Inhaled Nitric Oxide in Acute Pulmonary Embolism: A Systematic Review

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Acute pulmonary embolism (PE) is usually a complication secondary to migration of a deep venous clot or thrombi to lungs, but other significant etiologies include air, amniotic fluid, fat, and bone marrow. Regardless of the underlying etiology, little progress has been made in finding an effective pharmacologic intervention for this serious complication. Among the wide spectrum of PE, massive PE is associated with considerable morbidity and mortality, primarily due to severely elevated pulmonary vascular resistance leading to right ventricular failure, hypoxemia, and cardiogenic shock. We currently have limited therapeutic options at our disposal. Inhaled nitric oxide (iNO) has been proposed as a potential therapeutic agent in cases of acute PE in which hemodynamic compromise secondary to increased pulmonary vascular resistance is present, based on iNO's selective dilation of the pulmonary vasculature and antiplatelet activity. A systematic search of studies using the PubMed database was undertaken in order to assess the available literature. Although there are currently no published randomized controlled trials on the subject, except a recently publish phase I trial involving eight patients, several case reports and case series describe and document the use of iNO in acute PE. The majority of published reports have documented improvements in oxygenation and hemodynamic variables, often within minutes of administration of iNO. These reports, when taken together, raise the possibility that iNO may be a potential therapeutic agent in acute PE. However, based on the current literature, it is not possible to conclude definitively whether iNO is safe and effective. These case reports underscore the need for randomized controlled trials to establish the safety and efficacy of iNO in the treatment of massive acute PE. The purpose of this article is to review the current literature in the use of iNO in the setting of PE given how acute PE causes acute onset of pulmonary hypertension.

> ### KEY WORDS
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> Nitric oxide • Pulmonary embolism • Pulmonary hypertension

Acute pulmonary embolism (PE) is usually a complication secondary to migration of a deep venous clot or thrombi to the lungs, but other significant etiologies include air, amniotic fluid, fat, and bone marrow. Regardless of the underlying etiology, little progress has been made in finding an effective pharmacologic intervention for this serious complication. Massive PE is associated with considerable morbidity and mortality due to right ventricular (RV) failure, hypoxia, and cardiogenic shock. The incidence of acute PE in 2006 was reported to be 112.3 per 100,000 US adults, with a 7.8%

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mortality rate.[1] Mortality is especially high in patients with hemodynamic instability or signs of RV dysfunction (RVD) and can range from 14% to 18% in patients with RVD.[2] Acute PE increases pulmonary vascular resistance due to mechanical obstruction and arterial vasoconstriction, which is secondary to vasoactive mediators, such as thromboxane A2 and serotonin released by entrapped activated platelets.[3] There are limited therapeutic options available for managing acute PE with severe RV failure and cardiogenic shock; these primarily include systemic anticoagulation, thrombolysis, and embolectomy, each of which has its own limitations. The elevated pulmonary resistance due to acute PE leads to an increase in RV afterload, which leads to RV failure and subsequent circulatory failure and death.[4]

Employing a therapeutic strategy to reduce RV afterload can prove pivotal in managing these patients. The possible therapeutic role of vasodilators in this situation is limited by their systemic vasodilatation and hypotension.[5] In these situations, selective pulmonary vasodilators can have a significant role; thus, inhaled nitric oxide (iNO) has been proposed as a potential therapeutic agent in cases of acute PE with associated increased pulmonary vascular resistance.[6]

Background

Nitric oxide (NO) is a naturally occurring, colorless, odorless gas that is synthesized endogenously by NO synthase and is involved in the modulation of vascular tone. NO diffuses freely across cell membranes, thus diffusing rapidly from the alveoli to the highly resistant pulmonary arterioles.[7] It activates guanylate cyclase, which activates cyclic guanosine monophosphate (GMP). Cyclic GMP, in turn, activates protein kinase, which dephosphorylates the myosin light chain, making it less sensitive to calcium, and inhibits release of calcium from the sarcoplasmic reticulum. These effects promote relaxation of the vascular smooth muscle (Figure 1).[8]

In an early study, iNO was shown to reverse pulmonary hypertension that was induced in healthy subjects breathing low concentrations of oxygen, without causing systemic vasodilation.[9] However, the high cost of long-term iNO, along with concern for rebound hypoxemia and respiratory failure when use of the drug is abruptly discontinued, have been limiting factors in use of the agent in adult patients with pulmonary hypertension.

Because NO was shown to have limited effects on the peripheral vasculature, there was hope that the administration of NO could provide benefit in patients with acute respiratory distress syndrome (ARDS) and hypotension.[10] One study in patients with acute lung injury (currently classified as mild ARDS) showed that iNO at a dose of 40 ppm induced pulmonary vasodilation and reduced the risk of pulmonary edema.[11] Additionally, because iNO is administered by inhalation, it preferentially causes vasodilatation in areas of the lung that are well ventilated, improving ventilation/perfusion matching and decreasing pulmonary shunting.[12] However, several large, randomized placebo-controlled trials failed to prove benefit with regard to duration of ventilation or mortality in ARDS patients administered NO, despite a short-lived increase in arterial partial pressures of oxygen.

Although iNO is available commercially, it is currently licensed only for persistent pulmonary hypertension and respiratory failure in the neonate. As a therapeutic agent, it can be administered to patients undergoing mechanical ventilation, as well as via face mask or nasal cannula.
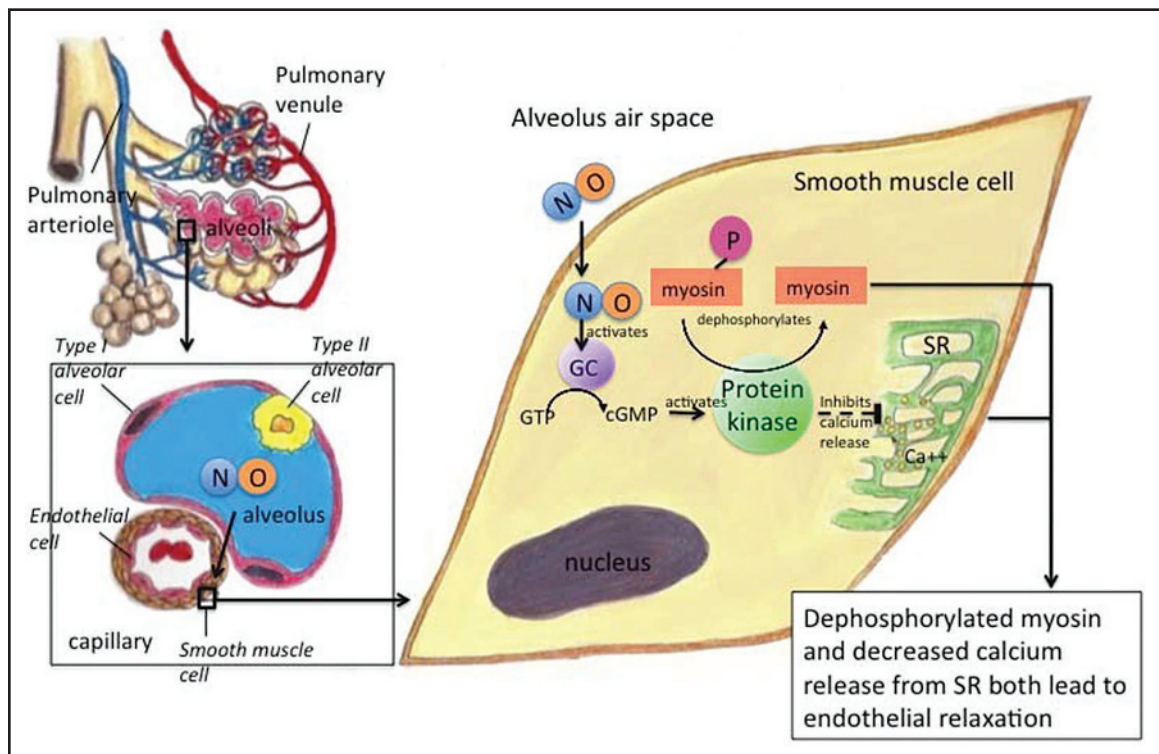
Methods

A systematic search of studies concerning use of iNO in acute PE was conducted using the PubMed

Figure 1. Schema of some of the vasodilatory effects of inhaled nitric oxide. Inhaled NO diffuses across the alveolus to the pulmonary arteriole in which, among other effects, it activates GC. This causes a cascade to eventually dephosphorylate myosin, as well as inhibit calcium release from the SR, both of which contribute to pulmonary arteriole endothelial relaxation and therefore decreased pulmonary pressure. cGMP, cyclic guanosine monophosphate; GC, guanylate cyclase; GTP, guanosine-5′-triphosphate; NO, nitric oxide; SR, sarcoplasmic reticulum.

database from January 1990 to June 2013. The search terms used were *acute pulmonary embolism*, *acute PE*, *acute thromboembolism*, and *acute VTE*, together with *inhaled NO*, *iNO*, and *NO*. Articles that were found with the term *NO* were screened for whether or not the authors used iNO. Given the lack of large, randomized controlled trials involving iNO in acute PE, we included all case series and case reports. We limited studies to those published in 1990 or later. References of all included articles were reviewed in order to identify additional relevant studies. We excluded case reports describing patients who had underlying chronic pulmonary hypertension, or had a diagnosis of chronic pulmonary thromboembolic disease. The recently published small clinical trial did not include detailed information of the patients' hemodynamic response; thus, although

cited, it was excluded from analysis. In all relevant case series and reports, we extracted data including the dose and duration of iNO, imaging, and interventions that were performed, and treatment outcomes.

Results

To date, no large, randomized controlled studies have been performed that compare the use of iNO with placebo in acute PE. Recently, a small phase I clinical trial was published that concluded that iNO reduced dyspnea without adverse events in eight studied patients with severe submassive PE. In this study, eight patients with submassive PE diagnosed by computed tomography were administered NO using a commercial device and a nonrebreathing face mask. NO concentration was increased at 1 ppm/min until a maximum of 25 ppm

and continued for 120 minutes and then weaned at 1 ppm/min. Dyspnea was assessed with the Borg score, oxygenation by pulse oximetry, and hemodynamic status by shock index (heart rate/systolic blood pressure). All patients tolerated the entire protocol without adverse events, and all had decreased numerical Borg score (a subjective measure of exertion) by $> 50\%$. The changes from baseline to 155 minutes were as follows: Borg score 7.5 ± 2.5 to 2.3 ± 1.9 ($P = .06$; signed-rank test), arterial oxygen saturation 93 ± 5 to 97 ± 3, and shock index 1.0 ± 0.11 to 0.86 ± 0.09. No patient showed signs of worsening during weaning.[13]

Additionally, 18 patients have been described either through case reports or case series who have been administered iNO for PE (Table 1). Many described improvement in hemodynamics and oxygenation following administration

TABLE 1

Summary of Reported Cases of iNO Use for Acute PE

Age, Sex	Study	Context of PE[a]	Imaging	NO via Mask or ETT	Right Heart Strain on TTE	Heparin	Embolecomy or IA tPA (B, A, N)	IV tPA (B, A, N)	Vasopressors	Dose of iNO	Duration of iNO	Clinical Effect of NO	Survived to d/c From ICU?
20 W	Tulleken JE et al[20]	Acute shortness of breath	V/Q scan: b/l defects	E	b	b	N	B	b	10-20 ppm	15 min	Worsening of SpO2	No
61 M	Capellier G et al[17]	POD #7: esophagectomy for esophageal cancer	Pulmonary angiograph: PE	M	b	Y	N	N	No	10 ppm	b	Improved SpO2, CO, PVR	Y
58 W	Capellier G et al[17]	SLE, progressive shortness of breath	Pulmonary angiograph: PE	M	b	No	N	N	No	5 ppm	b	Initial improvement in SpO2, CO, PVR, PAP, then deterioration after accidental NO removal	No
83 b	Capellier G et al[17]	Hx PE, respiratory distress	CTA: PE	M	b	No	N	B	No	5-20 ppm	b	Improvement in SpO2, CO, PVR, PAP, but subsequent fatal arrhythmia	No
62 b	Capellier G et al[17]	s/p debridement of sacral ulcer	Clinical dx	E	Y	Y	N	N	Y	5-20 ppm	b	Improvement in MAP, SpO2, CO, then deterioration after accidental NO removal	Y
66 W	Schenk P et al[7]	Cardiopulmonary arrest in PE patient 2 d after diagnosis, tPA administration	CTA: b/l PE	E	Y	Y	N	B	Y	50 ppm	< 24 h	Improvement in MAP, PaO2	No
39 W	Crerar-Gilbert and Boots[18]	Cardiac arrest after cesarean delivery	Angiography: b/l PE	E	b	Y	A	A	Y	40 ppm	24 h	Improvement in MAP, PaO2, deterioration upon cessation of NO	Y
69 W	Trummer G et al[19]	Acute respiratory failure	2D echo: floating mass in RA/RV	E	Y	Y	B	N	Y	20 ppm	10 h	Improvement in PAP, no change in SpO2	Y
36 M	Faintuch S et al[14]	Acute respiratory failure 6 d s/p trauma 2° MVA; underwent suction thrombectomy	CTA: b/l PE	E	Y	Y	B	B	Y	20 ppm	2 d	Immediate improvement in MAP, PAP, PaO2	Y

Age/Sex	Author	Presentation	Dx							ppm	Duration	Outcome	
62 M	Faintuch S et al[14]	Acute shortness of breath, on chemo for renal cell carcinoma; underwent suction thrombectomy	CTA: saddle embolus	E	b	Y	B	N	Y	40 ppm	b	Improvement in PaO$_2$, no change in PAP	Y
25 W	Szold O et al[15]	POD #4: laparotomy for intussusception; received streptokinase	CTA: left main PE	E	Y	Y	N	A	Y	12-14 ppm	2 d	Improvement in MAP, PaO$_2$	Y
58 M	Szold O et al[15]	POD #2: pancreatoduodenectomy for pancreatic cancer; received streptokinase	CTA: b/l PE	E	b	Y	N	A	Y	17 ppm	2 d	Improvement in MAP, PaO$_2$	Y
52 M	Szold O et al[15]	POD # 2: hemi-pelvectomy for renal cell carcinoma; NO was initial therapy without heparin; later underwent embolectomy	CTA: right main PE	E	Y	No	A	N	No	25 ppm	b	Improvement in MAP, PaO$_2$	Y
55 M	Szold O et al[15]	Acute shortness of breath; not given heparin	CTA: b/l PE	E	b	No	N	N	Y	25-27 ppm	b	Improvement in PaO$_2$, PAP	Y
66 W	Summerfield DT et al[16]	Acute shortness of breath, Hx of brain tumor; treated with embolectomy after NO	VQ scan: b/l defects	E	Y	Y	A	N	Y	10 ppm	< 24 h	Improvement in PaO$_2$, MAP	Y
62 M	Summerfield DT et al[16]	Found unconscious	Clinical dx, dilated RV on TTE	E	Y	Y	N	N	Y	15 ppm	4 d	Improvement in PaO$_2$, MAP	Y
60 M	Summerfield DT et al[16]	Hypoxia after transatlantic flight	CTA: multiple large PEs	E	Y	Y	N	N	No	20 ppm	6 d	Improvement in PaO$_2$, MAP; difficulty in weaning NO	Y
66 W	Summerfield DT et al[16]	Hypoxic after induction of anesthesia for repair of femur fx; received rtPA prior to NO	LE duplex: DVT	E	Y	Y	N	B	Y	15 ppm	< 24 h	Improvement in PaO$_2$, MAP	Y

aUnless noted, all patients received heparin.
bNot reported.

2D, two-dimensional; A, after; B, before; b/l, bilateral; chemo, chemotherapy; CO, cardiac output; CTA, computed tomography angiography; d/c, discharge; DVT, deep vein thrombosis; dx, diagnosis; echo, echocardiography; ETT, endotracheal tube; fx, fracture; Hx, history; IA, intra-arterial; ICU, intensive care unit; iNO, inhaled nitric oxide; IV, intravenous; LE, lower extremity; M, men; MAP, mean arterial pressure; N, never; NO, nitric oxide; PaO$_2$, partial pressure of oxygen; PAP, pulmonary arterial pressure; PE, pulmonary embolism; POD, postoperative day; ppm, parts per million; PVR, pulmonary vascular resistance; rtPA, recombinant tissue plasminogen activator; RV, right ventricle; SLE, systemic lupus erythematosus; s/p, status post; SpO$_2$, percutaneous oxygen saturation; tPA, tissue plasminogen activator; TTE, transthoracic echocardiography; V/Q, ventilation/perfusion; W, women; Y, yes.

Summary of Outcomes From Analyzed Patients

Improvement in MAP/CO	Improvement in PAP/PVR	Improvement in PaO^2/ SpO^2	Survival From ICU
14/14 who reported (100%)	6/7 who reported (86%)	16/18 who reported (89%)	14/18 (78%)

CO, cardiac output; ICU, intensive care unit; MAP, mean arterial pressure; PaO^2: partial pressure of oxygen; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; SpO^2: percutaneous oxygen saturation.

of iNO, often instantaneously upon administration.[14,15]

In the case reports, iNO was at times used to improve oxygenation and hemodynamics in conjunction with either chemical and/or mechanical thrombolysis. In three cases, iNO was delivered before thrombolysis, whereas in three others it was delivered after thrombolysis. Patients were between ages 25 and 83 years. Most patients had signs of RV strain on transthoracic echocardiography and received vasopressors in order to maintain systemic blood pressure. In the case reports, iNO was administered at a dose of 10 to 50 ppm for up to 6 days.

A total of 14 of 18 patients survived the intensive care unit, and there were no reported cases of clinical methemoglobinemia. In one case, the authors reported initial difficulty weaning patients from NO due to rebound hypoxemia.[16] In three cases, accidental interruption of iNO resulted in an immediate drop in mean systemic arterial pressure, venous oxygen saturation, and cardiac output, which resolved after readministration.[17,18] Another patient had recurrent pulmonary hypertension after being weaned off iNO, and the agent had to be used a second time.[19]

One early case report[20] described rapid oxygen desaturation after iNO was administered to a patient with acute PE and shock. In this case, iNO was discontinued after 15 minutes, and partial pressures of oxygen only returned to preadministration levels after several hours. The patient underwent mechanical embolectomy but did not survive. The negative effect of iNO on oxygenation in this patient could not be readily explained, and was inconsistent with its effects in the other case reports.

In all, 14 patients in whom systemic hemodynamics (mean arterial pressure or cardiac output) was documented experienced improvement, often immediately. Additionally, 86% of those documented experienced improvement in pulmonary pressures, and 89% in oxygenation. Only one patient had worsening of any of these

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parameters upon initiation of iNO (Table 2).[20]

Discussion

Acute PE is associated with high morbidity and mortality, and the mainstay of treatment is anticoagulation. When associated with hypotension, and particularly in the context of RV compromise, treatment options include thrombolytic therapy and mechanical embolectomy. However, thrombolysis is contraindicated in many patients, and mechanical embolectomy may be associated with unacceptable risk in patients with hemodynamic instability. In some cases, complicating factors, such as active gastrointestinal bleeding and recent surgery, may preclude or delay the implementation of these therapies. Therefore, there is a need for additional agents for those patients in whom thrombolysis and mechanical embolectomy is either delayed or contraindicated.

iNO has multiple effects that suggest a potential therapeutic role in the treatment of acute PE. Prognosis in acute PE has been linked to the degree of pulmonary resistance.[21] It has been proposed that the dramatic increase in pulmonary resistance and resultant RV failure in massive PE may be due to pulmonary vasoconstriction secondary to the initial embolic event. This would suggest that the reduction of RV afterload may be critical to the treatment of PE. iNO, as noted above, has been established as a potent and selective dilator of pulmonary vasculature.[21] In one study involving the use of microspheres to model massive PE in piglets, NO was shown to decrease pulmonary vascular resistance without affecting systemic blood pressure.[22] Furthermore, it has been shown that—in patients with acute PE—free hemoglobin formed

from hemolysis (either as a result of the embolism or the thrombolytic therapy) increases NO consumption and lowers the endogenous NO bioavailability.[23]

In addition, NO has been shown in both human and animal studies to inhibit platelet adhesion and aggregation, prolong bleeding times, and reduce fibrinogen binding.[24] These factors may prevent additional clot formation in acute PE.

Concerns regarding treatment with iNO include rebound pulmonary hypertension and hypoxia upon withdrawal of the agent and methemoglobinemia. However, with regard to rebound effects, clinical experience has shown that they can usually be avoided with gradual as opposed to abrupt withdrawal of iNO. A small study in patients with ARDS demonstrated that doses of 1.25 to 40 ppm of iNO are generally well tolerated.[25] Methemoglobinemia is also unlikely to occur at levels lower than doses of 40 ppm, except in patients with methemoglobin reductase deficiency (a relatively rare condition).

The available literature suggests that there is potential for iNO as a therapeutic agent in conjunction with available therapies, including anticoagulation and thrombolysis. This review has several limitations, including—most prominently—a lack of large, randomized controlled trials to assess the efficacy of iNO versus placebo. In addition, reporting bias most likely contributed to the relative lack of case reports documenting treatment failure or adverse effects. The mortality rate in patients with PE and hemodynamic compromise is high, and the fact that nearly all of the patients in the case reports survived suggests that many cases in which iNO is used are not being reported. On the other hand, iNO is likely to be given only to the patients with very poor prognoses, given the current lack of evidence regarding its role in PE. Additionally, iNO was given in conjunction with other established treatments and it is difficult to ascribe improvements to the iNO as an independent factor. However, in most patients, improvement was immediate upon iNO initiation; in some cases of accidental iNO interruption, the patient exhibited immediate clinical deterioration.[17,18]

Large, randomized controlled trials need to be performed to determine if iNO provides a mortality benefit in acute PE. Other issues that require clarification include the optimal dose and duration of iNO, whether NO should be administered to all patients with evidence of RV strain or limited to those with hemodynamic instability, and how best to monitor patients for methemoglobinemia.

Conclusions

In a review of 18 patients receiving iNO for acute PE, all but one

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MAIN POINTS

- Acute pulmonary embolism (PE) is usually a complication secondary to migration of a deep venous clot or thrombi to the lungs; other significant etiologies include air, amniotic fluid, fat, and bone marrow. Massive PE is associated with considerable morbidity and mortality due to right ventricular failure, hypoxia, and cardiogenic shock, but little progress has been made in finding an effective pharmacologic intervention for this serious complication.

- Inhaled NO (iNO) has been reported to improve oxygenation and hemodynamics in conjunction with either chemical and/or mechanical thrombolysis in massive PE.

- iNO has multiple effects that suggest a potential therapeutic role in the treatment of acute PE. In addition, in both human and animal studies, NO has been shown to inhibit platelet adhesion and aggregation, prolong bleeding times, and reduce fibrinogen binding; these factors may prevent additional clot formation in acute PE.

- Large, randomized controlled trials need to be performed to determine if iNO provides a mortality benefit in acute PE. Whether NO should be administered to all patients with evidence of RV strain or limited to those with hemodynamic instability also requires further clarification.

showed improvement in either systemic or pulmonary pressures or oxygenation. Additionally, a recent phase I trial showed improvement in Borg score, pulse oximetry, and hemodynamics. Our hope is that this article will encourage investigators to conduct a large, randomized control trial to evaluate the efficacy and safety of iNO, as well as proper patient selection, timing, and dosage in those with acute PE. ■

The authors report no real or apparent conflicts of interest.

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