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ORIGINAL CONTRIBUTIONS

Inhaled Nitric Oxide Improves Pulmonary Functions Following Massive Pulmonary Embolism: A Report of Four Patients and Review of the Literature

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Abstract Acute pulmonary embolism increases pulmonary vascular resistance and may lead to acute right ventricular failure and cardiocirculatory collapse and respiratory failure, possibly resulting in substantial morbidity and mortality. Inhaled nitric oxide (NO) dilates pulmonary blood vessels and has been used to reduce pulmonary vascular resistance in patients with chronic thromboembolic pulmonary hypertension and acute respiratory distress syndrome. This case series describes our experience with inhaled NO administered to four patients suffering from acute massive pulmonary embolism following abdominal surgery. The four described patients recovering from small bowel resection, pancreatoduodenectomy, hemipelvectomy, or recent gastrointestinal bleeding had severe respiratory and hemodynamic deterioration due to pulmonary embolism. Each received inhaled NO (20–25 ppm) via the inspiratory side of the breathing circuit of the ventilator. Pulmonary and systemic blood pressures, heart rate, and lung gas exchange improved in all the patients within minutes after the initiation of NO administration. Inhaled NO may be useful in treating acute massive pulmonary embolism. This potential application warrants further investigation.

Keywords Pulmonary embolism · Pulmonary hypertension · Nitric oxide

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Introduction

Massive pulmonary embolism is associated with severe hypoxemia, right-sided heart failure, and cardiogenic shock, with mortality exceeding 50% within the first two hours after the onset of symptoms [21]. Acute pulmonary embolism increases pulmonary vascular resistance by reducing the cross-sectional area of the pulmonary vascular bed and by pulmonary arterial vasoconstriction—the latter caused by the release of vasoactive mediators, such as thromboxane A2 and serotonin, from the entrapped activated platelets [10]. The subsequent elevated right ventricular afterload induces right ventricular failure leading to circulatory failure and death [13]. Reducing the right ventricular afterload is, therefore, a pivotal therapeutic strategy in the acute phase [2]. The administration of vasodilators may be considered a therapeutic option but their use is limited by systemic vasodilatation and hypotension [5]. These situations require the administration of pulmonary vasodilators [3, 18].

In 1991, Pepke–Zaba et al. [16] demonstrated that inhaled nitric oxide (NO) decreased pulmonary artery pressure and pulmonary vascular resistance in patients with

Table 1 Characteristics of Case 1

Time to drug administration (min)	Heartrate (bpm)	Mean bloodpressure (mmHg)	Dobutamine ($\mu g\ kg^{-1}\ min^{-1}$)	Norepinephrine ($\mu g\ kg^{-1}\ min^{-1}$)	PaO_2/FiO_2	NO, STK
−10	160	80	16	0.06	176	NO start
0	152	86	16	0.02	210	
10	146	93	12	0.08	344	
20	136	93	10	0.07	344	STK start
60	126	95	8	0.06	344	
240	112	93	7	0.01	377	

NO, nitric oxide; STK, streptokinase

primary pulmonary hypertension. This effect was achieved within minutes and was reversible within minutes of its discontinuation, without subsequent systemic vasodilatation. The powerful selective pulmonary vasodilation of NO [10, 20] is rapidly inactivated by NO binding with hemoglobin, thus circumventing the potential systemic vasodilatation [24]. The very few reports on the use of inhaled NO in patients with massive pulmonary embolism described conflicting results, possibly because of the inclusion of patients with a single acute massive embolism and those with chronic recurrent emboli [6, 20].

We now contribute a series of four cases to the sparse pool of existing data on the value of inhaled NO in treating acute pulmonary embolism.

Case Series

Case 1 (Table 1)

A 25-year-old woman suffering from Peutz–Yegher syndrome with multiple polyps in the small bowel and colon was admitted to hospital complaining of abdominal pain. A laparotomy revealed intussusceptions of two segments of the small bowel and multiple polyps throughout the entire small bowel for which a reduction without resection was carried out. On the fourth postoperative day, she complained of mild dyspnea and underwent pulmonary ventilation/perfusion scan, which yielded low probability for pulmonary embolism. On the following day, she experienced a sudden onset of dyspnea, which was immediately followed by loss of consciousness and ventricular fibrillation. Sinus rhythm was restored after a short external cardiac massage, intubation, and institution of mechanical ventilation. Her heart rate was 160/min, blood pressure was maintained at 100/60 mmHg with the support of intravenous (IV) epinephrine and dobutamine, and arterial pulse-derived oxygen saturation (SpO_2) was 91% when fractional inspiratory oxygen (FiO_2) was 1. A transthoracic echocardiogram demonstrated massive dilation of the right ventricle with severely reduced outflow and a compressed intraventricular septum toward the left side, all highly suggestive of massive pulmonary embolism. NO by inhalation was administered at a rate of12–14 ppm via the breathing circuit of the ventilator (Puritan Bennet 7200™, Carlsbad, CA). Within 15 min the patient's heart rate decreased, blood pressure increased, and both norepinephrine and dobutamine were continued for 4 h when they were safely tapered off (Table 1). At the same time, oxygenation improved and the FiO_2 could be decreased to 0.4. A repeated echocardiogram demonstrated improved right heart function. Since none of the parameters returned entirely to precrisis values, streptokinase (1.5×10^6 units over 24 h) was given 20 min after NO had been initiated.

Four hours later, a left main pulmonary artery embolism was diagnosed by high-speed computerized tomographic (CT) angiography. The patient continued to improve under both drugs; streptokinase was replaced by heparin within 8 h because of the risk of bleeding, although the patient's hemoglobin count remained unchanged. She was slowly weaned off NO inhalation over the next two days and could be safely disconnected from mechanical ventilation after two more days, whereupon she was discharged from the ICU.

Case 2 (Table 2)

This 58-year-old man underwent pancreatoduodenectomy because of adenocarcinoma of the head of the pancreas. On the second postoperative day, the patient complained of sudden dyspnea and immediately underwent CT angiography, which showed a massive embolism in the right upper and lower pulmonary arteries and in two segments of the left lower lobe. Intravenous heparin was initiated (rather than streptokinase because the patient was only several hours out of a major operation), but oxygenation continued to worsen during the following hours to the degree that the patient required intubation and mechanical ventilation with $FiO_2 = 1$ in order to maintain an SpO_2 level >90%. He also

Table 2 Characteristics of Case 2

Time to drug administration (min)	Heartrate (bpm)	Mean bloodpressure (mmHg)	Epinephrinez ($\mu g\ kg^{-1}\ min^{-1}$)	PaO_2/FiO_2	NO, STK
−10	160	76	0.2	66	
0	160	76	0.2	66	NO start
10	137	72	0.2	278	
20	130	82	0.1	312	
40	126	85	0.1	310	
60	122	93	0.1	300	STK start
240	121	92	0.1	330	

NO, nitric oxide; STK, streptokinase

Table 3 Characteristics of Case 3

Time to drug administration (min)	Heart rate (bpm)	Mean bloodpressure (mmHg)	PaO_2/FiO_2	NO
−10	155	69	166	
0	155	69	166	NO start
10	150	68	170	
20	142	76	182	
40	122	82	220	
60	117	84	240	
240	110	84	263	

NO, nitric oxide

developed hemodynamic instability and required the administration of vasoactive drugs (epinephrine, 0.2 $\mu g\ kg^{-1}\ min^{-1}$). NO (17 ppm) was administered via the breathing circuit of the ventilator. There was an almost instant marked improvement in oxygenation and his blood pressure improved as well, allowing for the epinephrine drip to be tapered off during the ensuing 24 hours (Table 2). Despite this beneficial effect and the risk of bleeding, thrombolysis (streptokinase 1.5×10^6 units over 24 h) was started; the patient did not bleed nor did he require a blood transfusion. He slowly improved, allowing for streptokinase to be terminated approximately 30 hours before NO, and he was later taken off mechanical ventilation.

Case 3 (Table 3)

A 52-year-old man who had undergone hemipelvectomy because of an extensive recurrence of renal cell carcinoma developed sudden dyspnea on the second postoperative day. He was immediately ventilated because of borderline SpO_2 (88%–91% on $FiO_2 = 1$). CT angiography revealed pulmonary emboli in the right main pulmonary artery. Heparin was not given because of bleeding from both the trachea and the surgical wound. Inhaled NO (25 ppm) was started, oxygenation improved, and FiO_2 was reduced to 0.6 (Table 3) within 30 min after initiation of treatment. All cardiopulmonary parameters improved to the extent that it was safe to carry out transvenous embolectomy and place an inferior vena cava filter. The patient was discharged home four weeks later.

Case 4 (Table 4)

A 55-year-old male was admitted less than 2 weeks after being treated medically for a bleeding duodenal ulcer because of sudden onset of dyspnea, hemoptysis, and subsequent hypotension. He was intubated, mechanically ventilated, and rushed to the imaging facilities where CT angiography showed bilateral pulmonary artery emboli. Heparin was not given because of his bleeding history. NO (25–27 ppm) and epinephrine were initiated whereupon oxygenation and systemic and pulmonary blood pressures rapidly improved (Table 4), allowing for the placement of an inferior vena cava filter. The patient was weaned off the ventilator and discharged from the hospital three weeks later.

Discussion

Massive pulmonary embolism is an acute event associated with a high mortality rate. Nearly 25,000 patients died of massive pulmonary embolism in 1998 in the United States [12]. The overwhelming increase in pulmonary vascular arterial resistance (due to the mechanical obstruction and the humorally induced inflammatory activity [10]) requires a quick breakdown of the blood clot (either by medication,

Table 4 Characteristics of Case 4

Time to drug administration (min)	Heart rate (bpm)	Mean bloodpressure (mmHg)	Epinephrine ($\mu g\ kg^{-1}\ min^{-1}$)	Pulmonaryartery pressure(mmHg)	PaO_2/FiO_2	NO
−10	116	71	0.09	76/30	195	
0	116	71	0.09	71/31	192	NO start
10	109	80	0.09	68/30	234	
20	105	88	0.07	69/30	290	
60	104	96	0.04	60/30	312	
240	95	62	0.02	48/24	300	

NO, nitric oxide

surgical procedure, the administration of vasodilators) to unload the failing right heart. Since the use of systemic vasodilators is limited by the concomitant hemodynamic instability, the use of inhaled NO and/or prostacyclin, which are selective pulmonary vasodilators, would appear to be reasonable alternatives.

Our four patients had pathognomonic signs and symptoms of pulmonary embolism. They were confirmed both by imaging studies and by the later effectiveness of NO, either alone or together with streptokinase. All patients depicted subsequently improved oxygenation.

NO diffuses freely across cell membranes, thus diffusing rapidly from the alveoli to the highly resistant pulmonary arterioles [18]. It is an endogenous vasodilator that activates the smooth muscle–soluble guanylate cyclase by increasing cyclic guanosine monophosphate (GMP) levels. Cyclic GMP activates protein kinase, resulting in dephosphorylation of the myosin light chain, which leads to arterial muscle relaxation [1]. Since NO is administered by inhalation, it will cause vasodilatation only in the well-ventilated lung regions, thereby improving the ventilation/perfusion ratio and decreasing pulmonary shunt [24]. In this way, NO not only decreases pulmonary artery pressure but improves arterial oxygenation as well.

Inhaled NO was shown to reduce pulmonary hypertension and improve gas exchange in adult respiratory distress syndrome (ARDS) [24], in a post-cardiac surgery infant [19], after heart transplantation [15], in patients suffering from primary pulmonary hypertension [20], and in patients suffering from pulmonary hypertension that started after pulmonary thromboendarterectomy [3, 9].

The role of platelets in clot formation and in inducing pulmonary vasoconstriction by releasing vasoactive mediators during ARDS, arteriosclerosis, primary pulmonary hypertension, and in pulmonary embolism has been well documented [8]. Platelet aggregation and the release of potent vasoconstrictors, such as serotonin and thromboxane A_2, further aggravate right ventricular afterload. Thus, it stands to reason that treatment with NO, which has antiplatelets activity, may modify the ongoing inflammatory reaction driven by platelet or pro-aggregation factors released by the platelets [14]. Indeed, Nong et al. [15] showed that inhalation of NO significantly reduced *ex vivo* collagen-induced platelet aggregation and attenuated the subsequent rise in pulmonary artery pressure.

The above-mentioned effects of NO are reversed within 15 min after inhalation ceases, a feature which may be particularly desirable in cases of hemorrhage due to other causes [14]. These data are compatible with our current findings. Because the clinical effects of streptokinase start from 30 minutes to several hours after its therapeutic blood levels are reached, it was unethical to withhold its administration from those patients who were on the verge of total cardiovascular collapse and for whom it was not contraindicated (e.g., bleeding). The rapid improvement in the respiratory and hemodynamic conditions clearly followed the administration of NO and not that of streptokinase in three of our four patients.

A word of caution is in order. Although NO is safe in low and moderate doses (i.e., up to 40 ppm), several side effects have been described in the literature, although our patients did not experience them. The development of methemoglobinemia is dependent on the concentration of the patient's hemoglobin, oxygen saturation, activity of methemoglobin reductase, and the dose of NO [23]. None of our patients demonstrated symptoms of methemoglobinemia. NO_2, the reactive metabolite of NO, may increase airway reactivity in subjects with asthma [4]; it damages lung epithelial cells and induces type II epithelial cell proliferation and hyperplasia, including epithelia of the end alveoli [17]. Moreover, unlike our patients, several case reports have documented life-threatening rebound hypoxemia and pulmonary hypertension after withdrawal of inhaled NO, mostly in patients with ARDS.

The literature contains reports of only nine patients in whom inhaled NO was used for the attenuation of the effects of massive pulmonary embolism; it resulted in immediate and significant hemodynamic and gas exchange improvements in all of them [6, 7, 18, 22]. Among the reported patients, however, there were some with chronic

recurrent embolism and some with pulmonary hypertension following pulmonary thrombectomies, which represent inhomogeneous populations. Our patients comprise a homogeneous group in which each patient had acute postoperative pulmonary embolism with no previous chronic pulmonary disease. Based on a previous report by Capellier et al. [6], we elected to give our patients a moderate dose of NO (up to 25 ppm). In addition, none of our postsurgical patients had a significant bleed despite the combination of NO and thrombolysis or heparin, the ''gold therapeutic standard'' in intravascular thrombotic events, that was given to two of them.

In conclusion, our results indicate a beneficial potential of NO in patients with acute massive pulmonary embolism. We believe that these findings should encourage controlled studies to assess the value of inhaled NO in critical life-threatening situations such as acute massive pulmonary embolism.

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