Inhaled Nitric Oxide as Salvage Therapy in Massive Pulmonary Embolism: A Case Series

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Inhaled nitric oxide (INO) has been shown to preferentially lower resistance in the pulmonary vasculature. The relative selectiveness of INO in accomplishing this effect makes it an attractive drug to administer as salvage therapy in patients with acute right ventricular failure secondary to pulmonary embolism. We describe 4 cases in which INO was used as a temporizing agent to decrease right ventricular after-load following massive near-fatal pulmonary embolism. All 4 patients survived to hospital discharge. *Key words: massive pulmonary embolism; acute cor pulmonale; right heart failure; inhaled nitric oxide.* [Respir Care 2012;57(3):444–448. © 2012 Daedalus Enterprises]

Introduction

"The occlusion of the pulmonary artery causes a striking rise of the pressure in these vessels. This rise, which the right heart must fight in order to ensure circulation, will lead to cardiac arrest." As illustrated by this quotation by Picot in *Leçons de Clinique Médicale*, dating back to 1884,[1] the management of patients with massive pulmonary embolism (PE) complicated by acute cor pulmonale is challenging. Thrombolytic therapy with recombinant tissue-type plasminogen activator (rt-PA) is considered the treatment of choice in the presence of persistent hypotension (systolic blood pressure < 90 mm Hg).[2] Thrombolytic therapy can also be considered in patients with severe hypoxia, a large clot burden on computerized tomographic (CT) scans, and those with severe right ventricular dysfunction. However, the use of thrombolytic therapy in the absence of persistent hypotension is controversial.[3-6] Most deaths due to PE occur within 2 hours of the embolus and before lytic therapy is likely to have an effect.[7] In addition, rt-PA is contraindicated in many patients. Additional pharmacologic agents are therefore required as a bridge in patients with massive PE.

Inhaled nitric oxide (INO) has been approved by the FDA for the treatment of premature infants with hypoxic respiratory failure associated with pulmonary hypertension, and as a vasodilatory challenge during hemodynamic studies in the cardiac catheterization laboratory to determine whether patients with primary pulmonary hypertension would be candidates for calcium channel blocker therapy. It is used as an off-label medication for acute respiratory distress syndrome (ARDS), sickle cell crisis, and following cardiac surgery.[8-10] Sporadic case reports have described the use of INO in patients with PE, most commonly following surgical thromboembolectomy.[11-18] We present a case series of patients who received INO as salvage therapy following massive PE.

Case 1

A 66-year-old woman was transferred to our intensive care unit (ICU) from a short-term rehabilitation ward with acute shortness of breath. The transferring physician obtained a ventilation-perfusion ($\dot{V}/\dot{Q}$) scan that revealed near absence of perfusion in her entire left lung, as well as the superior lobe of her right lung (Fig. 1). Her past medical history was notable for a glioblastoma multiforme. The patient was realistic about her prognosis; however, she had

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Fig. 1. Perfusion scan on case 1, demonstrating perfusion of the right lower lobe, with total absence of flow to the right upper lobe and the entire left lung.

specific short-term goals she wanted to realize. As such, the decision was made to aggressively treat the patient. Thrombolytic therapy was contraindicated in the presence of her intracranial neoplasm. After consultation with neurosurgery, a heparin infusion was started. An echocardiogram revealed a markedly dilated right ventricle. After admission to the ICU the patient's condition deteriorated, with hemodynamic instability requiring initiation of a norepinephrine infusion. Additionally, she required intubation and mechanical ventilation for progressive hypoxemia. INO was initiated at 10 ppm, after which her blood pressure and oxygenation improved (Table 1). Once the patient was stabilized on the INO, pulmonary angiography and mechanical thrombectomy were performed (Figs. 2 and 3). INO was slowly titrated off the following day, and the patient was successfully extubated. She subsequently made an uneventful recovery.

Case 2

A 62-year-old man was brought to the emergency department (ED) after being found unconscious in a pool of dark black emesis. His medical history was notable for hypertension, diabetes mellitus, and multiple sclerosis, which required him to use a motorized wheelchair for mobility. Emergency medical service was called, and the patient was intubated for airway protection. An oral gastric tube placed in the ED revealed coffee-ground emesis. The patient's vital signs demonstrated a heart rate of 140 beats/min and a blood pressure that trended down to 85/50 mm Hg despite fluid boluses and norepinephrine. The patient's creatinine was 5.8 mg/dL (baseline 1.2 mg/dL). An electrocardiogram showed the classic $S_1Q_3T_3$ pattern associated with right ventricular strain. A CT angiogram to rule out PE could not be obtained, due to the patient's acute renal insufficiency. A bedside echocardiogram demonstrated a markedly dilated right ventricle. Endoscopy performed in the ED demonstrated a large adherent clot in the esophagus. Heparin infusion was started, with high index of suspicion for PE; however, rt-PA was considered contraindicated because of the acute upper gastrointestinal bleed. Due to refractory hypoxemia and persistent hypotension, INO was initiated at 15 ppm with substantial improvement in oxygenation and hemodynamic profile (see Table 1). Norepinephrine was discontinued the following day, and the INO was titrated to 10 ppm. The INO was subsequently titrated off by the fourth ICU day, and the patient was successfully extubated. He was discharged on hospital day 10 to a skilled nursing facility.

Case 3

A 60-year-old man presented to our ED with acute numbness, tingling, and weakness of his left forearm and wrist. These symptoms began soon after arriving in the United States, after a transatlantic flight from London. On examination in the ED he was noted to be hypertensive, with a blood pressure of 184/114 mm Hg, and hypoxic with an oxygen saturation of 88% on room air. The left radial pulse was not palpable. Doppler studies demonstrated the absence of blood flow in the branchial artery; the venous system demonstrated no clots. Vascular surgery was consulted, and the patient was emergently taken to the operating room, where a large arterial clot was discovered. He subsequently underwent an emergent subclavian and brachial artery embolectomy. His postoperative course was complicated by severe hypoxia and hemodynamic instability. A bedside echocardiogram demonstrated a markedly dilated right ventricle. As thrombolytic therapy was contraindicated, given his recent vascular surgery, a heparin infusion was started. INO was initiated at a dose of 20 ppm for refractory hypoxemia (see Table 1). A CT angiogram confirmed multiple large central PEs. Over the next 3 days the F_{IO_2} was decreased to 50%; however, attempts at decreasing the INO resulted in hypoxemia. The patient remained on INO at 8 ppm until hospital day 7, at which time the INO was slowly titrated off and the patient was extubated. A paradoxical embolism was suspected as the source of the arterial clot, although a bubble study performed on day 4 was negative for intracardiac shunts. The patient made an uneventful recovery.

Case 4

The ICU team was consulted by orthopedic surgery on a 66-year-old woman who had fallen and fractured her

Table 1. Oxygenation and Hemodynamic Data Prior to and 1 and 6 Hours Following Inhaled Nitric Oxide

Case	P_{aO_2}/F_{IO_2}			pH			Mean Arterial Pressure (mm Hg)*		
	Before INO	After 1 Hour INO	After 6 Hours INO	Before INO	After 1 Hour INO	After 6 Hours INO	Before INO	After 1 Hour INO	After 6 Hours INO
1	46	138	210	7.29	7.31	7.32	67	89	98
2	160	315	344	7.32	7.39	7.38	61	80	86
3	43	91	162	7.31	7.37	7.36	65	119	110
4	152	266	294	7.17	7.31	7.36	56	76	92

* Mean arterial pressure obtained from an arterial line (averaged over 1 min).

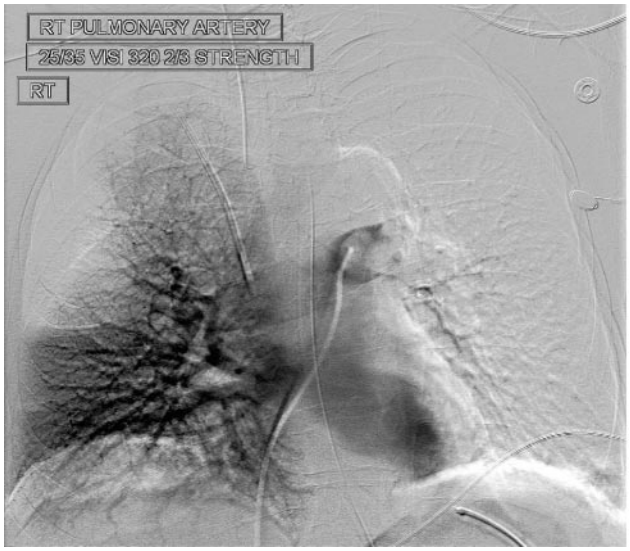

Fig. 2. Pulmonary angiogram from case 1, demonstrating perfusion of the right lower lobe, with total absence of flow to the right upper lobe and the entire left lung.

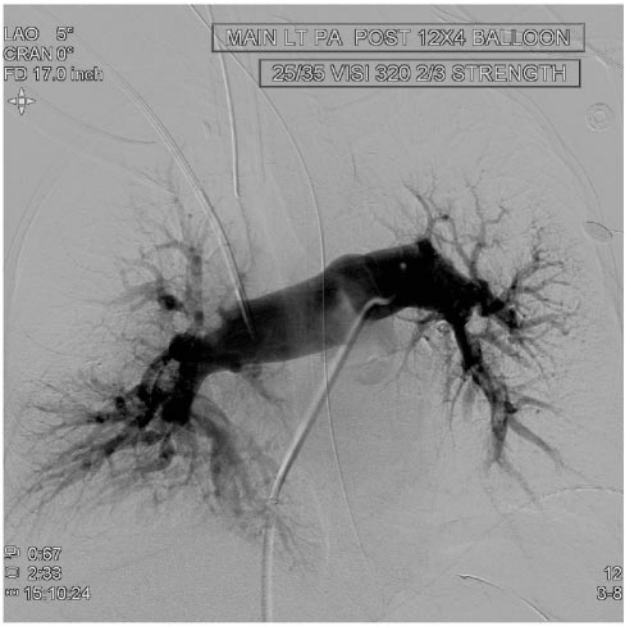

Fig. 3. Pulmonary angiogram from case 1, after mechanical thrombectomy, demonstrating reestablished blood flow in the upper lobe branch of the right pulmonary artery and in the left pulmonary artery.

right femur. The patient was in the operating room when, 10 min into the case and prior to the first incision, she became hypotensive and bradycardic after induction of anesthesia (neuromuscular blocking agents, fentanyl, and midazolam). The patient was resuscitated with 1 mg each of atropine and epinephrine, 500 mL fluid bolus, and was started on a norepinephrine infusion. She was then transferred to the ICU with a heart rate $>$ 180 beats/min and a systolic blood pressure of 90 mm of Hg. A bedside cardiac ultrasound revealed a markedly dilated right ventricle; the McConnell sign (right ventricular free wall hypokinesis in the presence of normal right ventricular apical contractility) was present. Electrocardiogram revealed right heart strain. Dobutamine was initiated to maintain the mean arterial pressure $\geq$ 60 mm of Hg. Due to the strong suspicion of PE, low dose (50 mg/2 h) rt-PA was given.[2] As the patient remained severely hypoxic and hypotensive while the rt-PA was infusing, INO was initiated at a dose of 15 ppm. Following initiation of INO the patient's blood pressure stabilized and the dobutamine was titrated off (see Table 1). By the next day the INO and norepinephrine were titrated off. Lower extremity compression ultrasound revealed a large clot burden. She remained on a heparin drip and a removable inferior vena cava filter was placed. The patient subsequently had her femur fracture repaired and was discharged to a rehabilitation facility on hospital day 28.

Discussion

We present 4 cases of massive PE in which the use of INO appeared to be life-saving. In each case INO provided

additional support until therapeutic, mechanical, or spontaneous thrombolysis could be achieved. INO administration resulted in the improvement of gas exchange and hemodynamics in all 4 cases. This effect was observed at a dose between 10 and 20 ppm. The therapeutic benefit of INO suggests that secondary pulmonary vasoconstriction plays a major role in the hemodynamic derangement following PE.

These cases support the notion of Picot[1] that patients with acute pulmonary artery occlusion die from acute right ventricular failure (acute cor pulmonale). Therefore, reducing the right ventricular afterload is a pivotal therapeutic strategy in the acute phase of PE. This may be achieved by the use of thrombolytic agents and/or the use of pulmonary vasodilators. The administration of intravenous vasodilators may be considered a therapeutic option, but their use is limited by systemic vasodilatation and hypotension. Furthermore, systemic vasodilators may worsen $\dot{V}/\dot{Q}$ mismatch. Inhaled pulmonary vasodilators, which improve $\dot{V}/\dot{Q}$ mismatch and reduce the pulmonary arterial pressure, would seem to be a viable therapeutic option. Improvement in oxygenation is usually achieved with lower doses of INO (1–2 ppm); however, to obtain an antihypertensive effect, larger doses up to 20 ppm may be required.[19,20] A dose of between 10 and 20 ppm was used in our case series, which is the dose that has been reported in patients with ARDS.[8] The initial starting dose was, however, chosen arbitrarily by the treating intensivist. In 2 of the patients the INO was weaned off within 24 hours; however, in the remaining 2 patients attempts at early weaning resulted in worsening oxygenation. These 2 patients required INO to maintain adequate oxygenation for 4 and 7 days, respectively.

As invasive hemodynamic monitoring is considered to be contraindicated in patients with acute PE, we were unable to obtain more detailed hemodynamic information on our patients. However, the hemodynamic improvement noted after initiating INO suggests that this therapy was effective in reducing pulmonary vascular resistance and thereby improving right ventricular function and cardiac output. Additional inhaled vasodilators (not considered for use with our patients) have been delivered clinically and experimentally, and include milrinone, nitroglycerin, prostacyclins, nitroprusside, nitric oxide donors, phosphodiesterase inhibitors, endothelin receptor antagonists, and agonist of soluble guanylate cyclase.[9]

INO reduces pulmonary vascular resistance through smooth muscle relaxation by increasing cyclic guanosine monophosphate (cGMP). Through its kinase, intracellular calcium concentrations are decreased as calcium-sensing potassium channels are activated. In addition, the release of calcium from the sarcoplasmic reticulum is inhibited and the sensitivity of myosin to calcium is reduced. This results in smooth muscle relaxation, which leads to pulmonary vasodilation. In addition to its direct vasodilatory effect, INO inhibits platelet aggregation, with the subsequent release of vasoactive mediators. Increased cGMP levels in platelets decrease intracellular calcium concentration, which decreases glycoprotein (GP) IIb/IIIa receptor binding to fibrinogen.[21-23] The maximal inhibition of platelets has been described as occurring at 3 ppm.[24]

Conclusions

In conclusion, we believe INO should be considered as a temporizing agent in patients with life-threatening PE, until therapeutic, mechanical, or spontaneous thrombolysis can be achieved and pulmonary hemodynamics have improved. INO should be used at a dose of 10–20 ppm and then slowly titrated (to prevent hypertensive rebound) as the patient improves.

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