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CASE REPORT

Inhalation of nitric oxide as a life-saving therapy in a patient after pulmonary embolectomy†

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We describe a 54-yr-old man with cardiogenic shock caused by acute right heart failure after pulmonary embolectomy. Inhalation of nitric oxide led to immediate improvement in respiratory and haemodynamic variables. Inhaled nitric oxide can be used to reduce acute right heart failure until conventional therapy can provide successful haemodynamic stability.

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The simple molecule nitric oxide, formed from the semi-essential amino acid L-arginine by the action of the enzyme nitric oxide synthase, is involved in the regulation of a wide range of functions, including blood vessel tone, cardiac contractility, platelet aggregation, neurotransmission, host defence and cytotoxicity.[1] Inhaled nitric oxide (iNO) acts as a powerful selective pulmonary vasodilator, and can reduce pulmonary hypertension and improve gas exchange in acute respiratory distress syndrome.[2] It has been used to treat other causes of pulmonary hypertension, such as after cardiac surgery,[3] mitral valve replacement,[4] implantation of a left ventricular assist system[5] and heart transplantation.[6] In addition, iNO has become the ideal substance for testing the acute reactivity of the pulmonary vascular bed to vasodilators in primary pulmonary hypertension.[7]

In this report, we describe the use of iNO in a patient with acute right heart failure after pulmonary embolectomy.

Case report

A 54-yr-old man fainted for a few seconds 5 days before admission to the intensive care unit (ICU). Four days later he experienced another syncope followed by increasing dyspnoea, and was admitted to hospital. Deep venous thrombosis of the left lower extremity (calf, popliteal and thigh veins) was diagnosed and anticoagulation with heparin was initiated. As dyspnoea increased further and pulmonary embolism, together with intracardiac thrombi, were suspected, the patient was transferred to our ICU. A chest x-ray showed a small degree of cardiac enlargement, predominantly of the right heart, no pulmonary oedema, no pulmonary infiltrate and no lung congestion. Thoracic spiral computer tomography revealed massive pulmonary embolism with a large embolus in the pulmonary artery trunk straddling the bifurcation and extending into the major branches of the left and right pulmonary arteries. Transthoracic echocardiography showed several thrombi in the right atrium, partially prolapsing across the tricuspid valve into the right ventricle. The echocardiograph also showed signs of pulmonary hypertension: a balloon-like dilated right atrium and an enlarged right ventricle with paradoxical interventricular septal motion (with flattening and systolic bulging of the septum towards the left ventricle) and concomitant reduced left ventricular size. Measurement of pulmonary artery pressure and cardiac output by passage of a pulmonary artery catheter was avoided because of the high risk of displacement of the intracardiac thrombi by the catheter. The patient was haemodynamically stable with an infusion of crystalloid 250 ml h^{-1}, without the need for catecholamine support.

Thoracotomy with removal of the intracardiac thrombi and

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Table 1 Gas exchange, and systemic arterial and central venous pressures after weaning from cardiopulmonary bypass and after starting inhaled nitric oxide (NO) therapy. Pa_{O_2}=arterial partial pressure of oxygen, FI_{O_2}=fractional inspired concentration of oxygen, MAP=mean arterial pressure, CVP=central venous pressure

	0	10 min	20 min	30 min	60 min	90 min	120 min
NO (ppm)	0	0	0	15	15	15	15
Pa_{O_2}/FI_{O_2} (mm Hg)	69	65	60	86	109	118	126
MAP (mm Hg)	61	50	45	80	82	92	105
CVP (mm Hg)	19	21	25	14	11	12	11
Epinephrine ($\mu g\ kg^{-1}\ min^{-1}$)	0.06	0.19	0.19	0.19	0.11	0.09	0.05

Table 2 Effect of stopping nitric oxide (NO) on gas exchange and haemodynamic state

	Time after starting NO					
	15 h	15h 5 min	15h 7 min	27h 7 min	27h 15 min	27h 18 min
NO (ppm)	10	0	10	1	0	1
Pa_{O_2}/FI_{O_2} (mm Hg)	202	153	193	164	129	164
MAP (mm Hg)	70	61	69	69	60	70
CVP (mm Hg)	10	14	11	11	13	10

pulmonary embolectomy was performed. Before cannulation for cardiopulmonary bypass (CPB), the patient was given sodium heparin 300 iu kg^{-1}. CBP was initiated when activated clotting time (ACT) was greater than 480 s. Blood flow was maintained using a cardiac index of 2.5 litre m^{-2} throughout the procedure. Mean arterial pressure remained greater than 50 mm Hg throughout the whole period of CPB and temperature was 35°C. Bypass time and aortic clamping time were 66 and 39 min, respectively. After termination of bypass, the effects of heparin were antagonized by peripherally administered protamine. The immediate postoperative course was uncomplicated, with stable arterial pressure and respiratory function. Approximately 9 h after surgery, while weaning from the ventilator, the patient's condition suddenly deteriorated, with progressive hypotension and impaired gas exchange. Transoesophageal echocardiography showed enlargement of the right heart chambers and reduced right ventricular function compared with the immediate postoperative echo, suggesting a recurrent embolic event, even though the patient received heparin (1000 iu h^{-1}) for anticoagulation. Despite high doses of catecholamines, cardiovascular stability could not be obtained and therefore a repeat thoracotomy was performed. Several newly formed emboli were removed from the truncus, lobe and segment branches of the pulmonary artery. The patient was actively cooled to 28°C and rewarmed at the end of CPB while maintaining a 6–8°C gradient between venous blood and water temperature. Bypass time and aortic clamping time were 78 and 59 min, respectively. The effects of heparin were antagonized by protamine at the end of bypass, with no change in haemodynamic state. At the end of operation, an inferior vena caval filter was inserted. After weaning from CBP, mean arterial pressure and gas exchange deteriorated rapidly despite increasing inotropic therapy. Echocardiography showed right heart failure: an enormously enlarged right atrium (8 cm in diameter) and right ventricle with dilated superior and inferior venae cavae and dilated hepatic veins. The pulmonary artery was dilated and pulsed Doppler echocardiography of pulmonary blood flow showed a shortened acceleration time (50 ms), consistent with increased pulmonary artery pressure.[8] Colour flow Doppler showed massive tricuspid insufficiency (grade IV). Measurement of maximal velocity of tricuspid regurgitation by continuous wave Doppler[8] was not sufficiently possible because of an inadequate Doppler angle.

At this time iNO (AGA-Austria) at a concentration of 15 ppm was started with continuous delivery into the inspiratory limb of the ventilator before the Y-piece, first via a flowmeter and then via a special nitric oxide delivery system (Nodomo, Dräger, Germany) connected to the ventilator (Evita 2, Dräger, Germany) after transfering the patient to the ICU. With the Nodomo delivery system, concentrations of nitric oxide and nitrogen dioxide in the inspiratory limb of the breathing system were monitored continuously by electrochemical cells (nitrogen dioxide never exceeded 2 ppm). Methaemoglobin concentrations did not increase above 1%.

Continuous positive pressure ventilation was used, with an FI_{O_2} of 1.0, respiratory frequency 15 bpm, tidal volume 600 ml, I:E 1:1 and PEEP 0.7 kPa. Intravascular continuous blood-gas analysis was performed using a radial artery indwelling catheter by Paratrend (Paratrend 7, intravascular blood gas monitoring system, Biomedical Sensors Ltd, Pfizer Inc., New York, NY, USA).

Gas exchange, expressed as Pa_{O_2}/FI_{O_2} ratio, and haemodynamic status, improved rapidly after starting iNO (Table 1). FI_{O_2} was reduced to 0.6 after 4 h and to 0.5 after 5 h. Inotropic therapy with epinephrine was reduced and stopped after 14 h. Transoesophageal echocardiography 2 h after starting nitric oxide therapy showed markedly decreased right atrial and ventricular size and improved right

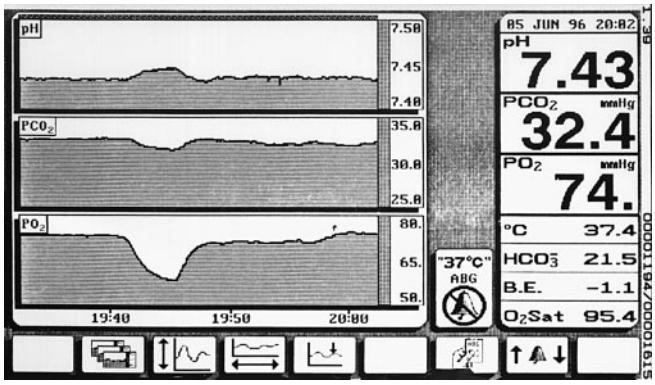

Fig 1 Intravascular continuous blood-gas analysis by Paratrend. Stopping inhalation of nitric oxide (NO) caused an immediate decrease in arterial P_{O_2} with a small reduction in arterial P_{CO_2}. Baseline values were regained within minutes after restarting NO therapy.

ventricular function, normal interventricular septal motion with normal left ventricular size and compliance. The degree of tricuspid insufficiency was reduced (from grade IV to II) and the measured acceleration time of pulmonary blood flow velocity was increased to near-normal (from 50 to 100 ms), strong evidence of a reduction in pulmonary artery pressure.

The concentration of iNO was reduced to 10 ppm after 3 h with no change in gas exchange or haemodynamic state. Several attempts to stop iNO failed causing immediate deterioration of gas exchange (Fig. 1) and haemodynamic state within the next 36 h (Table 2), even at low nitric oxide concentration (1 ppm). Pa_{O_2}/FI_{O_2} and MAP returned to baseline values immediately (within 2 min) after restarting iNO. Pa_{CO_2} and pH changed only slightly compared with Pa_{O_2} during interruptions of iNO (Fig. 1).

The patient was weaned successfully from iNO after 72 h, extubated 12 days after operation, discharged from the ICU after 14 days and left hospital on day 20.

Discussion

We have reported the use of iNO as a successful feature in the treatment of cardiogenic shock caused by acute right heart failure immediately after pulmonary embolectomy. To our knowledge, this is the first report of the use of iNO after pulmonary embolectomy.

In acute pulmonary embolism, pulmonary vascular resistance increases. Emboli reduce the cross-sectional area of the pulmonary vascular bed, and active pulmonary vasoconstriction is caused by release of vasoactive humoral factors from activated platelets that accumulate at the side of a new clot. Serotonin and thromboxane A_2 are considered to be the most important vasoactive factors.[9]

CPB itself can cause pulmonary hypertension from pulmonary arterial constriction, caused by increased vasoconstrictor mediators[10] or impaired vasodilatation.[11]

In our patient, acute right heart failure from an increase in right ventricular afterload developed after the second pulmonary embolectomy, despite removal of emboli from the truncus and the larger branches of the pulmonary artery. As only large emboli could be removed, remaining emboli in the small pulmonary arteries could have caused a persistent reduction in the cross-sectional area of the pulmonary arterial bed. Additional contributory factors leading to failure of the right heart in our patient could be active pulmonary vasoconstriction from release of vasoconstrictors from the clot and/or increased vasoconstrictors (or impaired vasodilatation) after CPB, as described above. Because active vasoconstriction (or impaired vasodilatation) contributes to the development of pulmonary hypertension, administration of vasodilators may be a therapeutic option. However, the use of i.v. vasodilators is limited by systemic vasodilatation and hypotension, so that an alternative in a patient with pre-existing severe hypotension is to use a selective pulmonary vasodilator, such as iNO or prostacyclin. iNO has been used successfully to treat various causes of pulmonary hypertension. In a case of pulmonary embolism, it reversed the flow through a patent foramen ovale by reducing pulmonary hypertension.[12] Capellier and co-workers described improvement in haemodynamic state and gas exchange in four patients with pulmonary embolism,[13] Platelet aggregation is enhanced in acute pulmonary embolism[14] causing release of vasoconstrictors which increases right ventricular afterload even more. In addition to vasodilatation, iNO inhibits platelet aggregation[15] as shown in an experimental study of acute pulmonary embolism.[16] By reducing release of vasoconstrictors and diminishing additional clot formation, this anti-aggregatory effect might be another beneficial effect of nitric oxide treatment for severe pulmonary embolism.

In our patient, stopping iNO caused immediate decreases in Pa_{O_2} and arterial pressure within the first 2 days after starting nitric oxide, even at the low concentration of 1 ppm. This suggests that the state of increased pulmonary vasoconstriction lasted for several hours.

We found that inhalation of nitric oxide was therapeutically valuable in acute severe pulmonary embolism. As suggested by Capellier and co-workers,[13] its selective pulmonary vasodilating effect may be useful for acute right heart failure with a marked decrease in cardiac output, pending the effects of thrombolysis, heparin therapy and/or surgery. It can give supportive therapy until conventional therapy leads to successful haemodynamic stabilization.

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