study was conducted from two tertiary care centers within a single health system from March 2020 to May 2020. These hospitals both have shared guidelines

for COVID-19 patients but does not address iEpo. All patients were diagnosed and confirmed with laboratory testing for COVID-19, were mechanically ventilated, and were receiving iEpo. Eighty patients were included in this study. The median age was 59 and 59% of patients were male. Of these 80 patients, 56% were of African American descent. The most common co-morbidities were hypertension (50 patients or 63%), diabetes mellitus (32 patients or 40%), and chronic kidney disease (20 patients or 25%). Median BMI of patients was 30 IQR (27-38). Morbid obesity was seen in 14 patients (18%). The amount of time between intubation and iEpo initial administration was variable. The median was 17 hours and IQR (8-74). The complete time spent intubated and on mechanical ventilation was a median of 13 days (7-21). Forty-eight patients died while in the hospital (60%) while the remaining patients survived and were then discharged. The main outcome of this study was a change in oxygenation that was measured by PaO_2/FiO_2. This is also known as the PF ratio. This was measured before and after initiation of iEpo with arterial blood gases (ABGs). A median time of 2.9 hours (1.5- 5.0) was noted for ABG collection before iEpo was initiated, and a median time of 2.9 hours (1.3- 4.9) was noted after initiation of iEpo for ABG collection. Patients were excluded if changes were made to the ventilator mode, PEEP, FiO_2, patient position (prone or supine), or initiation/ removal of neuromuscular blockade between the PF ratio measurements. If any changes were made as stated above, 24 hours were given between ABGs before initiation of iEpo. Two variables were allowed between ABG measurements; these were changes in tidal volume or respiratory rate. The term “iEpo responders” was given to anyone who showed a clinically significant improvement in the PF ratio of 10%. The dose of iEpo was started at 50 nanograms/kg of ideal body weight per minute. This was delivered through a syringe attached to an infusion pump which was then placed in the inspiratory limb of the ventilator tubing. At the start of iEpo

dispensing, median PF ratio was 92 (74-122). The most common ventilator mode of patients was AC/VC (88%). The remainder of patients were on APRV. The median PEEP of patients on AC/VC was 12 cm H_20 (10-15). The median FiO_2 was 90 (70-100). The median change in PF ratio after iEpo was 9 mmHg (-9- 37). Fifty percent (40/80) were considered "iEpo responders". The study found that there was not a correlation between the time on iEpo and PF ratio. Prone positioning and a lower PF ratio at initiation of iEpo were associated with iEpo responsiveness. Forty-six patients were proned (56% of total patients) and had a median improvement in PF ratio of 14 mmHg (-6 to 45) (vs. 3 mmHg [-11 to 20], p= .04 for supine patients). This corresponds to a 16% (-6 – 51) change from baseline (vs. 4% [-11 – 25], p= 0.05). Patients with ARDS (defined as PF ratio < 100) were found to be more likely to have a 10% improvement in the PF ratio post-iEpo (59% vs. 35%, p=0.03) and a median improvement of 16 mmHg (-2 – 46). This correlates with a 17% change (-2 – 59) overall. There was also a subset of patients who had considerable changes in both directions. After iEpo administration 38% (n=30) had a 25% improvement in PF ratio over pre-iEpo values while 16% (n=13) had a 25% decrease. Patients with a 25% improvement had lower PF ratios (85 mmHg [69 – 104] vs. 97 [84 – 125], p=0.01). These patients were also found to have a trend toward the greater likelihood of prone positioning not meeting statistical significance (67% vs. 48%, p=0.10). This study was effective in showing that use of iEpo as a rescue strategy may be useful in mechanically ventilated patients with COVID-19.

A strength of this study was the documentation of patient characteristics that included different comorbidities such as cancer, cirrhosis, and organ transplant. Another strength would be the documentation of fluid balance daily, respiratory parameters, ventilator parameters, other therapies such as neuromuscular blockade, anticoagulation, steroids, and other lab data such as

CRP and D-dimer. A weakness of this study is the shared guidelines were not protocolized with iEpo; therefore, it was at the clinician's discretion within each hospital. This study did not track additional PF ratio measurements while on continuous iEpo which did limit the ability to point out differences in respect to concentration of iEpo or the length of time a patient was on iEpo (Sonti et al., 2020).

Ziehr et al. (2021) conducted a retrospective study evaluating prone positioning (PP) with and without the use of iNO. A large singe center study of the physiologic response to PP in patients with mild, moderate, and severe COVID-19 ARDS, which was based on the Berlin definition of ARDS, was completed to understand the effect PP has on gas exchange. This study was conducted between March 2020 and May 2020. All adults that were intubated and on mechanical ventilation with ARDS from COVID-19 were included in this study. Patients were excluded if they were at an outside facility in an ICU prior to transferring or if the PF ratio was greater than or equal to 300 mmHg prior to PP. Patients were also excluded if they were newly started on iNO or a neuromuscular blockade right before PP while supine or immediately after PP. One hundred twenty-two patients were included in this study. The institution advised to have tidal volumes less than 6 mL/kg of predicted body weight, conservative fluid management, and consideration of PP when the PF ratio was below 150 mmHg. PP was also advised to be 16 hours per session. Ultimately, these conditions were up to the physicians since no protocols were in place. The institution did have a multidisciplinary PP team that consisted of experienced ICU registered nurses and respiratory therapists to assist with PP. PEEP was optimized while supine and evaluated after PP. iNO was used at a dose of 20-80 ppm. Four time points were used to assess gas exchange and pulmonary mechanics. The times included immediately after intubation while the patient was still supine (post intubation), pre-PP, post-PP, and the nearest available

time to 16 hours after PP while the patient was still prone (16-hr post PP). The median age of patients was 60 years (51-71 yrs), and the median BMI was 31.5 kg/m^2 (27-35 kg/m^2). Fifty patients or 41% were female. Median hospital day that intubation occurred was one (1-2), and median time from intubation to PP was 37 hours (15-80 hrs). Thirteen patients (10.7%) had pre-PP PF ratios less than 100 mmHg, 102 patients (83.6%) had PF ratios of 100-200 mmHg, and seven patients (5.7%) had PF ratios of 200-300 mmHg. Median time between intubation and post-intubation data was three hours (1-5 hrs). Median time between the pre-PP and the initiation of PP was two hours (1-3 hrs). Median time between the proning maneuver and post-PP data was one hour (1-2 hrs). Median time from the proning maneuver and 16-hour post-PP data was 15 hours (14-18 hrs). PP was seen to have an increase in the PF ratio (median 149 [123-170] to median 226 [169-268] mmHg, $p< 0.001$). Out of the 122 patients, 110 or 90% experienced an increase in the PF ratio with PP. Patients with higher PEEPs (≥14 cmH20) experienced similar benefits to PP as did patients with lower PEEPs. Patients with a BMI greater than or equal to 30kg/m^2 experienced similar oxygenation improvements to those with lower BMIs. Sixty-two patients had pre-PP PF ratios less than 150 mmHg and 60 patients had pre-PP PF ratios greater than or equal to 150 mmHg. When evaluating the change in PF ratio relative to pre-PP PF ratio a greater change was seen in patients with a PF ratio less than 150 mmHg compared to patients with a PF ratio greater than or equal to 150 mmHg (62% [29-107%] vs 30% [10-70%], $p= 0.002$). Twelve patients were started on iNO while supine and a median time of 16 hours (2-36 hrs) later had the addition of PP. Starting iNO pre-PP was associated with a significant increase in the PF ratio (136 [77-168] to 170 [138-213] mmHg, $p= 0.003$). Ten patients or 83% had an increase in PF ratio with iNO alone. Median increases in PF ratio with iNO was 31.6% (19.4-42.6%). Nine patients experienced a 20% improvement or more in the PF ratio. The addition of

PP to iNO increased the PF ratio (145 [122-183] to 205 [150-232] mmHg, p= 0.017). Ninety percent of patients in this study had an improvement in oxygenation with PP. It was effective in showing that PP and iNO increased oxygenation in these patients.

A strength of this study was having almost 50/50 for male to female ratio. A limitation of the study was the lack of protocols for ventilator management as well as prone positioning. Comorbidities were also not considered pre study.

Safety and adverse effects of proning and respiratory pharmacotherapeutics

Binda et al. (2021) conducted a cross sectional study to determine the prevalence of complications in patients with COVID-19 undergoing prone positioning. This study was conducted between March 2020 to June 2020. Patients were included in this study if they had a laboratory confirmed COVID-19 infection, admitted to the ICU, intubated on mechanical ventilation, and treated with prone positioning. Patients were excluded if they were treated with noninvasive ventilation or intubated but not initiated on prone positioning. Prone positioning (PP) was used for all patients as a rescue measure in severe impairment of gas exchange (PF ratio ≤ 100 mmHg) while supine. To prone a patient, at least four healthcare professionals and one experienced team leader were needed to coordinate each step. Before going prone, each patient would have their NG tube suctioned of gastric contents to avoid inhalation. Patients would be rolled prone with their face turned to one side toward a flexed arm and the other arm behind the patient (swimmer position). Each patient would be repositioned every two hours. To prevent/ protect facial points at the most risk of pressure ulcers, a hydrocolloid dressing was placed. The skin and ocular area were assessed before and after PP to look for infection, skin damage, and vascular or thrombotic complications. Sixty-three patients were included in this study. Median age was 59.6 (50.5-65.8 years) with a majority being male (51 [81%]). Median

BMI was 31 and comorbidities were associated with age (p= 0.0299) but not nutritional status (p= 0.1572). The most common comorbidity seen was cardiovascular related. Two hundred nineteen prone cycles were seen throughout this study with a median duration of 18 (IQR 15-20) hours. Thirty-two patients had at least one complication and 15 prone cycles (6.8%) were interrupted requiring the patient to be placed supine. PP was interrupted for prolonged desaturation in seven patients (11.1%) and hemodynamic instability in six patients (9.5%). A pneumothorax was documented on one patient (1.6%) and required an interruption of PP. Bleeding was seen in 25.4% (16/63) of patients with just one requiring intervention for bleeding control and further cessation of proning. Bleeding in the upper airways was seen in 17.5% (11/63) of patients. The mouth and lips were the most common site of bleeding with the nose being second. Eight patients (12.7%) had medical device displacement. For four patients (6.3%), the displacement involved their endotracheal tube. Three patients (4.8%) had their NG tube displaced, and one patient (1.6%) had a vascular catheter displaced. Unplanned extubations or chest tube removals were not recorded during this study. The occurrence of prone related pressure ulcers was 30.2%. Thirty-two pressure ulcers were seen on the head and associated with proning. The cheekbone had eight pressure ulcers documented, the chin had nine documented, the forehead, eyelid, and lips all had three each documented, and the nose had two documented. The occipital area had four documented pressure ulcers as well. The time a patient was in prone position was a significant predictor for prone-related pressure ulcers (p= 0.039).

A strength of this study was the training provided for their staff to have a designated proning team as well as the relatively low number of proning related pressure ulcers. A limitation of the study was being broad with comorbidity such as cardiovascular or saying “others”. This

study was also predominately male, and race/ethnicity were not factored in either. Another limitation is the frequency of repositioning was not recorded while prone.

Degrado et al. (2020) as mentioned previously also had adverse effects seen within the patient population of the study. Twenty-five patients out of 38 were on vasopressors during their ICU admission. These adverse events were evaluated using a certain criterion. This included bleeding using the bleeding assessment tool, methemoglobinemia (> 2%), tachycardia (new heart rate > 100 beats/min or 20% increase within two hours), hypotension (new MAP < 65 mmHg or 20% increase in vasopressors over two hours), and thrombocytopenia (platelet count decreased < 50,000/μL during therapy). Hemodynamic adverse effects were evaluated within two hours of starting therapy. All 38 patients received iEpo during the study. While receiving iEpo, new hypotension occurred in one patient (2.6%), new tachycardia was seen in one patient (2.6%), bleeding was seen in four patients (10.5%) with two patients receiving PRBCs (5.3%), and thrombocytopenia was seen in one patient (2.6%). Eleven patients were transitioned to iNO. While receiving iNO, bleeding was seen in two patients (18.2%) and both of those received PRBCs (18.2%), and methemoglobinemia was seen in six patients (55%). ICU mortality was seen in 19 (50%) patients. Six patients (16.8%) were reintubated during their stay while six other patients (15.8%) received a tracheostomy.

Safaee Fakhr et al. (2021) as mentioned previously conducted a study with 29 patients. The face mask that was built was to provide safe and efficacious breathing of iNO at such high doses. Due to the inhaled concentration of NO and nitrogen dioxide (NO_2), transcutaneous methemoglobin (MetHb) levels and vital signs were taken before, during, and five minutes after stopping iNO treatment. Four indications were used as endpoints for safety: incidence of MetHb elevation above 5% during treatment, occurrence of rebound pulmonary hypertension following

stopping treatment, occurrence of acute hypotension or acute desaturation during treatment, and proportion of patients who developed an acute kidney injury (AKI). Serum creatinine levels were measured to determine AKI. Rebound pulmonary hypertension was monitored clinically and by ECHO. Signs included tachypnea, SpO2 < 80%, decreased MAP by ≥ 50 mmHg, and increased estimated right ventricular systolic pressure by ≥ 10%. The max level of MetHb measured during iNO therapy at 160 ppm was 4.7% and no treatments were stopped because of MetHb levels. No patients developed rebound pulmonary hypertension after cessation of NO therapy. No hypotensive or hypoxemic effects were noted during therapy. Three patients stopped therapy due to mask discomfort. One patient experienced nausea and stopped therapy. No patients developed AKI during hospitalization.

Discussion

What are the outcomes associated with using respiratory pharmacotherapeutics in hospitalized COVID-19 patients?

Acute respiratory distress syndrome (ARDS) is frequently seen within hospitalized COVID-19 patients. This has been associated with capillary endothelial injury and alveolar damage leading to varying degrees and severities of pulmonary artery vasoconstriction. Inhaled pulmonary vasodilators such as nitric oxide (iNO) and epoprostenol (iEpo) have been shown to improve hypoxemia by increasing blood flow to portions of the lungs that are well ventilated which ultimately has led to improvements in ventilation and perfusion matching. Due to the fast spread of the COVID-19 pandemic, there is concern about how effective these pulmonary vasodilators actually are within this patient population.

Degrado et al. (2020) used iEpo as a first line pulmonary vasodilator and escalated to iNO when a 10% change in PF ratio was not reached. iNO and iEpo were both noted to have

improvements in oxygenation but overall did not improve mortality outcomes. Patients within this study were all intubated and on mechanical ventilation. Thirty-eight patients received iEpo and 16 were considered responders as a 10% or greater increase in PF ratio was seen. The iEpo responders had a median change in PF ratio of 34.1 (24.3-53.9) mmHg. Eleven patients were escalated to iNO and seven were considered responders with a median increase in the PF ratio of 23.2 (16.5-28.2) mmHg. Other therapies that were trialed without success before iEpo included neuromuscular blockade, prone positioning, hydroxychloroquine, and tocilizumab. Steroids were trialed only within four patients before iEpo administration. It can be concluded from this study that iEpo and iNO both were efficacious in increasing the PF ratio in the responders' group, but there are many patients who were not responders and therefore did not see benefit from either therapy.

Kataria et al. (2022) looked at how effective iEpo was in non-intubated patients. Patients were on a HFNC with a flow ≥ 50 LPM and FiO2 ≥ 80% and were being actively treated with corticosteroids. It was found that the iEpo treatment group still experienced 70% of patients requiring intubation/mechanical ventilation. The control group who did not receive iEpo experienced an intubation/mechanical ventilation rate of 90%. Although iEpo did not significantly decrease the rate of intubation/mechanical ventilation, it did prolong the time from HFNC initiation to intubation within the treatment group by a median of 3.4 days. It was also found that iEpo responders ultimately had decreased FiO2 requirements (90% to 75%) within 24 hours after receiving iEpo compared to 100% FiO2 in non-responders. Responders had a lower rate of mechanical ventilation (50% vs 88%, p= 0.025 and mortality 21% vs 63%, p= 0.024) compared to non-responders. Something to keep in mind for this study is that patients were

deemed responders if they had a 10% or more reduction in FiO2 within the first 24 hours of treatment instead of a 10% increase in PF ratio compared to other studies.

All COVID-19 patients within the study conducted by Matthews et al. (2022) were required to have a trial of non-invasive ventilation first, followed by intubation with mechanical ventilation if deterioration occurred. Corticosteroids and IL-6 inhibitors such as tocilizumab and sarilumab were utilized before initiation of intubation. IL-6 inhibitors have previously not been studied in any of the other literature used within this project. If patients were intubated, they would each undergo a minimum of three proning cycles and were started on a neuromuscular blocker. A barrier within this study is the use of kilopascals (kPa) instead of millimeters of mercury (mmHg). iNO as well as Iloprost were used for hypoxemia as well. Iloprost is a synthetic prostacyclin whereas epoprostenol is a prostacyclin. These are both prostaglandin analogues which reduce platelet aggregation and cause smooth muscle relaxation. However, when looking at other medications used within other studies, Iloprost has not been a medication of choice. iNO was started if the PF ratio was less than 13.3 kPa (or 100 mmHg). If improvement was seen in oxygenation with iNO, it was then weaned down and Iloprost nebulizers were initiated. Fifty-nine patients received a pulmonary vasodilator with nine receiving only iNO, 11 receiving Iloprost, and 39 receiving a combination of iNO and Iloprost. Two hundred forty-one patients did not receive any pulmonary vasodilator. Patients who received only iNO had a quicker and higher improvement in oxygenation compared to Iloprost. Only 55% of patients receiving a pulmonary vasodilator survived to ICU discharge compared to 81.9% of patients that did not receive treatment who survived until discharge. It is also of note that patients receiving a pulmonary vasodilator had lower initial PF ratios and higher APACHE-II scores indicating a more severe illness was noted in these patients. It can be concluded from this study that iNO was

a better choice of medication compared to Iloprost with improvements seen, but ultimately these patients had more severe illnesses based on the APACHE-II scores and succumbed to mortality while in the ICU.

Niss et al. (2022) looked at different variables that could be associated with a positive response to iEpo. The positive response was a 10% improvement in PF ratio within six hours of starting iEpo. Research found that as the baseline PF ratio increased it was less likely to see a positive response to iEpo ($p< 0.001$) and SARS-CoV-2 ARDS (COVID-19 ARDS) was significantly associated with a decreased likelihood to have a positive response to iEpo ($p=0.007$). Patients who did not have COVID-19 ARDS (such as pneumonia) were seen to have a response rate of 72.7% and SARS-CoV-2 ARDS had a 59.5% response rate to iEpo. Despite longer duration of iEpo therapy in the SARS-CoV-2 ARDS patients, a smaller change in the PF ratio was seen. Overall, for this study there was still a median increase in PF ratio from 71 to 95 mmHg ($p<0.001$) with iEpo therapy. It is also of note that neuromuscular blockers, prone positioning, corticosteroids, bronchodilators, vasopressors, and diuretics were all therapies trialed before initiation of iEpo. We can conclude from this research that iEpo was still effective in improving oxygenation, but COVID-19 ARDS did have a lower response rate when compared to ARDS from other disease processes.

Safaee Fakhr et al. (2021) looked further at the efficacy of iNO in non-intubated, spontaneously breathing patients. High doses of 160 ppm were utilized twice daily through a face mask built by the research team. When looking at this in contrast to other studies using iNO, the highest iNO dose was 80 ppm in intubated patients. To be included for this study patients had to have “COVID-19 symptoms” that included a respiratory rate ≥ 24 breaths/min (tachypnea) and a cough. It was found that during iNO therapy, patients who had tachypnea experienced a

decrease in their respiratory rate which demonstrates the role nitric oxide plays in relieving respiratory distress. Patients who were hypoxemic before treatment also experienced improvements in oxygenation during iNO therapy. The respiratory rate was seen to decrease by one breath per minute each day of iNO treatment. Only one patient out of the 29 needed intubation and no deaths were seen. It was also noted that no hospital readmissions were noted after iNO therapy. iNO was found to be very efficacious within these non-intubated patients. Kataria et al. (2022) was the only other study to look at non-intubated patients. This study did not use iNO and instead used iEpo, which saw a decrease in FiO2 requirements. The response seen with iNO in Safaee Fakhr et al (2021) had greater longer lasting effects and higher improvements in oxygenation.

Overall, studies did show improvements in oxygenation with iNO, iEpo, and Iloprost. iNO did have greater impacts on respiratory rate and longer lasting improvements in oxygenation than the prostaglandin analogues; however, iEpo is less expensive and has less toxicities than iNO. There were many variables within each study along with comorbidities, BMIs, other medications, and therapies that could have further impacted results.

Is the addition of prone positioning associated with increased or better outcomes than respiratory pharmacotherapeutics alone in hospitalized COVID-19 patients?

Prone positioning has been widely used in ARDS patients as an adjuvant treatment along with a neuromuscular blocker, and low tidal volumes. Prone positioning has been shown to improve ventilation by affecting recruitment of dorsal lung regions, increasing end-expiratory lung volumes, increasing chest wall elasticity, decreasing alveolar shunting, and improving tidal volumes. The literature also questions if COVID-19 ARDS is the same as ARDS within other disease processes.

Bagate et al. (2020) put this to the test within their study population. Patients were placed on a neuromuscular blocker and initiated on lower tidal volumes. Prone positioning was then initiated in 16- or 18-hour cycles before returning to a supine position. iNO was then started once the patient was supine at 10ppm followed by iNO with Almitrine at 10 mcg/kg/min. This was a very interesting variable that no other literature from my research has evaluated. Almitrine is a selective pulmonary vasoconstrictor and was proposed several decades ago to be given with iNO to improve the ventilation perfusion mismatch. Echocardiograms were done to assess right ventricular function with the use of Almitrine since it is a vasoconstrictor and can increase right ventricular afterload. Another new variable within this study is a patient was a responder if a 20% or 20 mmHg increase was seen within the PF ratio. The overall PF ratio increased from 77 mmHg supine to 137 mmHg prone. A downside to this study is when patients were supine, they were found to still be hypoxic. While supine the only treatment that increased PaO2 significantly was the addition of Almitrine to iNO. Almitrine and iNO together had the highest PF ratio increase to 180 mmHg and 70% of patients had more than a 50% increase in PaO2. Unfortunately, a huge barrier within this study was the use of Almitrine was limited and a shortage of the drug occurred. Due to this shortage, when refractory hypoxemia happened, 50% of patients ended up dying during the study. A conclusion from this study was made that the addition of Almitrine to iNO produced a very favorable increase in PF ratio; however, it was not seen to correlate with the benefit proning produced on PaO2.

Bell et al. (2022) had 125 patients undergo proning 309 times and deemed certain patients as prone responders and sustained responders. A prone responder was a 10% increase in the PF ratio while prone and a sustained responder was a 10% increase in the PF ratio after returning supine. There were 176 prone responders and 173 sustained responders found. Prone

responders were more likely to be on iEpo. It was also found that patients with a lower PF ratio and on iEpo would respond to prone positioning more favorably. It was speculated by the research team that improved ventilation from iEpo was due to better drug distribution while prone.

Prone positioning was found to correlate with improved PF ratios in the study conducted by Berrill (2021) as seen with Bagate et al. (2020) and Bell et al. (2022). A total of 131 proning sessions were demonstrated with this study and 81% of patients were found to have an improvement in their PF ratio. The median overall PF ratio at the start was 99.8 mmHg and at the end was 151.9 mmHg for a median increase of 46%. Proning was also found to have a significant reduction in FiO2 over the course of this study and arterial oxygenation was seen to significantly increase within most patients.

Most patients within the study conducted by Imtiaz et al. (2022) were receiving hydroxychloroquine, tocilizumab, convalescent plasma, remdesivir, and/or corticosteroids. iEpo was used within this study due to its lower cost and reduced toxicities compared to iNO. Eleven out of the fifteen patients were started on proning before iEpo administration. After initiation of iEpo the mean PF ratio was 119 mmHg. Ten patients had an increase of 10% in their PF ratio at the first ABG check and the number of patients needing to be proned decreased by 46.7%. The second ABG after iEpo had a mean PF ratio of 131.8 mmHg. Nine patients were considered to have severe COVID-19 ARDS before starting iEpo and saw a mean improvement in their PF ratios from 66.1 to 95.7 mmHg. Non-proning patients had an improvement in their PF ratio of 36.1 mmHg after iEpo, whereas prone patients had an improvement of 26.5 mmHg. This conflicts with other studies that showed an added benefit of prone positioning with higher

increases in the PF ratio. However, a mean improvement of 37.3% in the PF ratio was seen within 48 hours of receiving iEpo.

Li et al. (2020) considered a positive response when a 20% improvement in the PF ratio was noted which was also seen in the study conducted by Bagate et al. (2020). iEpo was administered with a mean time of 5.4 hours after being proned. A significant improvement in the PF ratio was noted from 83.3 to 124.7 mmHg. It was found that when prone positioning and iEpo were initiated separately the PF ratio was not significantly different pre- and post- treatments. iEpo and prone positioning were initiated at the same time within 14 patients. This was found to have the biggest increase in PF ratio from 78.9 to 150.2 mmHg. Ultimately 63% of patients had a 20% or greater improvement in the PF ratio when iEpo and prone positioning in combination together.

Sonti et al. (2021) found that prone positioning and a lower PF ratio at the start of iEpo therapy were associated with iEpo responsiveness. Forty-six out of 80 patients were proned and had a median increase in the PF ratio of 14 mmHg which is rather low compared to other studies. Patients with COVID-19 ARDS were found to be more likely to have a 10% improvement in the PF ratio post-iEpo treatment and had a mean increase in PF ratio of 16 mmHg. This study did have the highest mortality rate with 60% of patients ultimately dying in the hospital. It was also found that a subset of patients receiving iEpo had a 25% decrease in their PF ratio. This study showed a wide and modest variability with respect to the benefit of iEpo and prone positioning when compared to other studies.

Ziehr et al. (2021) evaluated prone positioning with iNO in patients with mild, moderate, and severe COVID-19 ARDS and had 122 total patients. Proning was considered for a PF ratio at or below 150 mmHg which is higher when compared to 100 mmHg seen in other studies. This

is also the first study within the research to have a prone positioning multidisciplinary team. Before proning was initiated, seven patients had baseline PF ratios of 200-300 mmHg, 102 patients had PF ratios 100-200 mmHg, and 13 patients had PF ratios less than 100 mmHg. Proning was seen to have a median increase in the PF ratio of 149 to 226 mmHg. Patients with higher PEEPs had the same benefits as patients with lower PEEPs, and patients with higher BMIs also experienced the same benefits as patients with lower BMIs. A greater change after prone positioning was noted within patients that had a PF ratio of less than 150 mmHg at baseline. Starting iNO before proning was associated with significant increases in the PF ratio from 136 to 170 mmHg and 83% of patients receiving iNO had an increase in the PF ratio with iNO alone. Prone positioning and iNO together showed the greatest increase in PF ratio from 145 to 205 mmHg. Overall, 90% of patients within this study experienced an increase in oxygenation and PF ratio with prone positioning.

Overall, the studies suggested that the addition of prone positioning was largely associated with increases in the PF ratio and improvements in oxygenation. The biggest PF ratio improvements were seen with the use of iNO and prone positioning, but iEpo was still effective in showing improvements in the PF ratio as well.

Is it safe to use prone positioning and respiratory pharmacotherapeutics for hospitalized COVID-19 patients? What are the documented adverse effects associated with these treatments?

Prone positioning was widely used as a rescue maneuver throughout the COVID-19 pandemic if PF ratios were < 100 mmHg or if all other options were exhausted. Due to this being a rescue maneuver, more research needs to be conducted regarding the actual safety of proning.

At this time, the safety of proning is weighed using a risk versus benefit approach since the complications and adverse effects have been studied and documented within the literature.

Binda et al. (2021) mentions out of the 63 patients included, 32 had at least one complication from proning. Complications of desaturation, hemodynamic instability, pneumothorax, bleeding, medical device displacement, and pressure ulcers were seen. The duration of proning cycles or the time spent prone was seen to be a significant factor for pressure ulcers ($p= 0.039$). It was also noted in this study that 32 pressure ulcers were documented on the head and were considered to be directly associated to proning. A prone positioning team was used to try to prevent adverse reactions associated with going from supine to prone and was implemented to reposition a patient every two hours while prone. A hydrocolloid dressing was also applied to the head to help prevent pressure ulcers. It is unclear if the prone positioning team or hydrocolloid dressings to patients' heads was ultimately beneficial since pressure ulcers were still reported and adverse effects like medical device displacement were noted with position changes.

Assessment of the adverse effects of iEpo and iNO was conducted by Degrado et al. (2020). While receiving iEpo, evidence found that hypotension, tachycardia, bleeding, and thrombocytopenia were experienced in a small margin of patients. Bleeding was experienced the most at 10.5% of the 38 patients who received iEpo. iNO was transitioned to after iEpo in 11 patients. Evidence showed bleeding and methemoglobinemia within these patients. Methemoglobinemia was seen in 55% of the 11 patients. ICU mortality rate was 50% for this entire study population.

Safaee Fakhr et al. (2021) further assessed the safety and effectiveness of iNO. A higher dose of iNO (160 ppm) was given through a facemask built by the research team. Safety

endpoints were established that would terminate treatment. Methemoglobinemia, rebound pulmonary hypertension after treatment, hypotension or desaturation during treatment, and development of acute kidney injury (AKI) were these endpoints. No treatments were stopped due to methemoglobinemia, no patients developed rebound pulmonary hypertension, no hypotension or hypoxemia was seen, and no patients developed AKI during the study. The mask caused discomfort within three patients which ultimately terminated treatment. Safety was assessed in this study by the outcomes of no adverse reactions at higher doses of iNO than have previously been researched.

While there are a number of studies included within this research, one cannot make conclusions solely based on these findings reported above due to a wide variety of different variables. COVID-19 is still very prevalent with new developments and treatments being researched as new strains and variants are available. Further research needs to be done on this topic to truly understand the disease process of COVID-19, the changes it makes in the long haul, and the efficacy and safety of proning and respiratory pharmacotherapeutics.

Conclusion

Application to Clinical Practice

Due to the field of medicine constantly changing, as well as different treatments and therapy modalities for COVID-19, it is very important to understand the different options available for use. This project was aimed towards the respiratory treatment side of COVID-19 including pulmonary vasodilators and prone positioning.

This research found that with pulmonary vasodilators such as iEpo, iNO, and Iloprost, oxygenation did improve in patients with COVID-19 ARDS. iNO was found to have greater impacts on the patient's respiratory rate and maintained longer lasting improvements in

oxygenation than iEpo or Iloprost. iEpo is used more frequently within these patients due to it being more cost effective and having less toxicities than iNO. The addition of prone positioning with pulmonary vasodilators was largely associated with increases in the PF ratio and further led to improvements in oxygenation. The use of iNO with prone positioning generally produced the largest increase in PF ratios. Adverse effects seen within the research with prone positioning included desaturation, hemodynamic instability, pneumothorax, bleeding, medical device displacement, and pressure ulcers. With the use of iEpo, the most common adverse effect that was seen was bleeding, but hypotension, tachycardia, and thrombocytopenia were also seen. iNO use was shown to have bleeding and methemoglobinemia within intubated patients, whereas the use of iNO in non-intubated patients did not have any adverse effects seen.

The medical field is still learning more and more about COVID-19 every single day. Within future studies, more research needs to be done that analyzes the effects of pulmonary vasodilators and prone positioning within COVID-19 patients to control for comorbid conditions, social demographics, ventilator settings, and various other factors that could influence prognosis.

References

Bagate, F., Tuffet, S., Masi, P., Perier, F., Razazi, K., de Prost, N., Carteaux, G., Payen, D., Mekontso Dessap, A. (2020). Rescue therapy with inhaled nitric oxide and almitrine in COVID-19 patients with severe acute respiratory distress syndrome. *Annals of Intensive Care.* https://doi.org/10.1186/s13613-020-00769-2

Bell, J., William Pike, C., Kreisel, C., Sonti, R., & Cobb, N. (2022). Predicting Impact of Prone Position on Oxygenation in Mechanically Ventilated Patients with COVID-19. *Journal of Intensive Care Medicine*, *37*(7), 883–889. https://doi.org/10.1177/08850666221081757

Berrill M. (2021). Evaluation of Oxygenation in 129 Proning Sessions in 34 Mechanically Ventilated COVID-19 Patients. *Journal of intensive care medicine*, *36*(2), 229–232. https://doi.org/10.1177/0885066620955137

Binda, F., Galazzi, A., Marelli, F., Gambazza, S., Villa, L., Vinci, E., Adamini, I., & Laquintana, D. (2021). Complications of prone positioning in patients with COVID-19: A cross-sectional study. *Intensive & critical care nursing*, *67*, 103088. https://doi.org/10.1016/j.iccn.2021.103088

Cascella M, Rajnik M, Aleem A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2022 Oct 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK554776/

DeGrado, J. R., Szumita, P. M., Schuler, B. R., Dube, K. M., Lenox, J., Kim, E. Y., Weinhouse, G. L., & Massaro, A. F. (2020). Evaluation of the Efficacy and Safety of Inhaled Epoprostenol and Inhaled Nitric Oxide for Refractory Hypoxemia in Patients With Coronavirus Disease 2019. Critical care explorations, 2(10), e0259. https://doi.org/10.1097/CCE.0000000000000259

Imtiaz, K., Jodeh,W., Sudekum, D., DiGiovine, B. & Hecht, J. (2022).The Use of Inhaled Epoprostenol for Acute Respiratory Distress Syndrome Secondary due to COVID-19: A Case Series. The Journal of Critical Care Medicine, 8(1) 33-40. https://doi.org/10.2478/jccm-2021-0037

Kataria, V., Ryman, K., Tsai-Nguyen, G., Wakwaya, Y., & Modrykamien, A. (2022). Evaluation of aerosolized epoprostenol for hypoxemia in non-intubated patients with coronavirus disease 2019. *Hospital practice (1995)*, *50*(2), 118–123. https://doi.org/10.1080/21548331.2022.2047310

Li, J., Fink, J. B., Augustynovich, A. E., Mirza, S., Kallet, R. H., & Dhand, R. (2020). Effects of Inhaled Epoprostenol and Prone Positioning in Intubated Coronavirus Disease 2019 Patients With Refractory Hypoxemia. Critical care explorations, 2(12), e0307. https://doi.org/10.1097/CCE.0000000000000307

Matthews, L., Baker, L., Ferrari, M., Sanchez, W., Pappachan, J., Grocott, M. P., & Dushianthan, A. (2022). Compassionate use of Pulmonary Vasodilators in Acute Severe Hypoxic Respiratory Failure due to COVID-19. *Journal of Intensive Care Medicine*. https://doi.org/10.1177/08850666221086521

Niss, H. L., Mohamed, A., Berry, T. P., Saettele, T. M., Haines, M. M., & Thomas, E. L. (2022). Evaluation of Continuous Inhaled Epoprostenol in the Treatment of Acute Respiratory Distress Syndrome, Including Patients With SARS-CoV-2 Infection. Annals of Pharmacotherapy. https://doi.org/10.1177/10600280211069182

Safaee Fakhr, B., Di Fenza, R., Gianni, S., Wiegand, S. B., Miyazaki, Y., Araujo Morais, C. C., Gibson, L. E., Chang, M. G., Mueller, A. L., Rodriguez-Lopez, J. M., Ackman, J. B., Arora, P., Scott, L. K., Bloch, D. B., Zapol, W. M., Carroll, R. W., Ichinose, F., Berra, L.,

& Nitric Oxide Study Investigators (2021). Inhaled high dose nitric oxide is a safe and effective respiratory treatment in spontaneous breathing hospitalized patients with COVID-19 pneumonia. *Nitric oxide: biology and chemistry*, *116*, 7–13. https://doi.org/10.1016/j.niox.2021.08.003

Sonti, R., Pike, C. W., & Cobb, N. (2021). Responsiveness of Inhaled Epoprostenol in Respiratory Failure due to COVID-19. *Journal of intensive care medicine*, *36*(3), 327–333. https://doi.org/10.1177/0885066620976525

U.S. Department of Health and Human Services. (2022, March 16). *Origins of Coronaviruses*. National Institute of Allergy and Infectious Diseases. Retrieved December 3, 2022, from https://www.niaid.nih.gov/diseases-conditions/origins-coronaviruses

Ziehr, D. R., Alladina, J., Wolf, M. E., Brait, K. L., Malhotra, A., La Vita, C., Berra, L., Hibbert, K. A., & Hardin, C. C. (2021). Respiratory Physiology of Prone Positioning With and Without Inhaled Nitric Oxide Across the Coronavirus Disease 2019 Acute Respiratory Distress Syndrome Severity Spectrum. *Critical care explorations*, *3*(6), e0471. https://doi.org/10.1097/CCE.0000000000000471