# The effect of inhaled nitric oxide on shunt fraction in mechanically ventilated patients with COVID-19 pneumonia

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Studies in patients with severe acute respiratory distress syndrome (ARDS) with refractory hypoxaemia suggest that inhaled nitric oxide (iNO) can be added to ventilatory strategies as a potential bridge to clinical improvement. However, the potential role of iNO as a management strategy in severe COVID-19 pneumonia remains unclear. The authors describe their clinical findings of using iNO for severe COVID-19 pneumonia in 10 patients with refractory hypoxaemia in a tertiary respiratory intensive care unit. The results showed an improvement in shunt fraction, P/F ratio, PaO2 and arterial oxygen saturation but the improvements did not translate into a mortality benefit. This report adds to the current body of literature indicating that the correct indications, timing, dose and duration of iNO therapy and how to harness its pleiotropic effects still remain to be elucidated.
**Keywords**. Acute respiratory dieases syndrome, COVID-19, inhaled nitric oxide.

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**What the study adds**
This brief report adds to the body of literature exploring the potential use of inhaled nitric oxide as a management strategy in patients with severe COVID-19 pneumonia with refractory hypoxaemia.
**What are the implications of the findings**
The findings of the report shows that there is a beneficial role of using inhaled nitric oxide to improve respiratory parameters, but that it does not translate to a mortality benefit. It adds to the investigation of establishing which patients, the duration and at what dose, inhaled nitric oxide should be used to gain maximum benefit for this subgroup of patients.

The initial wave of the COVID-19 pandemic will be remembered for the unprecedented burden of patients admitted to intensive care units (ICUs) with refractory hypoxaemic respiratory failure.[1] Studies in severe acute respiratory distress syndrome (ARDS) with refractory hypoxaemia suggest that inhaled nitric oxide (iNO) can be added to ventilatory strategies as a potential bridge to clinical improvement.[2,3] It is well described that iNO improves pulmonary ventilation-perfusion matching by dilating vessels in ventilated parts of the lungs, thereby improving ventilation and reducing pulmonary hypertension. Potential anti-inflammatory, antiviral and antioxidative effects have also been reported.[4,5] Given the pathophysiology of refractory hypoxaemia in severe COVID-19, iNO remains a potential management strategy despite its role in COVID-19 remaining unclear and under investigation.[6]

We report our experience in a tertiary respiratory ICU with the use of iNO in 10 mechanically ventilated patients with refractory hypoxaemia to temporarily improve oxygenation while waiting for clinical recovery. Refractory hypoxaemia was defined as an arterial oxygen pressure ($PaO_2$)/fraction of inspired oxygen ($FiO_2$) (P/F) ratio <100 despite an increased $FiO_2$, prone positioning, the application of high positive end-expiratory pressure of ≥10 $cmH_2O$ or the use of airway pressure release ventilation. A large proportion of our cohort had received neuromuscular blockade and was on vasoactive support, or had been at some point during their ICU stay. Extracorporeal membrane oxygenation was not available at our institution during this time. Our cohort included one patient with confirmed pulmonary embolism and myocarditis, one patient with global myocardial ischaemia, and one patient who was in peri-arrest at the time of iNO administration. All the patients had internal jugular central venous lines *in situ*, with the catheter tip confirmed at the cavoatrial junction.

The iNO mixture was introduced into the inspiratory limb of the ventilator tubing at a concentration of 15 - 20 ppm. Arterial and central venous blood was sampled immediately before iNO initiation and after one and a half hours of iNO therapy, with all other infusions and

**Table 1. Key results from patients receiving inhaled nitric oxide (*N*=10)**

| | Before | | | | | After | | | | | Net change | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Shunt fraction (%) | P/F ratio | $PaO_2$ (kPa) | Arterial $SO_2$ (%) | Central venous $SO_2$ (%) | Shunt fraction (%) | P/F ratio | $PaO_2$ (kPa) | Arterial $SO_2$ (%) | Central venous $SO_2$ (%) | Shunt fraction (%) | P/F ratio (%) | $PaO_2$ (kPa) | Arterial $SO_2$ (%) | Central venous $SO_2$ (%) |
| 1 | 46 | 60 | 7.2 | 84 | 65 | 25 | 90 | 9.7 | 93 | 72 | 21 | 52 | 2.5 | 9 | 7 |
| 2* | 35 | 71 | 9.5 | 92 | 77 | 40 | 57 | 7.6 | 88 | 70 | –5 | –20 | –1.9 | –4 | –7 |
| 3 | 58 | 59 | 6.3 | 73 | 54 | 26 | 91 | 9.8 | 92 | 70 | 32 | 56 | 3.5 | 18 | 16 |
| 4† | 80 | 51 | 5.5 | 79 | 74 | 33 | 71 | 7.6 | 92 | 78 | 46 | 38 | 2.1 | 13 | 4 |
| 5‡ | 79 | 31 | 4.2 | 35 | 19 | 73 | 30 | 4 | 39 | 16 | 7 | –5 | –0.2 | 3 | –3 |
| 6 | 24 | 85 | 8 | 92 | 68 | 20 | 100 | 9.4 | 94 | 70 | 4 | 18 | 1.4 | 1 | 1 |
| 7 | 31 | 67 | 8.5 | 92 | 76 | 8 | 140 | 17.8 | 98 | 86 | 23 | 109 | 9.3 | 6 | 9 |
| 8 | 72 | 40 | 5.4 | 74 | 64 | 37 | 46 | 6.2 | 84 | 56 | 35 | 15 | 0.8 | 10 | –7 |
| 9 | 75 | 32 | 4.3 | 59 | 45 | 62 | 46 | 6.2 | 81 | 70 | 13 | 44 | 1.9 | 22 | 25 |
| 10 | 54 | 38 | 5.1 | 73 | 50 | 31 | 57 | 7.6 | 90 | 70 | 22 | 49 | 2.5 | 17 | 19 |

P/F ratio = $PaO_2/FiO_2$ ratio; $PaO_2$ = arterial oxygen pressure; $FiO_2$ = fraction of inspired oxygen; $SO_2$ = oxygen saturation.
*Patient clinically deteriorated to peri-arrest state at time of nitric oxide administration.
†Patient with confirmed pulmonary embolism and myocarditis on inotropic support.
‡Patient in peri-arrest state with global myocardial ischaemia on inotropic support.

ventilator settings left unchanged. The shunt fraction was calculated using the Berggren equation with the central venous saturation used as a surrogate for the mixed venous saturation.[7]

The patients in our cohort were treated during the first wave of the COVID-19 pandemic from May to July 2020. We report the effect of iNO on shunt fraction, response, $PaO_2$ and central venous oxygen content. Responders to iNO therapy were defined as having a 20% increase in the P/F ratio.[8]

The results show that in our cohort there was a mean decrease in shunt fraction of 20%, an increase in $PaO_2$ of 2.2 kPa, an increase in arterial oxygen saturation ($SO_2$) of 10% and an increase in central venous $SO_2$ of 7%. There was an average increase in P/F ratio of 19. If patients 2 and 5 (iNO initiated as a salvage measure in a peri-arrest situation) are omitted from analysis, the mean decrease in shunt fraction is 25%.

The patient diagnosed with a pulmonary embolism (patient 4) had the greatest decrease in shunt fraction at 46%. While 4 patients (patients 1, 3, 7 and 10) had large increases in P/F ratio and $PaO_2$, all had a decrease in shunt fraction of at least 20%. Six of the 10 patients (60%) were considered responders to iNO therapy. Only 2 patients, patient 2 (peri-arrest) and patient 5 (peri-arrest, with global myocardial ischaemia on inotropic support), demonstrated worsening of their P/F ratio. No patient survived to ICU discharge.

Our findings are similar to existing reports on the effects of iNO therapy on oxygenation and P/F ratio. Both 'no change' and a 'significant change' in $PaO_2$ and P/F ratios have been reported at similar iNO concentrations and durations.[9,10]

Given our study population, namely only patients with refractory hypoxaemia (as defined above) and a mean P/F ratio of 53.7, for whom no other therapeutic options were available, the magnitude of the average improvement in shunt fraction is striking, with the majority of patients demonstrating >20% improvement in shunt fraction and $PaO_2$. These results included two peri-arrest patients, in whom the addition of iNO was a salvage attempt to reverse the decline.

The optimal dose, duration and timing of iNO to produce maximal clinical benefit are not known. Similar to previous studies, the positive change of parameters did not translate to an improvement in mortality. This may reflect both the extremely late application of iNO in the course of the disease pathology and the amount of iNO therapy we were able to provide, owing to its high cost. Earlier application of iNO may well have altered outcomes, given the clinical improvement and documented pleiotropic and antiviral properties of iNO.[5]

We found no other reports investigating the effect of iNO on shunt fraction specifically. The significant decrease in shunt fraction in the patient with pulmonary embolism, and its resultant effect on central venous and arterial oxygenation, demonstrated how the compounded pathophysiological effects of both pulmonary embolism and severe ARDS on shunting were attenuated by iNO.

The patients who deteriorated or failed to improve with iNO were both peri-arrest, and the lack of response can be explained by the negligible effect that an increase in arterial or central venous oxygen content might have in the presence of a low cardiac output.[11] We postulate that a positive response would have been seen if isolated right ventricular dysfunction was present, owing to the effect of iNO on pulmonary vascular resistance and the subsequent increase in cardiac output.

The limitations of our retrospective data analysis should be noted. We included unstable patients, with a mean P/F ratio of 53, in our cohort,

and there were no specific selection criteria for iNO administration other than refractory hypoxaemia, which had failed all other traditional ventilation strategies for ARDS. The benefit seen in our cohort could be influenced by the severity of hypoxaemia of the patients, where the effect of a positive change would be more evident. The use of central venous saturation as a surrogate for mixed venous saturation has many limitations, as mixed venous saturation is the flow-weighted average of coronary sinus and superior and inferior vena cava blood.[12] However, the error when using central venous oxygen content is more pronounced in patients with sepsis, where inferior vena cava and coronary sinus flow has a dominating influence, as well as in low cardiac output states. A strength of these findings is that the study population all had the same disease pathology, namely severe COVID-19 pneumonia, which was not the case in much pre-COVID-19 work with iNO and ARDS.

Despite the severity of disease, iNO therapy for severe ARDS with refractory hypoxaemia produced a positive change in $PaO_2$, P/F ratio and shunt fraction. This did not translate to a mortality benefit in our population, probably owing to the limited duration of therapy with iNO and the severity of illness. This report adds to the body of literature investigating the correct indications, timing, dose and duration of iNO therapy and how to harness the other pleiotropic effects of iNO to decrease mortality in patients with severe ARDS. An intriguing observation is the potential benefit of iNO for dual pathologies such as pulmonary embolism with severe ARDS, but this requires further investigation and confirmation.

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