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BRIEF REPORT

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Inhaled nitric oxide in patients with pulmonary embolism

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Abstract *Objective:* To describe the use of inhaled nitric oxide (NO) in four patients with severe pulmonary embolism.
Setting: The intensive care unit (ICU) of a university teaching hospital.
Patients: Four patients with severe pulmonary embolism on the basis of clinical, haemodynamic or blood-gas parameters received NO by inhalation either during spontaneous respiration (two cases) or while mechanically ventilated (two cases).
Interventions: Conventional management of pulmonary embolism in addition to the use of inhaled NO.
Measurements and results: Description of clinical course, haemodynamic and gas-exchange data. Dose-response data are also described for three patients.
Conclusions: We reported four cases of pulmonary embolism where the administration of inhaled NO resulted in an improvement in pulmonary haemodynamic and gas-exchange parameters. Two patients were weaned from NO and survived until discharged from the ICU. Inhaled NO might be a useful adjunct in pulmonary embolism to improve stability of the patient prior to thrombolysis or surgery.

Key words Pulmonary embolism · Nitric oxide · Pulmonary arterial hypertension · Cardiac failure · Treatment

Introduction

Acute pulmonary embolism (PE) continues to be associated with a high mortality rate. Right heart failure is secondary to a massive rise in pulmonary vascular resistance (PVR). It is in the initial phase of PE that the haemodynamic impact is most marked. Treatment of the acute stage of the disease relies on thrombolysis, which reduces pulmonary arterial pressure and vascular resistance [1].

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator (SPV) proposed for use in primary or secondary pulmonary arterial hypertension [2]. It is also recommended in acute respiratory distress syndrome (ARDS) to increase oxygenation by improving ventilation-perfusion matching [3]. NO also causes improvement in right ventricular function associated with ARDS [4]. Experimental studies have shown that NO causes a fall in PVR in a model of chronic PE in pigs [5]. It also resulted in the closure of the foramen ovale in a case of acute PE [6].

This report describes four cases of PE, management of which included the administration of NO by inhalation. Haemodynamic and blood-gas data in response to inhaled NO are described.

Case reports

Case 1

A 61-year-old patient with a chronic history of phlebitis and PE necessitating the insertion of an inferior vena cava filter underwent oesophagectomy for cancer. On the seventh post-operative day, he presented with severe dyspnoea, shock and supraventricular

rhythm disturbances. Arterial oxygen saturation (SaO_2) was at 75 % with supplemental oxygen via nasal prongs at a rate of 10 l/min. Pulmonary angiography confirmed the diagnosis of massive PE with a Miller score of 30 %. Thrombolytic therapy was not feasible in view of the recent surgery. Surgical thrombectomy was also not possible. Treatment included the administration of heparin (100 U/kg priming dose) and the use of inhaled NO. NO (CFPO, Nancy, France) was administered via a gas-flow meter placed into the inspired gas during spontaneous ventilation via a face mask (Airlife, adult oxygen mask, Baxter Healthcare Corporation, Valencia, USA), at a concentration of 10 ppm. The concentration of NO was measured by chemiilluminescence (Cosma, Igny, France) in the non-rebreather bag of the face mask using a continuous aspiration of 500 ml/min. SpO_2 (percutaneous oxygen saturation) rose rapidly from 75 % to 82 % (within 30 min), 88 % (60 min), 88 % (120 min). A Swan-Ganz pulmonary artery (PA) catheter (Opticath, Abbott, Rungis, France) was inserted about 1 h after initiation of treatment. PVR fell from 377 dynes/sec/cm^5 (60 min) to 203 dynes/sec/cm^5 (120 min) with an increase in cardiac output from 4 l/min to 5.1 l/min. Resolution of the clinical picture was rapid with SpO_2 reaching 96 % 20 h after the initial episode. The patient was discharged from the ICU 4 days later.

Case 2

A 58-year-old patient with lupus and a circulating anticoagulant, complicated by recurrent bouts of intra-alveolar haemorrhage, was admitted for progressive dyspnoea. A pulmonary angiogram revealed acute PE with a background of chronic pulmonary embolic disease. Thrombolysis was initially contraindicated and a PA catheter was inserted. Inhalation of NO via a facemask was commenced during spontaneous respiration, fractional inspiratory oxygen (FiO_2) [= 1]. NO concentration was increased by 5 ppm every 15 min. Haemodynamic and blood-gas data are shown in Table 1. The ensuing clinical improvement made it possible to avoid mechanical ventilation for a period of 8 h overnight. Unfortunately, the condition worsened in the morning, concurrent with the accidental removal of the oxygen mask and the interruption of NO inhalation. The deterioration in the clinical picture led to a late recommendation of thrombolysis (alteplase, 60 mg bolus, Boehringer Ingelheim, Paris, France) which was associated with pulmonary haemorrhage. Death occurred rapidly from hypoxaemia and cardiogenic shock.

Case 3

An 83-year-old patient with a history of PE was admitted to the emergency room with respiratory distress. A clinical diagnosis of PE was confirmed by high-speed computer tomographic (CT) angiography. Because of the severity of the symptoms, thrombolysis (alteplase, 70 mg) was instituted. The clinical picture of PE resolved by day 3. However, there was again evidence of reembolisation, confirmed by another CT angiogram. A PA catheter (Opticath, Abbott, Rungis, France) confirmed pulmonary hypertension. Thrombolysis (alteplase, 100 mg) was initiated and inhalation of NO was commenced. The patient received incremental doses of NO (range 5 to 20 ppm), administered via the breathing circuit of the mechanical ventilator. Haemodynamic and blood-gas data for this case are shown in Table 2. Clinical improvement was transitory and the patient developed severe ventricular rhythm abnormalities with a fatal outcome.

Table 1 Evolution of respiratory and haemodynamic parameters with incremental doses of inhaled NO in case 2. *SaO_2*, arterial oxygen saturation; *SvO_2*, mixed venous oxygen saturation; *mPAP,* mean pulmonary arterial pressure; *PVR,* pulmonary vascular resistance; *CO,* cardiac output

	O_2	NO			
		5 ppm	10 ppm	15 ppm	20 ppm
SaO_2 (%)	84	87	90	89	91
SvO_2 (%)	31	42	39	39	–
mPAP (mm Hg)	62	56	45	48	–
PVR (dynes/sec/cm^5)	1852	1880	1148	1248	–
CO (l/min)	1.9	2	2.3	2.5	2.6

Table 2 Evolution of respiratory and haemodynamic parameters with incremental doses of inhaled NO in case 3. *PaO_2*, arterial-oxygen partial pressure; *mPAP* mean pulmonary artery pressure; *RAP* right atrial pressure

	O_2	NO			
		5 ppm	10 ppm	15 ppm	20 ppm
SaO_2 (%)	86	–	94	–	–
PaO_2 (mm Hg)	58	–	83	–	–
mPAP (mm Hg)	47	38	36	26	33
RAP (mm Hg)	10	4	3	4	6
CO (l/min)	3.8	4.5	3.9	4.1	4.4

Case 4

A 62-year-old patient with Parkinson's disease was admitted to the ICU suffering from septic shock due to an abscess on the buttock. Emergency drainage of the abscess occurred after intubation, ventilation and vascular-fluid replacement had been attended to. On return from the operating room, haemodynamics were unstable and required the administration of vasoactive drugs (dopamine 15 μg/kg/min, epinephrine 0.6 μg/kg/min). Pulmonary arterial catheterisation [to continuously measure cardiac output and mixed venous oxygen saturation (SvO_2), Opti Q Abbott, Saint Remy sur Avre, France] demonstrated a rise in cardiac output (7 l/min), with an elevation of right and left filling pressures in response to this therapy. After a few hours the clinical picture deteriorated with a drop in blood pressure and cardiac output and the onset of acute renal failure. A transoesophagial echocardiography showed significant dilatation of the right heart cavities, paradoxical movement of the septum and major reduction of left ventricular volume. This was suggestive of acute cor pulmonale due to PE. Thrombolysis was contraindicated because the patient had recently undergone surgery. Therefore, the patient received a priming dose of heparin (100 U/Kg) via the intravenous route and inhalation of NO was instituted via the breathing circuit of the mechanical ventilator. The evolution of haemodynamic and blood-gas parameters, following incremental increases in concentration of NO (range 5 to 20 ppm) is shown in Table 3. Improvement was extremely rapid, with a rise in systemic arterial pressure without modification of the vasoactive drugs, an increase in cardiac output and spontaneous diuresis. Accidental interruption in the administration of NO was almost instantaneously accompanied by a drop in mean systemic arterial pressure (MAP), SvO2 and cardiac output. The clinical

Table 3 Haemodynamic and blood-gas evolution with incremental doses of inhaled NO in case 4. *MAP* mean systemic arterial pressure; *FIO_2* fractional inspiratory oxygen

	$FIO_2 = 1$	NO		
		10 ppm	15 ppm	20 ppm
SaO_2 (%)	95	99	99	99
SvO_2 (%)	43	61	67	68
MAP (mm Hg)	59	68	71	75
mPAP (mm Hg)	46	40	38	38
CO (l/min)	2.7	4.1	4.3	4.3

picture resolved and the patient was weaned from epinephrine and dopamine in 48 h. Weaning from NO was carried out very gradually on the third day over a 24-h period. The Duplex Doppler-ultrasound examination of the lower limbs was normal, but a pulmonary angiogram carried out on the tenth day of treatment revealed a right lower lobe pulmonary embolus. Staphylococcus aureus and Bacteroides fragilis were isolated from the bacteriological samples of the buttock abscess. The patient survived the acute episode and was discharged from the ICU 15 days later.

Discussion

In all four reported cases, NO was administered by inhalation in association with other standard therapeutic options because of the severity of the clinical picture. NO administration resulted in the improvement of gas exchange and haemodynamics in all four cases. This effect was observed at 10 and 15 ppm.

PE is a serious illness and the immediate prognosis is linked to the degree of elevation of pulmonary arterial pressure and PVR [7]. Several mechanisms are involved in this rise in PVR. These include the obstruction of the vascular bed by embolus, as well as vasoconstriction. An inflammatory reaction secondary to endothelial abnormalities rapidly supervenes, with the production of *A*rachidonic *A*cid metabolites, such as thromboxane A_2 derivatives and leucotrienes. Platelet aggregation is enhanced. Surfactant production may be disturbed resulting in oedema and atelectasis [7]. Hypoxaemia is multifactorial, but is related to the opening of intra-pulmonary shunts, with abnormalities of the ventilation-perfusion ratio and occasionally with opening of the foramen ovale [8]. Inhaled NO is a SPV [3, 9]. It re-established endothelial function in a model of pulmonary reperfusion ischaemia and also limited the activation of polynuclear neutrophils and inhibited platelet aggregation [10]. Experimental results show that it reverses pulmonary arterial hypertension induced by an analogue of thromboxane A_2 or by protamine inactivation of heparin [11].

Improvement of the ventilation-perfusion ratio is obtained with low doses of 1–2 ppm [12], but to obtain an antihypertensive effect, larger doses of 5–40 ppm may be required [2, 11]. In our patients, NO inhaled concentrations were between 5 and 20 ppm, with a maximal response observed in the 10 ppm range, as reported for primary pulmonary hypertension [2].

The pulmonary vasodilating action of inhaled NO has been useful following corrective surgery for mitral value disease, for primary pulmonary hypertension of the new-born, and for acute respiratory distress syndrome [3]. In a patient with cardiomyopathy, it produced an improvement of right ventricular function and of hepatic perfusion [13]. Furthermore, improvement of right ventricular function was obtained in ARDS following NO inhalation [4]. Inhaled NO enabled the closure of a foramen ovale in one case of PE [6]. When used in studies on pigs, inhaled NO caused a reduction in chronic pulmonary hypertension, induced by recurring emboli without modifying cardiac output [5]. A significant decrease in pulmonary arterial pressure was also obtained with NO (40 ppm) in a dog model of PE [14]. In our patients, the pulmonary arterial pressure decreased (17–47 %), whereas cardiac output increased (8–52 %) on the institution of NO therapy. This decrease in pulmonary arterial pressure may be accompanied by a rebound effect on interruption or cessation of the treatment [15]. As a result of this, we weaned or patients gradually from NO therapy.

In a patient receiving anticoagulant or thrombolytic treatment, NO might aggravate haemostasis problems. It is, however, difficult to give a precise evaluation of the risks involved [10]. Although case 2 had experienced pulmonary haemorrhage 1 year earlier unrelated to NO therapy, she received NO therapy for 8 h without demonstrating any signs of haemorrhage. We cannot completely rule out participation of NO in the bleeding that occurs after thrombolysis, but it seems limited to us.

Intravenous administration of vasodilators such as nitroglycerin or sodium nitroprusside is of limited value in patients suffering from massive PE. The resulting systemic vasodilation and hypotension may exacerbate right ventricular ischaemia. Recently, Webb et al. reported on the use of prostacyclin aerosols in the control of pulmonary arterial hypertension in acute PE. Haemodynamic improvements were recorded 4 h after use of the aerosol, that is, 7 h after the administration of the thrombolytic [16]. This makes the respective actions of the different treatments difficult to assess. Prostacyclin does offer theoretical advantages over NO in that it is the natural antagonist of thromboxane. As the authors pointed out, the safety of and tolerance to this form of administration of prostacyclin have yet to be established. In this respect, the experience acquired in some centres using inhaled NO in a large number of clinical situations seems to offer a greater degree of safety [2–4, 12]. Not, as yet, an approved therapy in the ICU, NO was used in our patients facing severe pulmo-

nary hypertension or hypoxaemia in accordance with current French medical recommendations.

In our spontaneously breathing patient, NO was delivered into the non-rebreather bag of an oxygen face mask at a flow of 0.3–1.2 l/min mixed with a flow of oxygen of 15 l/min. NO and NO_2 concentrations were measured in the gas reservoir. In the range of NO concentrations used, NO_2 concentrations ranged from 0.1–0.4 ppm. We did not measure NO and NO_2 concentrations in the patient's room, however because of the air-conditioning; very low concentrations are expected. In a previous study, very low NO room concentrations were recorded during NO therapy and health-care workers were not considered to be at risk [17].

Inhaled NO is a therapeutic option in PE. Its SPV effect might be indicated for marked decreases in cardiac output, pending the effects of thrombolysis, heparin therapy and/or surgery. An improvement in oxygenation as well as a reduction in PA pressure was seen in our four patients. Because of its action in inhibiting platelet aggregation and the rebound phenomena associated with its withdrawal, NO should be used with caution and reserved for severe acute PE. The practical aspects concerning its use, such as indications, dosage, duration and weaning, require further study.

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