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Nitric oxide: Clinical applications in critically ill patients

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Abstract

Inhaled nitric oxide (iNO) acts as a selective pulmonary vasodilator and it is currently approved by the FDA for the treatment of persistent pulmonary hypertension of the newborn. iNO has been demonstrated to effectively decrease pulmonary artery pressure and improve oxygenation, while decreasing extracorporeal life support use in hypoxic newborns affected by persistent pulmonary hypertension. Also, iNO seems a safe treatment with limited side effects. Despite the promising beneficial effects of NO in the preclinical literature, there is still a lack of high quality evidence for the use of iNO in clinical settings. A variety of clinical applications have been suggested in and out of the critical care environment, aiming to use iNO in respiratory failure and pulmonary hypertension of adults or as a preventative measure of hemolysis-induced vasoconstriction, ischemia/reperfusion injury and as a potential treatment of renal failure associated with cardiopulmonary bypass. In this narrative review we aim to present a comprehensive summary of the potential use of iNO in several clinical conditions with its suggested benefits, including its recent application in the scenario of the COVID-19 pandemic.

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Appendix A. Supplementary data

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Randomized controlled trials, meta-analyses, guidelines, observational studies and case-series were reported and the main findings summarized. Furthermore, we will describe the toxicity profile of NO and discuss an innovative proposed strategy to produce iNO. Overall, iNO exhibits a wide range of potential clinical benefits, that certainly warrants further efforts with randomized clinical trials to determine specific therapeutic roles of iNO.

Keywords

Nitric oxide; Critically ill; Clinical applications; Pulmonary hypertension; Ischemia/reperfusion injury; Toxicology; COVID-19

1. Introduction

Nitric oxide (NO) is an endogenous molecule produced by Nitric Oxide Synthases (NOS), through the oxidation of L-citrulline and L-arginine [1]. It is secreted tonically and in response to shear stress by healthy endothelial cells, where it acts as a major mediator of vascular relaxation [2]. This effect is determined by the NO-mediated activation of soluble guanylate cyclase, which catalyzes the formation of the second messenger cyclic guanosine monophosphate and eventually leads to vasodilation [3]. In addition, NO reduces smooth muscle cells proliferation [4], platelet aggregation [5] and endothelial leukocyte binding [6]. Consequently, it exerts a protective role on blood vessels and participates in vascular homeostasis [7]. NO bioavailability may be decreased, for example, by L-arginine deficiency and depletion of tetrahydrobiopterin, an NOS cofactor [8]. This determines a disproportion between antiproliferative, antithrombotic and vasodilatory effects and proliferative, prothrombotic and vasoconstrictive substances. This imbalance contributes to a pathological condition known as endothelial dysfunction, which has been involved in the pathogenesis of cardiovascular diseases [9].

As a therapeutic agent, NO is available as inhaled NO (iNO) or carried by NO donors, like sodium nitroprusside or organic nitrates administered via parenteral route [10]. iNO is a selective pulmonary vasodilator which exhibited no systemic vasodilating effects [11], even when inhaled at concentrations as high as 160 ppm [12], while, on the contrary, NO donors induce both pulmonary and systemic blood vessels relaxation [10]. Currently, iNO requires storage in tanks and its use is limited to short period treatment and inpatient settings.

At present, the only indication for iNO use approved by the Food and Drug Administration (FDA) is the treatment of persistent pulmonary hypertension of newborns (PPHN) [13]. Along with this indication, iNO has been considered as a potential treatment for other diseases, ranging from the pulmonary arterial hypertension (PAH) of the adults [14] to the acute respiratory distress syndrome (ARDS) [15]. Moreover, recent data investigated the use of iNO to prevent hemolysis-induced vasoconstriction [16], decrease the ischemia/reperfusion injury [17] and prevent the renal failure associated with cardiopulmonary bypass (CPB) [18]. In this review, we aim to describe the current evidence on the use of iNO in these various clinical situations, along with its toxicity profile. Moreover, a novel strategy to produce iNO will be discussed. A summary of the performed and ongoing randomized controlled trials (RCTs) administering NO therapy is presented in Table 1 and Table 2,

respectively. A concise representation of the potential benefits of NO in humans is depicted in Fig. 1.

2. Methods

A search of the literature of Medline database published until January 19, 2022 was performed to detect publications evaluating the use of NO in clinical context. Priority was given to RCTs, meta-analysis and guidelines. When this evidence was not available, observational studies and case series were considered. The Mesh term “Nitric Oxide” was used along with the Mesh Terms that identified the conditions and diseases treated in this review. Ongoing clinical trials were identified through search on clinicaltrials.gov, being RCT preferred over other study designs. “Nitric Oxide” was entered as drug name and descriptors of the conditions or diseases related to this review were used (see Supplement 1 for the complete list of search terms). Other relevant articles not included in our original search were identified through snowballing.

3. Clinical applications of NO

3.1. iNO for persistent pulmonary hypertension of the newborn

iNO is approved by the FDA for the treatment of PPHN at the dose of 20 ppm for up to 14 days [13]. iNO improves oxygenation and decreases extracorporeal membrane oxygenation (ECMO) use in term and late preterm newborns with PPHN. It was Kinsella et al. [74] and Roberts et al. [75], who first described the benefit of iNO up to 80 ppm on oxygenation in newborns with PPHN. Since then, many trials confirmed these results and found a reduction in ECMO use with iNO treatment [30,38,50,74,75]. More widely, the beneficial effect of iNO in newborns was confirmed by a Cochrane systematic review and meta-analysis in 2017 [76]. Indeed, iNO reduced the incidence of the combined endpoint of death or use of ECMO in term or near-term newborns with hypoxemic respiratory failure. However, this reduction was due to a decrease in the use of ECMO, while mortality was not affected. Moreover, oxygenation was improved. These beneficial effects occurred regardless of whether or not there was echocardiographic evidence of PPHN.

3.2. iNO for chronic pulmonary arterial hypertension

iNO is commonly used for vasoreactivity testing to identify patients with PAH primarily caused by increased pulmonary vascular resistances (PVR), in the absence of severe vascular remodeling. Only patients with idiopathic, heritable or drug-induced PAH are tested as they are the most likely to show vasoreactivity [77]. In the other forms of PAH the test is not indicated as iNO may exacerbate pulmonary edema due to left heart failure and in other types of PAH evidence is lacking [77]. As suggested by current guidelines this test is performed before the initiation of any PAH-specific treatment to identify potential responders to calcium channel blockers [78]. Although vasoreactivity testing is performed in those with idiopathic, heritable, or drug-induced PAH to determine candidacy for calcium channel blocker therapy, observed decreases in PVR and mean pulmonary arterial pressure (PAP) with iNO are independent predictors of survival across the broad range of etiologies for PAH [79,80]. Chronic vasodilatory therapy may precipitate pulmonary edema,

if pulmonary venous hypertension coexists. In such circumstances, short acting iNO can be used to establish whether pulmonary arterial vasodilator might be detrimental [81].

There are few studies evaluating the indication of iNO for the treatment of PAH, due to lack of accessibility of iNO in the out-patient settings. Data from case reports and observational studies showed that long term iNO improved PAH and sometimes relieved symptoms [14, 82–84]. Results from a randomized controlled trial are awaited (NCT01457781), albeit a beneficial effect on mortality was not reported so far. Moreover, a recent meta-analysis reported that perioperative administration of NO in patients with PAH undergoing cardiac surgery had no clinical benefits in term of ICU stay, mortality, duration of mechanical ventilation and reduction of PAP [85].

3.3. iNO for the treatment of ARDS in children and adult patients

Historically, a low dose of iNO (e.g. 5–20 ppm) was demonstrated to improve arterial oxygenation and reduce PAP, in patients with severe ARDS [44]. iNO is a potent selective pulmonary vasodilator. Indeed, it has a half-life of 2–6 s [86] as it is rapidly scavenged by hemoglobin [87] and is also metabolized to more stable nitrite dioxide and nitrite trioxide, which lack the vasodilatory properties of NO. Moreover, it is delivered locally by inhalation. These properties make iNO able to dilate selectively the pulmonary vessels of ventilated lung units, consequently improving ventilation/perfusion matching, without causing systemic hypotension [3]. Despite this physiologic effect, iNO is not part of routine therapy in ARDS, while it is suggested as one of the therapeutic “rescue” strategies for severe hypoxemia. This is because of its transient effects lost after 24–48 h and because no benefit on survival or other clinical outcomes (e.g., ventilator-free days (VFD), ICU length of stay) was demonstrated. Moreover, in some studies, iNO seemed to worsen renal function [88–90]. For these reasons, the United Kingdom Faculty of Intensive Care Medicine guidelines give a weak recommendation against the use of iNO in ARDS [91]. The current guideline of the American Thoracic Society for ARDS treatment does not make any recommendation about the use of iNO, however they consider inhaled vasodilators as an issue to be addressed in the future iterations of the guideline [15]. Nevertheless, although no clear clinical benefit was observed, iNO is still administered in up to 13% of severe ARDS patients worldwide [92].

Interestingly, the sepsis-associated ARDS deserves a particular mention. Indeed, it is well-known that endogenous NO is increased in sepsis due to upregulation of inducible NOS and plays a pivotal role in the sepsis-induced hypotension. Although hypotension is detrimental, NO vasodilation could have a role in keeping microvessels patent and thus preserve the microcirculatory perfusion [93,94]. A preclinical study showed that sepsis-associated endogenous NO upregulation may decrease iNO effect on pulmonary circulation [95]. Other evidence suggested that iNO diminished lung inflammation and injury and decreased endogenous NO upregulation at the lungs [96,97]. In this case, iNO would act as negative feedback on endogenous NO production. Data are limited and the effects of iNO in this subtype of ARDS have to be investigated to clarify whether iNO could improve the management of this disease.

3.4. iNO in Covid19 patients

The Covid19 pandemic has been challenging healthcare systems all over the world, due to the high hospitalization rate and the high incidence of ARDS, requiring ICU admission [98,99]. Severely hypoxemic patients may require ECMO, however due to limited resources this option might not be applicable. For this reason, iNO, due to its property to improve V/Q matching, may serve as an alternative or as a bridge to gain time for availability of resources or lung healing. Moreover, iNO may have a direct antimicrobial effect against Sars-CoV-2, as suggested by an *in vitro* study, in which Sars-CoV-infected cells had higher survival when exposed to *S*-nitroso-*N*-acetylpenicillamine (SNAP), an NO donor [100]. Similarly, also Sars-CoV-2-infected cells were exposed to SNAP and a dose-dependent inhibitory effect on replication of Sars-CoV-2 was observed. In addition, SNAP delayed or completely prevented the development of the viral cytopathic effect [101]. Other proposed potential benefits of iNO are a bronchodilatory [102] and anti-inflammatory effect [103]. To date, data are limited and mainly consist of case series and results are contrasting. iNO is administered at doses ranging from 10 to 80 ppm in mechanically ventilated patients. A report of 16 patients with Covid19-related refractory hypoxemia (defined as P/F ratio <100, despite PEEP ≥10 cmH2O and prone position) showed iNO at 20–30 ppm did not improve oxygenation. However, a trend towards a better response was observed in patients with concomitant Covid19 pneumonia and right ventricular dysfunction [104]. Similarly, a pilot study on 10 patients with severe hypoxemia (FiO2 80%, PEEP 15 cmH2O) showed no benefit on oxygenation after a trial of iNO at 20 ppm for 30 min [105]. In contrast, a study on 34 patients, showed that iNO at 10 ppm administered when P/F ratio was under 150 improved P/F ratio from a median of 70 to 144 in 65% of the subjects included in the study [106]. The responders had a lower P/F ratio compared to non-responders (70 vs 134, $P < 0.0001$). Similarly, another study on 12 patients demonstrated that iNO 20–80 ppm resulted in a P/F ratio change from 136 to 170 in the supine position and a decrease in the dead-space-to-tidal-volume ratio from 0.54 to 0.46. Subsequent prone positioning, further increased the P/F ratio from 145 to 205 [107]. However, differences in the iNO dose and the timing of iNO administration (early vs late-rescue therapy after intubation) might explain these different results. Moreover, combined iNO at 10 ppm and almitrine supplementation significantly increased P/F ratio from 102 at baseline to 180. As almitrine acts as a pulmonary vasoconstrictor, the iNO vasodilatory effect might have been enhanced by flow diversion towards better ventilated lung areas, thus improving V/Q matching [108].

iNO has also been suggested as adjuvant treatment in spontaneously breathing patients with severe Covid19. Twenty-nine patients with Sars-CoV-2 infection confirmed and cough or tachypnea (respiratory rate above 24 breaths/minute) received high dose iNO (160 ppm) twice a day for 30 min up to 14 days via a face mask, until resolution of symptoms, discharge, intubation, or transition to palliative care. iNO decreased respiratory rate in tachypneic patients and improved oxygenation when hypoxemia was present. Moreover, iNO was well tolerated in spontaneously breathing patients and it was safe as MetHb and nitrogen dioxide levels were below the safety threshold [109,110]. High dose iNO has also been tested on six pregnant patients with Covid19 hypoxic respiratory failure. iNO improved oxygenation and was well tolerated, suggesting a possible benefit of this treatment [103].

Thus far, no efficacy of iNO in Covid19 patients can be inferred, due to the lack of data and their limited quality. Randomized controlled trials could elucidate the role of iNO in this specific disease [71,72].

3.5. iNO and its role on hemolysis

Intravascular hemolysis increases levels of free hemoglobin in the blood. This causes a depletion of endogenous NO bioavailability and oxidative stress. This inflammatory state leads to endothelial dysfunction, impairment of the microvascular flow and vaso-occlusive organ damage [111]. Intravascular hemolysis is common to several diseases, such as severe malaria and sickle cell disease. These have been considered for adjunctive treatment with iNO. Indeed, severe malaria is characterized by decreased NO bioavailability and has a mortality rate of 10–30% [112], despite the availability of effective anti-malarial medications. Increasing evidence suggested that iNO may dampen endothelial activation, reduce injury in the pulmonary vessels and exert neuroprotective properties [113,114]. Moreover, in clinical trials, iNO did not affect levels of Angiopoietin 2, a biomarker of endothelial activation and malaria severity [69,70]. However, iNO administration up to 80 ppm was safe [68,70] and reduced the risk of fine motor impairment in patients affected by cerebral malaria [67]. No study evaluated the effect of iNO on survival as the primary outcome in patients with malaria.

Also sickle cell disease is associated with impaired NO metabolism [115], thus iNO was administered as possible adjuvant to improve clinical outcomes in patients with sickle cell disease complicated by veno-occlusive disease, presented as acute chest syndrome or acute painful crises. One small RCT found iNO to effectively decrease mean pain scores referred by the patients [64]. On the contrary, two more recent trials found iNO did not decrease either the duration of painful crisis [66], or the treatment failure rate of acute chest syndrome, defined as (1) death from any cause, or (2) need for endotracheal intubation, or (3) decrease of $PaO2/FiO2 \geq 15$ mmHg between days 1 and 3, or (4) augmented therapy defined as new transfusion or phlebotomy [65]. An ongoing study is evaluating whether iNO can improve PAH in patients with sickle cell disease (NCT00023296).

Another potential application of iNO is during transfusions of stored red blood cells (RBC). Stored RBC undergo hemolysis and thus have high concentrations of microparticles, free hemoglobin, heme and iron, which are then released into circulation when transfused [116]. Hemoglobin free in plasma and contained in microparticle rapidly depletes endogenous NO through its scavenging. This induces endothelial cells dysfunction and may result in pulmonary and systemic hypertension [16,117–120]. Risbano et al. demonstrated that arginase-1 and free hemoglobin levels increased in healthy volunteers who received an intraarterial transfusion of autologous 42-day-old RBC. Both arginase-1 and free hemoglobin have been associated with endothelial dysfunction. Moreover, they demonstrated that 42-day-old RBC decreased the expected vasodilatory response to intraarterial infusion of acetylcholine, probably by scavenging of NO or oxidative inactivation of endogenous NO. The administration of iNO proved to be effective in preventing these detrimental effects of stored RBC transfusion both preclinically and clinically [16,121]. Of note, Berra and colleagues demonstrated that transfusing 40-day

old blood increased mean pulmonary artery pressure (18 ± 2 to 23 ± 2 mmHg; $P < 0.05$) in obese adults with endothelial dysfunction, estimated through cardiac ultrasound. Whereas, breathing NO at 80 ppm during transfusion avoided the increase in pulmonary artery pressure (17 ± 2 to 12 ± 1 mmHg; $P < 0.05$), while transfusing aged stored RBC [16].

3.6. iNO and its role on myocardial injury

NO may exert cardioprotective properties. Although limited data are available, a study examined the role of NO at 20 ppm on 29 patients. NO was administered for 8 h during and after CPB. In this group, biomarkers of myocardial injury, like creatine kinase MB (CK-MB) fraction, total CK, and troponin I (TnI) were significantly lower than in the control group. This suggests that NO may blunt the subclinical myocardial injury typical of CPB. Another study on 69 patients undergoing coronary artery bypass graft, showed that adding NO at 40 ppm to the oxygenator of the CPB decreased the level of CK-MB and TnI and the inotropic requirement. Also, the effect of iNO on ischemic reperfusion injury in patients revascularized after ST-elevation myocardial infarction was explored. Although iNO at 80 ppm for 4 h after reperfusion was safe, no reduction in infarct size was observed. Moreover, the Kaplan–Meier analysis for the composite of death, recurrent ischemia, stroke, or rehospitalizations showed a tendency toward lower event rates with iNO at 4 months and 1-year follow-up, warranting further investigations. In addition, iNO determined acute hemodynamic improvements in 13 adults patients with right ventricle infarction and cardiogenic shock. Indeed, iNO significantly decreased mean right arterial pressure, mean pulmonary artery pressure and pulmonary vascular resistance and increased the cardiac and stroke volume indexes. The cardioprotective effects of NO donors were also evaluated in patients with acute ST-elevation myocardial infarction undergoing percutaneous coronary intervention. In these two RCTs it has been observed no reduction of infarct size in both systemic and intracoronary administration of sodium nitrite.

3.7. Protective role of NO on cardiac output and kidney function during cardiopulmonary bypass

Cardiac surgery for CHD is characterized by a CPB-induced systemic inflammatory response [122]. This determines the low cardiac output syndrome (LCOS) [123] and increases morbidity and mortality [124]. Supplemental NO, with its anti-inflammatory properties, may dampen the negative effects of CPB. A small study on 16 children found 20 ppm of NO halved the duration of mechanical ventilation and shortened the ICU length of stay of 1 day. It also lowered troponin levels and B-type natriuretic peptide concentrations when compared to the placebo group [59]. Another larger trial on 198 infants and children showed the NO group developed fewer LCOS than the control group (15% vs 31%, $p = 0.007$) [58]. Also, the ICU stay was nearly halved in the NO group and ECMO was used less frequently. This trial also showed a trend towards decreased duration of mechanical ventilation, especially in children aged less than 2 years old. To further investigate this latter result, the NITRIC trial was designed and is ongoing [125]. In addition, some other trials showed NO decreased the incidence of postoperative PAH crises when administered during CPB [60,61].

Another common complication of CPB is acute kidney injury (AKI) is [126,127]. To date, no therapeutic agent is available to prevent the postoperative decline in renal function. The mechanism is multifactorial. Advanced age, female sex, preoperative comorbidities (e.g., diabetes mellitus, heart failure chronic obstructive pulmonary disease, obesity) play a pivotal role in the development of AKI. Moreover, CPB- and cardiac surgery-related conditions (e.g., duration of aortic clamping and CPB, pulsatile vs non pulsatile flow, normothermic vs hypothermic CPB, hemolysis during CPB) has been involved in the pathogenesis of this complication [128]. Indeed, patients undergoing cardiac surgery often present endothelial dysfunction, which may play a role in increasing the risk of postsurgical AKI [73]. In addition, higher levels of free hemoglobin and NO consumption were identified in patients after CPB compared to preoperative levels and hemolysis correlated with the increase in pulmonary and systemic vascular resistances [120]. Therefore, it could be suggested a beneficial effect of exogenous NO on hemodynamics during CPB, which could improve the cardiac output and consequently the renal perfusion. Moreover, hemolysis induced by the CPB releases free hemoglobin, which is filtered by the kidney, may directly determine oxidative damage [129] and may deplete endogenous NO, causing vasoconstriction and inflammation [130]. Preclinical studies showed that NO regulates major metabolic pathways in the proximal tube of the kidney. These are important to prevent oxidative stress, which eventually leads to AKI [131]. A recent systematic review and meta-analysis of 5 trials found that NO was associated with a reduced risk of AKI, particularly when administered from the beginning of CPB (RR 0.71, 95% CI 0.54–0.94, I^2 = 10%). NO increased the MetHb level, but it had no clinical impact [132]. Of note, Lei et al. administered NO up to 80 ppm through the membrane lung and by inhalation during the postoperative period for 24 h to patients undergoing multiple cardiac valve replacement. NO proved to decrease AKI (RR 0.78 [95%CI 0.62–0.97]) and transition to stage 3 chronic kidney disease both at 90 days (RR 0.64 [95%CI 0.41–0.99]) and at 1 year follow-up (RR 0.59 [95%CI 0.36–0.96]). Furthermore, NO decreased major kidney adverse event (i.e. a composite outcome of loss of 25% of eGFR from baseline, end-stage renal disease requiring a continuous renal replacement therapy, and mortality) at 30 and 90 days and 1 year after ICU admission [18]. However, the study population was relatively young (mean age 48). Furthermore, rheumatic fever was the main cause of valvular heart disease. To test whether the beneficial effect of NO to prevent post cardiac surgery AKI may be widened to older patients in the presence of endothelial dysfunction, a trial is currently ongoing at Massachusetts General Hospital [73] (NCT02836899). Also, other studies are investigating whether NO prevents AKI after CPB in neonates undergoing cardiac surgery due to congenital heart diseases (CHD) (NCT04216927, NCT03946462).

3.8. iNO as a treatment during cardiac arrest

iNO has been considered as a potential therapeutic agent in patients with cardiac arrest (CA) [133]. Hypoxic-ischemic brain injury is a key component of the post-reperfusion state known as post-CA syndrome, accounting for poor neurological outcome and poor survival rates observed after return of spontaneous circulation (ROSC) [134]. Post-CA syndrome is characterized by systemic inflammation with diffuse endothelial dysfunction, increased vascular permeability, as well as platelet activation. Together with this pathophysiological alterations, endogenous NO depletion has been observed in this condition [17,135]. Among

the extrapulmonary effects of iNO, protection against brain injury in the post-CA period has emerged in experimental settings. Specifically, reduction of brain inflammation and oxidative stress represent some of the potential mechanisms for neurological preservation offered by NO through a guanylyl cyclase (GC) dependent or independent pathways [135,136]. Several preclinical studies showed that NO inhalation following resuscitation improved survival rate and neurological outcome while reducing brain edema, neuronal apoptosis and cerebral inflammatory cytokines levels [136,137]. Furthermore, iNO increased the proportion of ROSC [138,139], allowing for superior hemodynamics and higher cerebral blood flow [140] when administered during cardiopulmonary resuscitation (CPR) in a pediatric pig model of shock associated-CA [139,140]. Of particular interest for translation from experimental to clinical setting, NO inhalation during CPR has been observed also in a high proportion (~80%) of pediatric in-hospital CA subjects with PH [141]. Interestingly, all patients in whom iNO was increased or initiated during CPR achieved ROSC, and 50% survived to hospital discharge.

Finally, iNO lacks the effect on systemic pressure, typical of NO donor drugs, while it improves transpulmonary blood flow and RV function during CPR performed with a ventricular assist device [142, 143], making it an appealing option for unstable CA patients undergoing ECMO. A recent propensity-matched analysis comparing 20 in-hospital CA adult patients receiving iNO with age-matched controls receiving standard care, showed that iNO is feasible and might be beneficial [144]. Indeed, inhalation of NO 40 ppm starting following resuscitation until 24 h after ROSC was associated with a higher probability of survival at discharge compared to controls (35% vs 20%, $p = 0.034$). Although no difference in favorable neurological outcome was observed [144], the neuroprotective effect of iNO administration during CA until 24 h post ROSC is currently under investigation in a clinical trial (NCT04134078). The primary aim of this study is the rate of ROSC and cerebral oxygenation in patients with in-hospital CA. Also neurological outcomes at hospital discharge and 6-month survival will be evaluated.

3.9. NO as a neuroprotectant

The neuroprotective properties of NO has been shown also in various neurologic disorders. Preclinical data showed that it may dampen ischemic/reperfusion brain injury [17,145], preserve cerebral autoregulation after traumatic brain injury [146], prevent from cerebral vasospasm after subarachnoid hemorrhage [147], improve regional blood flow and decrease infarct size in ischemic stroke [148,149]. An analysis of the ENOS trial showed transdermal glyceryl trinitrate (GTN), a NO donor, improved functional outcomes and decreased deaths in the subgroup of patients which received GTN within 6 h from stroke [150]. The RIGHT trial showed the improvement in functional outcome, if GTN was administered in the acute stroke [151]. However, due to the small sample size, the RIGHT 2 trial was performed and did not confirm these findings [152]. As for iNO, an ongoing clinical study is aiming to analyze variations of cerebral blood flow after iNO in patients affected by ischemic stroke and to compare them to health subjects (NCT03023449). Moreover, results are pending from a small trial which primarily aimed to evaluate whether up to 40 ppm of iNO improved refractory vasospasm (NCT04988932).

3.10. Toxicology and adverse effects of iNO

Notwithstanding the illustrated benefits of iNO, the toxicologic profile and potential adverse effects of iNO should be mentioned [153]. Indeed, NO undergoes oxidation to nitrogen dioxide (NO_2) spontaneously. NO_2 is an airway irritant and can determine pulmonary edema. The permissible exposure limit for NO_2 is 5 ppm and doses of 20 ppm are considered as immediately dangerous to life or health by the Centers for Disease Control and Prevention [154]. However, in major clinical trials iNO up to 80 ppm was not associated with excessive levels of NO_2 and evidence of NO_2 intoxication [50,76]. Moreover, in patients receiving intermittent iNO at high doses (160 ppm), NO_2 levels of 5.6 ppm were reported during only one iNO administration out of 343 [12]. In addition, iNO reacts with superoxide anion, which is produced during ischemia/reperfusion injury [155] and forms peroxynitrite, a highly reactive oxidant species [156]. Peroxynitrite has showed ability to interfere with lung surfactant activity [157] and may affect mitochondrial respiration [158]. These detrimental effects have not been well investigated in human population, however they may affect the outcome when iNO is used as an organ protectant following ischemia/reperfusion injury. iNO may also alter DNA, thus making it a potential mutagen, although a carcinogenic effect has never been demonstrated so far [159–162]. iNO is associated with methemoglobinemia (MetHb) [163]. MetHb is usually <1% in healthy individuals [164] and does not usually have clinical implications until concentrations of 10%. This adverse effect is unusual at iNO doses below 40 ppm [157]. Treatment with methylene blue should be instituted for levels >20% in all patients and for lower levels in symptomatic patients (e.g., end-organ dysfunction) [165]. From a hemodynamic perspective, iNO could cause systemic hypotension (>2% higher incidence compared to placebo) [153] and could worsen left heart failure in patients with left heart dysfunction [166]. In these situations, it will be reasonable to interrupt the treatment with iNO. Moreover, since a rebound of pulmonary hypertension has been described in up to 25% of patients when iNO was interrupted abruptly, gradual tapering of iNO is suggested [167]. If this measure was unsuccessful, immediate reinstitution of iNO therapy and coadministration of sildenafil could be considered to allow the weaning from iNO [168,169]. Finally, iNO may worsen renal function in patients with ARDS. A meta-analysis of 1363 patients enrolled in 10 RCTs, showed iNO was associated to an increased risk of AKI compared to placebo (RR 1.4, 95% CI, 1.06–1.83) [170]. By contrast, limited data showed iNO protected against AKI in patients receiving prolonged CPB [18].

In conclusion, although rare, should any adverse effect appear at iNO therapeutic doses (less than 80 ppm), it is suggested to disrupt iNO administration immediately and institute supportive care and specific therapy, when available.

3.11. A novel strategy to produce NO: potential for clinical applications

Despite the demonstrated and potential benefits of the NO, its widespread use is limited because NO is stocked in cylinders which are cumbersome, expensive, require a distribution network and trained healthcare professionals. Moreover, iNO is one of the most expensive drug used in neonatal departments [171]. This limited the use of NO to short periods of therapy and to the inpatient setting. To overcome these drawbacks, a lightweight, portable, economical NO generator from air has been developed recently. It uses pulsed electrical

discharge and can produce therapeutic doses of NO for at least one month and can be powered with batteries [172,173]. This system has been already tested in humans and appeared safe. Indeed, two exploratory studies showed no adverse events occurred during or after the NO breathing through this novel system and MetHb and nitrogen dioxide levels remained within safety range [174,175]. Moreover, preliminary results evidenced that in patients with pulmonary hypertension, electrically generated NO induces pulmonary hemodynamics effects equivalent to NO from cylinders [174]. This device would allow the use of iNO in the ambulatory out-of-hospital setting and, as it is economical, would increase accessibility to NO treatment, including patients in developing countries. Moreover, it would permit to investigate NO as a potential chronic therapy [176].

4. Conclusions

NO has well-established clinical applications in PPHN as it decreases mortality and ECMO use. Some limited data also showed a benefit in improving oxygenation in ARDS and a reduction of the pulmonary artery pressure in patients with PAH. Limited data indicate the use of NO as a potential organ protective strategy. Altogether, NO shows a low toxicity profile at the suggested clinical doses (i.e. 1–80 ppm, up to 160 ppm for COVID-19 infections), thus randomized clinical trials should be endorsed not to overlook the potential clinical benefits of such a gas in the critically ill patients. In addition, considering the new development of a portable NO generator, which eliminates the need to stock NO and makes it more affordable compared to NO delivered by cylinders, the application of NO in chronic and out-of-hospital conditions should be further investigated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors of this review would like to dedicate this manuscript to the memory of Warren M. Zapol, M.D., a visionary scientist, a tireless mentor and a scientific father of generations of physicians. His discovery on the therapeutic use of inhaled nitric oxide gas is one of the major contribution he gave to the critical care fields which expanded tremendously since then and the focus of our present review.

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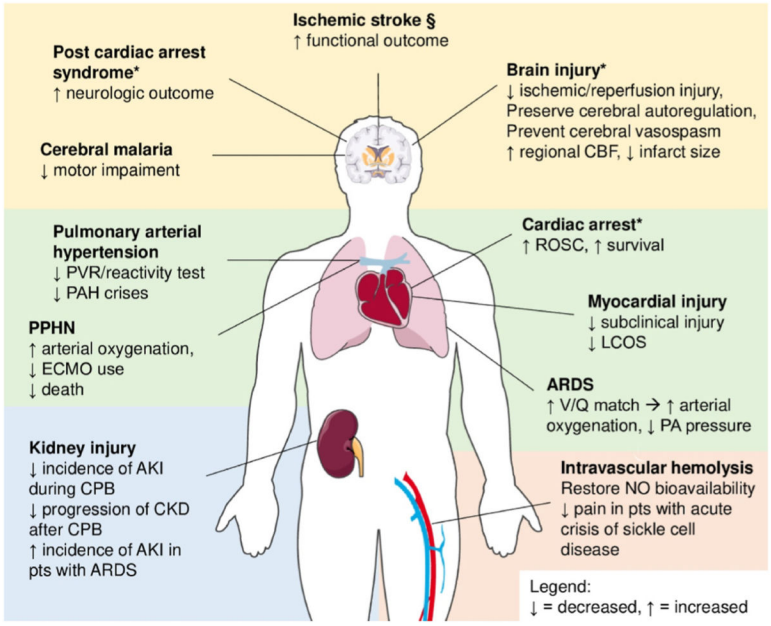

Fig. 1.

Clinical applications and effects of nitric oxide. Nitric oxide is currently approved by the FDA, with the sole indication for administration in patients with PPHN. iNO is sometimes used as a rescue therapy in severe ARDS. The other disease named in the figure represent potential target for iNO treatment. Clinical data are still poor. * diseases where only preclinical studies are available or clinical trials are ongoing. § conflicting data, see text for further details. Abbreviations: PVR, pulmonary vascular resistances; PPHN, persistent pulmonary hypertension of the newborn; ECMO, extracorporeal membrane oxygenation; ROSC, return of spontaneous circulation; LCOS, low cardiac output syndrome; ARDS, acute respiratory distress syndrome; V/Q, ventilation-to- perfusion ratio; PA, pulmonary artery; AKI, acute kidney injury; CPB, cardiopulmonary bypass; CKD, chronic kidney disease; pts, patients; NO, nitric oxide; PAH, pulmonary arterial hypertension.

Table 1

Randomized controlled trials on nitric oxide administration for the treatment of various clinical conditions.

Trial	Aim/hypothesis	Population (N)	Treatment group	Control group	NO dose	Primary endpoint	Main results
Respiratory failure							
Wu, 2016 [19]	Efficacy in PPHN	Newborns (86)	iNO + HFOV	HFOV	20–80 ppm	PAP, FiO2, OI, duration of MV and O2 therapy, mortality	All endpoints better in the iNO than in control group
Bronicki, 2015 [20]	iNO ↓ MV duration in HRF	Pediatric (55)	iNO until death or 28 d or ventilator free	Placebo until death or 28 d or ventilator free	5 ppm	VFD at 28 d	VFD greater in the iNO group (p = 0.05)
González, 2010 [21]	Early iNO prevents severe HRF in moderate HRF and PAH	Newborns (56)	iNO + conventional MV	Conventional MV	20 ppm	Rate of progression to OI > 40	25% iNO vs 61% control group (p < 0.05)
Su, 2008 [22]	iNO ↓ OI in HRF	Preterm infants (65)	iNO + conventional care	Conventional care	5–20 ppm	Mean OI at 24 h	OI ↓ in the iNO group (p < 0.01)
Dani, 2007 [23]	iNO ↓ BPD and/or death in HRF	Preterm infants (40)	iNO at 10 ppm for 4 h, then 6 ppm until extubation or FiO2 <30% w/MAP <8 cm H2O + conventional care	Conventional care	6–10 ppm	BPD incidence and death	50% iNO vs 90% control group (p = 0.016)
Lindwall, 2005 [24]	Effect of iNO on oxygenation in HRF	Preterm infants (15)	iNO for 30 min + nasal CPAP	Nasal CPAP + placebo	10 ppm	Changes in oxygenation measured as aAPO2	aAPO2 ↑ 20% in the iNO group (p = 0.006)
Schreiber, 2003 [25]	iNO ↓ incidence of chronic lung disease/ death	Preterm infants (207)	iNO 10 ppm day 1, then 5 ppm for 6 d	Placebo	5–10 ppm	Incidence of chronic lung disease/death	48,6% iNO vs 63.7% control group (p = 0.03)
Sadiq, 2003 [26]	iNO prevents worsening of PAH in PPHN	near-term and term infants (80)	iNO + conventional care	Conventional care	Up to 80 ppm	Development of severe PPHN	15% iNO vs 58% control group (p < 0.0005)
Srisuparp, 2002 [27]	Safety and effect of iNO on oxygenation in mild to moderate HRF	Preterm infants (34)	iNO 20 ppm, then weaned to 5 ppm over 1–2 d	Conventional care	5–20 ppm	IVH incidence, OI, paO2	No differences in IVH incidence between groups. OI ↓ 15% and paO2 ↑ by 50% in iNO group (p = 0.04 and 0.02, respectively)
Baxter, 2002 [28]	Efficacy of iNO on oxygenation, shunt and PVRI in HRF	Adults (14)	iNO + 100% O2 for 30 min, then 30 min wash-out, then no iNO + 100% O2 for 30 min.	Randomized cross-over	5–25 ppm	Shunt, PVRI, oxygenation	iNO ↓ pulmonary shunt (p = 0.002). Other endpoints: ns
Christou, 2000 [29]	iNO ↓ mortality and ↓ ECMO use in PPHN	near-term and term newborns (40)	iNO + HFOV	HFOV	Up to 40 ppm	Mortality, ECMO use	ECMO use: 14% iNO vs 55% control group (p = 0.007), Mortality: ns.
Clark, 2000 [30]	Low-dose iNO ↓ ECMO use in PPHN	near-term and term newborns (248)	iNO at 20 ppm up to 1 d, then 5 ppm up to 4 d	Placebo	5–20 ppm	ECMO use	ECMO use: 38% iNO vs 64% control group (p = 0.001)

Trial	Aim/hypothesis	Population (N)	Treatment group	Control group	NO dose	Primary endpoint	Main results
The Franco- Belgium Collaborative NO Trail Group, 1999 [31]	iNO ↑ oxygenation in HRF	preterm and near-term newborns (204)	iNO	Placebo	10 ppm	OI change at 2 h	OI ↓ 6.2 iNO vs 2.9 control group (p = 0.005)
Dobyns, 1999 [32]	iNO effect on oxygenation in HRF	Children (108)	iNO for minimum 3 d + MV	MV	10 ppm	OI	OI ↓ 10.2 iNO vs 2.7 control group (p < 0.05)
Troncy, 1998 [33]	iNO effect on lung function in ARDS	Adults (30)	iNO + conventional care	Conventional care	0.5–40 ppm	P/F, alveolar dead space, lung compliance, venous admixture	P/F ↑ 59% in INO vs 9.3% control group (p = 0.02). Other endpoints: ns
Michael, 1998 [34]	iNO effect on oxygenation in ARDS	Adults (40)	iNO + conventional care up to 3 d	Conventional care	5–20 ppm	P/F	P/F t in the first 24 h in the iNO group.
Dellinger, 1998 [35]	iNO effect on oxygenation in ARDS	Adults (117)	iNO	Placebo	1.25–80 ppm	paO2 ↑ >20%	~60% responders in iNO vs 24% control group in the first 4 h (p ≤ 0.021)
The NINOS Group, 1997 [36]	iNO ↓ ECMO use and/ or death in HRF	near-term and term newborns (235)	iNO	100% O2	20 ppm	ECMO use and/or death	64% iNO vs 46% vs control group (p = 0.006)
Wessel, 1997 [37]	iNO effect on mortality, ECMO use and oxygenation in PPHN	near-term and term Newborns (49)	iNO + conventional care	Conventional care	5–80 ppm	Mortality, ECMO use, OI	OI ↓ 31% iNO vs control group.Other endpoints: ns
Roberts Jr, 1997 [38]	iNO effect on oxygenation in PPHN	Term infants (58)	iNO + conventional care	Placebo + conventional care	80 ppm	Doubling rate of oxygenation	53% iNO vs 7% control group (p = 0.002)
NCT00240487	Determine iNO treatment timing in pediatric ARDS	Children (52)	iNO for the first 4 h, then no iNO for 4 h	No iNO for the first 4 h, then iNO for 4 h	10 ppm	Changes in P/F ratio	ns
Van Meurs, 2007 [39]	iNO ↓ BPD and/or death in HRF	Preterm infants (29)	iNO + conventional care up to 14 d	Conventional care	5–10 ppm	BPD incidence and death	ns
Field, 2007 [40]	Assess clinical and cost-effectiveness of iNO in HRF	Infants (60)	iNO + conventional care	Conventional care	5–20 ppm	Death and severe disability	ns
Kinsella, 2006 [41]	iNO ↓ BPD and/or death in HRF	Preterm infants (793)	iNO for 21 d or until extubation + conventional care	Conventional care	5 ppm	BPD incidence and death	ns
Meurs, 2005 [42]	iNO ↓ BPD and/or death in HRF	Preterm infants (420)	iNO	Conventional care	5–10 ppm	BPD incidence and death	ns
Hascoet, 2005 [43]	Safety and efficacy in infants w/HRF	Preterm infants (860)	iNO	Placebo	5 ppm	Intact survival at 28 d	ns
Taylor, 2004 [44]	Efficacy of iNO in ARDS	Adults (385)	iNO until 28 d or discontinuation of assisted breathing or death	Placebo until 28 d or discontinuation of assisted breathing or death	5 ppm	Days alive and off assisted breathing	ns

Trial	Aim/hypothesis	Population (N)	Treatment group	Control group	NO dose	Primary endpoint	Main results
Konduri, 2004 [45]	iNO ↓ incidence of ECMO/ death in HRF	near-term and term infants (299)	iNO	Placebo	5–20 ppm	Incidence of ECMO/ death	ns
Finer, 2001 [46]	No differences in oxygenation improvement between low and high dose of iNO in pts w/ HRF	near-term and term infants (36)	Low-dose iNO (LD)	High-dose iNO (HD)	LD: 1–2 ppm HD: 10–20 ppm	paO2, OI	ns
Cornfield, 1999 [47]	iNO ↑ oxygenation in PPHN	near-term and term infants (38)	iNO 2 ppm, 20 ppm if worsening oxygenation	Placebo, 20 ppm if worsening oxygenation	2–20 ppm	OI	ns
Kinsella, 1999 [48]	iNO ↑ survival in HRF	Preterm infants (80)	iNO	Placebo	5 ppm	Survival to discharge	ns
Lundin, 1999 [49]	iNO ↑ reversal of ALI in pts previously responder to iNO	Adults (268)	iNO up to 30 days or endpoint reached	Conventional care	1–40 ppm	Rate of ALI reversal	ns
Davidson, 1998 [50]	Efficacy of iNO on PPHN	Term infants (155)	iNO + conventional care	Conventional care	5–80 ppm	Major Sequelae Index (incidence of death, ECMO, neurologic	ns
The NINOS Group, 1997 [51]	iNO ↓ ECMO use and/ or death in HRF and congenital diaphragmatic hernia	near-term and term infants (53)	iNO	100% O2	20 ppm	injury, BPD) ECMO use/death	ns
Barefield, 1996 [52]	iNO ↓ ECMO use in PPHN	near-term and term infants (17)	iNO + conventional MV	Conventional MV	20–80 ppm	ECMO use	ns
Pulmonary Arterial Hypertension							
Nathan, 2020 [53]	iNO ↑ physical activity in PAH + pulmonary fibrosis	Adults (41)	Pulsed iNO for 8w	Placebo	30 μg/kg IBW/h	moderate/vigorous physical activity improvement	↑ in the iNO vs control group
Vonbank, 2003 [54]	iNO safety in pts w/ PAH due to COPD	Adults (40)	Pulsed iNO + O2 over 3 months	O2	20 ppm	Pulmonary and systemic hemodynamics. Arterial oxygenation. NO2	↑ in pulmonary hemodynamics. Other endpoints: ns
Hasuda, 2000 [55]	iNO ↑ exercise capacity in precapillary PAH	Adults (14)	iNO + exercise on a cycle ergometer	Exercise on a cycle ergometer (Randomized cross-over)	20 ppm	Peak exercise load, anaerobic threshold, VO2	Only VO2 ↑ in the iNO vs control group
Van Meurs, 1997 [56]	iNO effect on oxygenation HRF	Preterm (11)	iNO	Placebo, (Randomized, cross-over)	1–20 ppm	P/F	P/F ↑ >25% in 10 out of 11 participants
AKI prevention after CPB							
Lei, 2018 [18]	NO ↓ AKI after CPB	Adults (244)	NO for 24 h	Placebo	80 ppm	AKI occurrence	

Trial	Aim/hypothesis	Population (N)	Treatment group	Control group	NO dose	Primary endpoint	Main results
							50% NO vs 64% control group (p = 0.014)
NO during CPB for CHD							
Elzein, 2020 [57]	NO ↓ ischemia/ reperfusion injury	Newborns (24)	NO	Placebo	40 ppm	Multiple markers of organ injury	Only Tn lower in the iNO vs control group (p = 0.009)
James, 2016 [58]	NO ↓ LCOS	Children (198)	NO	Placebo	20 ppm	LCOS incidence	15% iNO vs 31% control group (p = 0.007)
Checchia, 2013 [59]	NO ↓ ischemia/ reperfusion injury	Children (16)	NO	Placebo	20 ppm	Duration MV, ICU LOS, TnI and BNP levels	All endpoints better in the iNO group (p < 0.05)
Miller, 2000 [60]	NO ↓ PAH crises	Infants (124)	NO	Placebo	10 ppm	Number of PAH crises	4 PAH crises NO vs 7 control group (p < 0.001)
Day, 2000 [61]	NO ↓ PAH crises	Infants (40)	NO	Placebo	20 ppm	Number of PAH crises	ns
Niebler, 2021 [62]	NO ↓ activation and depletion of PLTs	Infants (40)	NO	Placebo	20 ppm	PLTs count	ns
Resuscitation							
Sekar, 2020 [63]	Prevention of O2 exposure during resuscitation	Preterm infants needing help with breathing (28)	iNO for 17 min	Placebo for 17 min	20 ppm	Cumulative FiO2, time w/FiO2 >60%, pre/ postductal saturation, heart rate, need for intubation	Cumulative FiO**2** (p = 0.001) and time w/FiO**2** >60% (p < 0.0001) lower in the iNO group
Transfusions							
Berra, 2014 [16]	Blood transfusions older than 40 d ↑ PAP	Obese adults (14)	Transfusion with 3-d, 40-d, and 40-d old blood with iNO	Randomized cross-over	80 ppm	PAP	40 d old blood ↑ PAP. iNO prevents it
Sickle cell disease							
Head, 2010 [64]	iNO ↓ intensity of painful crisis	Adults (23)	iNO for 4 h	Room air	80 ppm	Mean change of pain score after 4 h of iNO	iNO ↓ pain scores (p = 0.02)
Maitre, 2015 [65]	iNO ↓ treatment failure in pts with acute chest syndrome	Adults (100)	iNO for 3 d	Placebo	80 ppm	Treatment failure rate at 3 d	ns

Trial	Aim/hypothesis	Population (N)	Treatment group	Control group	NO dose	Primary endpoint	Main results
Gladwin, 2011 [66]	iNO ↓ duration of painful crisis	>10 years old (150)	iNO up to 3 d	Placebo	40–80 ppm	Time to resolution of painful crisis	ns
Severe malaria							
Bangirana, 2018 [67]	Neuroprotective role of iNO	Children (130)	iNO up to 72 h	Room air	80 ppm	Neurocognitive outcomes	↓ fine motor impairment in iNO vs control group (RR, 95% CI: 0.36, 0.14–0.96)
Conroy, 2016 [68]	Safety of iNO	Children (180)	iNO for 3 d	Room air	80 ppm	MetHb levels >10% mandate treatment interruption	MetHb >10% in 5.7% patients in iNO group. Authors conclude iNO is safe if MetHb is measured during administration
Hawkes, 2015 [69]	iNO ↑ severe malaria outcome	Children (180)	iNO up to 3 d	Room air	80 ppm	Ang-2 levels in the first 3 d	ns
Mwanga-Amumpaire, 2015 [70]	iNO ↑ Ang-1	Children (92)	iNO for at least 2 d	Room air	80 ppm	Ang-1 levels at 2 d	ns

Legend:

↓ decreases/decreased

↑ increases/increased.

Abbreviations: aAPO2, alveolar-arterial oxygen tension difference; AKI, acute kidney injury; ALI, acute lung injury; Ang-1/Ang-2, angiotensin 1 and 2; ARDS, acute respiratory distress syndrome; BNP, B-type natriuretic peptide; BPD, bronchopulmonary dysplasia; CI, confidence interval; cmH2O, centimeters of water; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; d, day(s); d, day(s); ECMO, extracorporeal membrane oxygenation; FiO2, fraction of inspired oxygen; h, hour(s); h, hour; HFOV, high frequency oscillatory ventilation; HRF, hypoxic respiratory failure; IBW, ideal body weight; iNO, inhaled nitric oxide; IVH, intraventricular hemorrhage; LCOS: low cardiac output syndrome; LOS, length of stay; MAP, mean arterial pressure; MetHb, methemoglobin; MV, mechanical ventilation; n.a., not available; NO, nitric oxide; NO2, nitrogen dioxide; ns, not significant; O2, oxygen; OI, oxygenation index; P/F, partial oxygen pressure-to-fraction of inspired oxygen ratio; PAH, pulmonary artery hypertension; paO2, partial pressure of oxygen; PAP, pulmonary artery pressure; PLTs, platelets; PPHN, persistent pulmonary hypertension of the newborn; ppm, part per million; PVRI, pulmonary vascular resistances index; RR, relative risk; Tn, troponin; VFD, ventilator- free days; VO2, oxygen consumption; w, week(s); w/, with.

Table 2

Ongoing randomized controlled trials on nitric oxide for the treatment of various clinical conditions.

Trial	Aim/hypothesis	Population (N)	Treatment group	Control group	NO dose	Primary endpoint
Respiratory failure NCT04776408	Measure dead space or shunt fraction before and after iNO	Adults (100)	Lung recruitment maneuver + iNO	Lung recruitment maneuver	n.a.	V/Q mismatch through EIT
Covid19						
NO-COVID-19 NCT04388683	iNO ↓ progression to advanced disease	Adults (42)	iNO	Conventional care	20 ppm	Progression to ↑ FiO2, ventilatory support or death
NCT05012319	NO ↓ need of urgent care	Adults (500)	NO nasal spray	Placebo	n.a.	Need of urgent care
NCT04397692	Safety	Adults (20)	iNO	Conventional care	80 ppm	Time to deterioration
Lei, 2020 [71]	iNO ↑ oxygenation	Adults (200)	iNO 80 ppm for 2 d, then 40 ppm, then weaning	Conventional care	40 ppm	Change in P/F at 2 d
Lei, 2020 [72]	iNO prevents progression of mild/ moderate Covid19	Adults (70)	iNO for 20–30 min bid for 14 d + conventional care	Conventional care	140–180 ppm	Need for intubation and MV
NCT04601077	Safety	Adults (100)	NO lozenges	Placebo	30 mg	Low BP and dizziness incidence
NCT04383002	iNO safety, antiviral effect and prevention of progression to HRF	Adults (20)	iNO for 6 h/d for 2 days + standard of care	Standard of care	160 ppm	Covid19 PCR status at 7 d
NO COV-ED NCT04338828	iNO ↑ respiratory status, prevent hospitalization and t clinical course in ED	Adults (47)	iNO for 20–30 min	O2 2 l/min	140–300 ppm	Rate of return to ED w/in 28 d
COViNOX NCT04421508	Efficacy and safety of iNO	Adults (500)	Pulsed iNO	Pulsed placebo	125mcg/kg IBW/h	Death or HRF at 28 d
NICOR NCT04476992	Safety	Adults (20)	iNO high dose 30 min bid for 14 d	iNO high dose 30min bid + continuous iNO low dose for 14 d	High dose: 200 ppm Low dose: 20 ppm	Change in MetHb level at 2 d
NCT04443868	Efficacy of NO to ↓ infection duration	Adults (50)	NO nasal irrigation daily (240 ml)	Normal saline nasal irrigation (240 ml)	14 ppm	Sars-Cov-2 viral load baseline through 6 d
NCT04460183	Efficacy of RESP301 (NO generating solution) in ↓ progression of Covid19 and safety	Adults (300)	Inhaled RESP301 tid up to 10 d + conventional care	Conventional care	n.a.	Progression on the modified WHO ordinal scale by 14 d
Pulmonary Arterial Hypertension						
NCT01457781	Efficacy and safety	Adults (80)	Pulsed iNO up to 24h/ day for 16 w	Placebo	0.025–0.075 mg/kg IBW/h	Change in PVR

Trial	Aim/hypothesis	Population (N)	Treatment group	Control group	NO dose	Primary endpoint
NCT03267108	Efficacy and safety	Adults (300)	Pulsed iNO	Placebo	0.045 mg/kg IBW/h	Change in moderate to vigorous activity, adverse events
NCT03576885	iNO ↓ death, PAH and BPD incidence	Newborns (138)	iNO for 14 d or resolution of PAH	Placebo	20 ppm	Death, BPD incidence
NO during CPB						
Marrazzo, 2019 [73]	NO ↓ AKI in pts w/endothelial dysfunction	Adults (250)	NO	Placebo	80 ppm	AKI occurrence
NCT03946462	NO ↓ AKI	Newborns (24)	NO	Placebo	20 ppm	NGAL/Cystatin-C levels
NCT04216927	NO ↓ AKI after CPB	Newborns (40)	NO	Placebo	20 ppm	AKI incidence
Schlapbach, 2019	NO ↓ MV duration	Infants (1320)	NO	Placebo	20 ppm	VFD at 28 d
NASO NCT03661385	NO ↓ post-operative MAEs	Children, Adults (900)	NO	Standard care	20 ppm	MAEs: cardiac arrest, emergency chest
NCT05101746	NO is neuro and renal protective	Children (50)	NO	Standard care	20 ppm	opening, ECMO, death GFAP and NGAL levels
Brain Injury						
NCT03260569	Effect of iNO on gas exchange in TBI	Adults (38)	iNO	Placebo	20 ppm	Change in paO2

Legend:

↓ decreases/decreased

↑ increases/increased.

Abbreviations: AKI, acute kidney injury; bid, bis in die; BP, blood pressure; BPD, bronchopulmonary dysplasia; CPB, cardiopulmonary bypass; d, day(s), ECMO, extracorporeal membrane oxygenation; EIT, electrical impedance tomography; FiO2, fraction of inspired oxygen; GFAP, glial fibrillary acid protein; h, hour(s); HRF, hypoxic respiratory failure; IBW, ideal body weight; iNO, inhaled nitric oxide; MAE, major adverse event; MetHb, methemoglobin; min, minutes; MV, mechanical ventilation; n.a., not available; NGAL, neutrophil gelatinase-associated lipocalin; NO, nitric oxide; P/F, partial oxygen pressure-to-fraction of inspired oxygen ratio; PAH, pulmonary arterial hypertension; paO2, partial pressure of oxygen; PCR, polymerase chain reaction; ppm, part per million; PVR, pulmonary vascular resistances; tid, tris in die; VFD, ventilator-free days; w/with; w/in, within.