

## Pulmonary vasodilators and critically ill patients with severe SARS-CoV-2 infection: a review.

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Pulmonary vasodilators are an important treatment for pulmonary arterial hypertension. They reduce pulmonary artery pressure; improve hemodynamic function; alter ventilation/perfusion matching in the lungs; and improve functional quality of life, exercise tolerance, and survival in patients with severe pulmonary arterial hypertension. This paper reviews the currently available pulmonary vasodilators and those under development, many of which can be administered via inhalation. I will also give an overview of the clinical pharmacology of, the indications for, and the evidence supporting pulmonary vasodilators, their delivery via inhalation, and potential toxic and adverse effects.

### Background

The ongoing SARS-CoV-2 pandemic causing COVID-19 spread to the United Kingdom in late January 2020. By 30 June there had been 313,483 confirmed cases and 43,906 deaths overall. Information about the pathophysiology of SARS-CoV-2 is evolving. There is an increasing understanding that mechanism of profound hypoxemia in SARS-CoV-2 is unlike non COVID ARDS; with a greater emphasis on diffuse vascular endothelial dysfunction. Abolition of hypoxic pulmonary vasoconstriction, endothelial inflammation and pulmonary thrombosis have all been reported. This prompted us to re-evaluate the impact of pulmonary vasodilators on oxygenation, pulmonary artery pressures and right heart function in patients with COVID lung injury.

### Methods

In this single-centred, retrospective, observational study, we selected 13 critically ill adult patients with SARS-CoV-2 infection who were admitted to our Intensive Care Unit between 16th March and 31st May 2020. Demographic data, acute and chronic comorbidities, symptoms, blood results, echocardiographic findings, treatments and outcomes were analysed. The outcomes of interest were the impact of pulmonary vasodilators on oxygenation, pulmonary artery pressures and right heart function. For comparison, we also took in consideration a control group formed by 7 patients who did not received treatment but did have 2 Echocardiograms.

Data were compared between survivors and non-survivors. The outcomes of interest were the impact of pulmonary vasodilators on oxygenation, right heart function, pulmonary artery pressures and 28-day mortality.

### Findings

Between 16th March and 31st May 2020 we admitted 80 patients with SARS-CoV-2 to our ICU. We enrolled 20 patients. In the treatment group (n=13), 10 patients had confirmed pulmonary artery hypertension on echocardiogram and were treated with epoprostenol and/or sildenafil. Within the treatment group we then identified a survivors group (n=8) and a non-survivors group (n=5). In the control group (n=7) only 2 patients showed pulmonary artery hypertension but were not treated with pulmonary vasodilators. All patients received mechanical ventilation according to lung protective ventilation strategies and were therapeutically anticoagulated. In the survivors group the post treatment PaO<sub>2</sub>/FiO<sub>2</sub> ratio increased by a mean value of 140.440 (SD 90.629, p value 0.010), pulmonary artery pressure decreased by a mean value of 11.0 mmHg (SD 20.43, p value 0.440) and Tricuspid Regurgitation Velocity Max decreased by mean of 45.8 cm/s (SD 93.5, p value 0.302). The survivor group showed a statically significant increase in PaO<sub>2</sub>/FiO<sub>2</sub> ratio compared with non-survivor (140.440 Vs 1.470 p value 0.10). Qualitative assessment of RV function/impairment did not show any significant difference between the 2 groups, with overall a preserved function. Mortality was 39% in the treatment group (n=13), whilst in the non-treatment/control group (n=7) was 29%. The overall mortality (n=78, critically ill patients with confirmed SARS-CoV-2) was 62%.

Numerous conditions give rise to pulmonary arterial hypertension (PAH), with most of them being idiopathic. Signs and symptoms are generally difficult to recognize initially because they present as nonspecific and typically are mistaken for age-related physiological processes or alternate medical conditions. Many advances have been made toward PAH-specific therapies that have led to advanced clinical management of the disease. The present investigation describes new pulmonary vasodilator agents that are currently

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available or under development that could impact perioperative management. The 6-min walk test is the gold standard in assessing the efficacy of any pulmonary hypertension treatment, and the only drug to show any mortality benefit in pulmonary hypertension is epoprostenol. There was a statistically significant improvement in oxygenation with the use of pulmonary vasodilators. There was no improvement in any other outcomes. As has been reported in non COVID ARDS, the use of pulmonary vasodilators improved oxygenation in COVID lung injury. Our study shows that pulmonary vasodilators has a place and can contribute in COVID management. It is safe to use, and by improving oxygenation, they can provide valuable holding measure while other treatment strategies take effect. This small study has its own limitations and should pave way for larger well conducted studies to better evaluate the role of these medications in COVID lung injury.