Clinical Reports

Treatment of pulmonary hypertension during surgery with nitric oxide and vasodilators

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Purpose: To describe the effects of the combination of several therapies on the pulmonary circulation and cardiac function in a patient with severe pulmonary hypertension.

Clinical features: We report the case of a female patient with chronic secondary pulmonary hypertension and cardiac failure who underwent right hemicolectomy under general anesthesia. Insertion of a pulmonary artery catheter before the operation revealed pulmonary artery pressure (PAP) of 55/24 mmHg which was lowered moderately by 40 parts per million (ppm) inhNO. During surgery, the patient presented an episode of atrial fibrillation with a slow, irregular heart rate of 45-50 min^{-1} and variable systemic pressure. A dipyridamole DPD (0.2 $mg{\cdot}kg^{-1}$) bolus stabilized systemic pressure and increased heart rate and cardiac output. However, PAP did not change. Nitroglycerine infusion was started at 10 $mg{\cdot}hr^{-1}$ shortly after the initiation of DPD. The patient responded favourably to combined inhNO, intravenous DPD and NTG therapy with a marked and sustained reduction of PAP and a systemic hemodynamic stability.

Conclusion: We conclude that: 1) in combination with inhNO, DPD does not augment the inhNO-induced decrease in PAP; 2) DPD improves the hemodynamic profile and elevates cardiac output; 3) therapeutic combination (inhaled NO, NTG, DPD) has a potent effect on pulmonary pressure in cardiac failure patients.

Objectif : Décrire les effets d'une combinaison de thérapies sur la circulation pulmonaire et la fonction cardiaque chez une patiente qui présente une sévère hypertension pulmonaire.

Éléments cliniques : Il s'agit d'une patiente, atteinte d'hypertension pulmonaire secondaire chronique et d'insuffisance cardiaque, qui a subi une hémicolectomie droite sous anesthésie générale. L'insertion préopératoire d'un cathéter dans l'artère pulmonaire a révélé une pression artérielle pulmonaire (PAP) de 55/24 mmHg, modérément abaissée par 40 parties par million (ppm) de NOinh. Pendant l'opération, la patiente a présenté un épisode de fibrillation auriculaire accompagné d'une fréquence cardiaque lente et irrégulière de 45-50 min^{-1} et une pression générale variable. Un bolus de dipyridamole (DPD 0,2 $mg{\cdot}kg^{-1}$) a permis de stabiliser la pression générale et d'augmenter la fréquence et le débit cardiaques. La PAP n'a toutefois pas changé. Une perfusion de nitroglycérine a été amorcée avec 10 $mg{\cdot}h^{-1}$ peu après le début du DPD. La patiente a bien réagi à la thérapie combinée de NOinh, de DPD intraveineux et de NTG, ce qui a entraîné une réduction marquée et soutenue de la PAP et une stabilité hémodynamique générale.

Conclusion : Nous en concluons que : 1) en combinaison avec le NOinh, le DPD n'accentue pas la baisse de PAP induite par le NOinh 2) le DPD améliore les caractéristiques hémodynamiques et augmente le débit cardiaque 3) la NTG stimule la vasodilatation pulmonaire induite par le NOinh chez les patients atteints d'insuffisance cardiaque.

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INHALED nitric oxide (inhNO) causes potent and selective pulmonary vasodilatation in diverse clinical conditions associated with pulmonary hypertension.[1] However, some patients with persistent pulmonary hypertension respond incompletely[2] or require prolonged therapy. Dipyridamole (DPD) is also used to treat pulmonary hypertension;[3,4] as it inhibits phosphodiesterase V and cyclic guanosine 3',5' monophosphate (cGMP) degradation. Concomitant therapy may be of some benefit in patients who respond inadequately to inhNO alone. Nitroglycerine (NTG) is another drug that is often given to control pulmonary hypertension, but systemic side-effects[5] limits its application. We report the clinical effect of DPD and NTG on the response to inhNO in a patient with chronic secondary pulmonary hypertension and cardiac failure who underwent sigmoid resection under general anesthesia.

Case report

A 48-yr-old woman with sigmoid adenocarcinoma was scheduled for a right hemicolectomy. She also suffered from severe secondary pulmonary hypertension and cardiac failure. When she was 30 yr old, she had a ventricular septal defect repaired to correct a major left-to-right shunt and marked pulmonary artery hypertension of 125/55 mmHg. Despite aggressive treatment with digitalis, a calcium channel blocker and an anticoagulant after surgical closure of the ventricular-septal defect, she developed atrial fibrillation with an intraventricular conduction defect and maintained high pulmonary pressure. In the past year, the patient complained of abdominal pain and intermittent constipation. She underwent double contrast radiography and colonoscopy which revealed a 3.5 cm diameter adenocarcinoma in the ascending colon. She was scheduled for laparotomy in a community hospital. One hour after the induction of anesthesia, she had an acute episode of pulmonary hypertension with severe hypoxemia (pulse oximetry: 56%) and systemic hypotension (80/40 mmHg). Anesthesia and surgery were stopped immediately and the patient was transferred to our university hospital as it has the technology to deliver inhNO.

On arrival, she was anticoagulated with heparin until the day of surgery. Electrocardiography revealed atrial fibrillation with a ventricular rate of 60-65 min^{-1}, complete right bundle-branch block and right ventricular hypertrophy. Chest X-ray showed moderate enlargement of the right heart with signs of pulmonary hypertension. Transesophageal echocardiography presented a 6 mm patent foramen ovale associated with considerable bidirectional shunt. The left ventricular ejection fraction was estimated to be 40% with severe biventricular diastolic dysfunction. The left atrium was dilated with moderate mitral regurgitation. The right heart was markedly dilated and hypokinetic. No arteriostenosis was observed by coronary angiography.

Surgical procedure

After receiving 2 mg ativan as premedication, anesthesia was induced with 68 μg sufentanil, 100 mg propofol and 80 mg rocuronium, and maintained by continuous infusion of 130 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol, 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ sufentanil and intermittent vecuronium for muscle relaxation. The trachea was intubated and the lungs ventilated with oxygen 100%, adjusted to keep partial pressures of arterial carbon dioxide ($PaCO_2$) in the low range (35 mmHg). Inhaled nitric oxide (40 parts per million ppm) was injected cyclically into an inspiratory line by NO injector, with NO and nitrogen dioxide (NO_2) concentration being monitored via an electrochemical NO and NO_2 analyser. An arterial cannula and pulmonary artery flotation catheter were inserted for continuous monitoring of systemic and pulmonary pressures.

In the perioperative period, pulmonary artery pressure (PAP) decreased from 55/24 to 41/18 mmHg following inhNO. During the surgical procedure, the patient presented rapid atrial fibrillation with a slow, irregular heart rate of 45-50·min^{-1} and fluctuation of systemic pressure from 80/30 to 145/70 mmHg. A DPD bolus (0.2 $mg \cdot kg^{-1}$) was injected to augment inhNO-induced pulmonary vasodilatation. Heart rate increased to its preoperative level, systemic pressure stabilised at 135/70 mmHg and cardiac output increased from 5.1 to 5.8 $L \cdot min^{-1}$. However, pul-

TABLE Cardiac indices before and during inhaled nitric oxide (inhNO), infusion of dipyridamole (DPD) and nitroglycerine (NTG)

	Before inhNO	*After inhNO*	*InhNO+DPD*	*InhNO+DPD+NTG*
Heart rate ($beat \cdot min^{-1}$)	70-100	45-50	70-100	55-60
Systemic AP (mmHg)	120/70	80/30-145/70	135/70	115/60
Pulmonary AP (mmHg)	55/24	41/18	41/18	26/7
Cardiac output ($litre \cdot min^{-1}$)	5,1	not recorded	5,8	5,8
SaO_2 (FIo_2 =100%)	98%	98%	99%	99%

monary pressure did not change. A NTG infusion was then started at a rate of 10 mg·hr^{-1}; this combined treatment effectively reduced PAP from 41/18 to 26/7 mmHg and systemic pressure from 135/70 to 115/60 mmHg (Table).

Surgery was completed successfully. The patient was then transferred to the intensive care unit (ICU) where inhNO was discontinued two days later. However, she experienced an episode of pulmonary hypertension and acute hypoxemia. Inhaled nitric oxide was restarted with immediate improvement of oxygenation and pulmonary pressure. Nitric oxide administration was continued for a week as she developed postoperative pneumonia. Her pulmonary status improved and she was weaned progressively from inhNO without further problem. The trachea was extubated on the eighth postoperative day. She was discharged on the 15th day post-surgery in good condition, and six-month follow-up was satisfactory.

Discussion

The management of patients with pulmonary hypertension and cardiac failure during surgery is complex. Minor stimuli, such as insertion of a peripheral cannula, endotracheal suction and surgical stress, can cause arrhythmias and increase pulmonary vascular resistance. General anesthesia can produce unpredictable reductions in pulmonary blood flow,[6] especially in the presence of chronic cardiac failure.

Recently, pulmonary endothelial damage was demonstrated to be an early histological finding in children with congenital heart disease and pulmonary hypertension.[7] It appears that longterm left-to-right shunt through a VSD results in a persistent increase of pulmonary flow, leading to pulmonary endothelial injury. In addition, the endothelial injury coupled with excessive release of locally active mediators produces vascular structural changes such as smooth muscle hypertrophy, intimal fibrosis, irregularity of elastic fibres, vessel wall infiltration with erythrocytes and inflammatory cells. This process is characterized by an inexorable cycle of endothelial dysfunction with decreased production of endothelium-derived vasodilators or an increase of vasoconstrictors.[8]

Inhaled nitric oxide is now regarded as a very potent pulmonary vasodilator that effectively reduces PAP and pulmonary vascular resistance by stimulating guanylate cyclase in pulmonary vascular smooth muscle to produce cGMP and cause vascular smooth muscle relaxation.[9] Cyclic guanosine 3',5' monophosphate production in vascular smooth muscle cells is countered by its degradation by cGMP-specific phosphodiesterases.[10] Recently, inhNO was confirmed to induce pulmonary vasodilatation in primary pulmonary hypertension,[11] in pulmonary hypertension resulting from congenital heart disease,[12] in the adult respiratory distress syndrome[13] and in patients after cardiac surgery.[14] However, some patients may show partial[2] or no clinical responses to inhNO therapy. The vasodilator effect of DPD is mediated by: 1) inhibiting cGMP degradation in vascular smooth muscle[9] via suppression of phosphodiesterase V to cause pulmonary vasodilation; 2) blockade of adenosine cellular reuptake, leading to adenosine accumulation in interstitial spaces around the arterioles, which results in dilation of the coronary, systemic and pulmonary vasculature.[15] Ovine models of pulmonary hypertension have shown that the effect of DPD on pulmonary vasodilation is not influenced by adenosine receptor blockade.[16] This observation has established that cGMP-specific phosphodiesterase inhibition is the main mechanism by which DPDs reduce pulmonary vasodilation.

Fullerton *et al.*[9] reported DPD-induced augmentation of pulmonary vasodilatation in 10 postoperative cardiac patients treated with inhNO. On the opposite, except for two subjects with pulmonary hypertension resulting from longstanding left atrial hypertension, Ziegler *et al.*[3] found no increase of pulmonary vasodilatation with DPD in eight patients given inhNO.

In the present case, DPD did not alter PAP during inhNO treatment but improved the hemodynamic profile by stabilizing systemic pressure, increasing heart rate and cardiac output. It is not surprising that the vasodilating effect of DPD is not specific to the pulmonary circulation, since cGMP modulation of vascular tone is located in both pulmonary and systemic vessels.[3] It is unclear whether the action of DPD on the pulmonary circulation could be augmented through an increase of initial doses in patients with chronic heart failure. Kinsella *et al.*[4] have described their successful experience with combined treatment of a neonate after extracorporeal membrane oxygenation; their DPD dose was 0.6 mg·kg^{-1}. Ivy *et al.*[1] who reported the hemodynamic effects of DPD (0.6 mg·kg^{-1}) and inhNO (20 ppm) in 13 pediatric patients with pulmonary hypertension, found that DPD augmented the NO-induced fall in the pulmonary vascular resistance index in 50% of these subjects. Thus, a positive clinical response to DPD in terms of the potentiated effect of inhNO may depend on its dose and on underlying cardiac function.

Nitroglycerine is a NO donor that has the same mechanism of action as inhNO via the cGMP pathway, but its effect is produced only after intracellular NO release.[17] Intravenous NTG alone has been shown to reduce pulmonary pressure and pulmonary vascular

resistance effectively while increasing cardiac indices in patients with severe pulmonary hypertension.[6] The addition of NTG (10 mg·kg^{-1}) to our patient's ongoing inhNO and intravenous DPD regimen effectively decreased PAP from 41/18 to 26/7 mmHg with recovery of preoperative systemic pressure. This result suggested that NTG not only potentiated the inhNO-induced pulmonary vasodilation, but also modulated left ventricular afterload since it releases NO and activates guanylyl cyclase in both the pulmonary and systemic circulations.[1 8] Why was the addition of a small NTG dose more effective in reducing pulmonary hypertension than the combination of inhNO and DPD? Several explanations can be offered: (1) The inhNO dose was not high enough to stimulate cGMP production maximally, (2) NTG dilated some peripheral pulmonary vessels where inhNO was not present. Furthermore, NTG had more pronounced beneficial effects on the heart than inhNO. It decreased left ventricular afterload and improved ventricular relaxation as well as diastolic distensibility[19] by increasing cGMP in the systemic circulation and myocardium.

From these findings, we speculate that DPD may enhance the response to inhNO therapy in some patients with chronic pulmonary hypertension and cardiac failure, and this effect is dependent on a suitable dose. We conclude that to control chronic pulmonary hypertension effectively in patients with cardiac failure, an improvement of hemodynamic profile is required. This appears to be achieved more readily by the use of combined therapy with inhNO, intravenous DPD and NTG during surgery.

References

1 *Ivy DD, Ziegler JW, Kinsella JP, Wiggins JW, Abman SH.* Hemodynamic effects of dipyridamole and inhaled nitric oxide in pediatric patients with pulmonary hypertension. Chest 1998; 114: 17S.

2 *Fullerton DA, McIntyre RC Jr.* Inhaled nitric oxide: therapeutic applications in cardiothoracic surgery. Ann Thorac Surg 1996; 61: 1856–64.

3 *Ziegler JW, Ivy DD, Wiggins JW, Kinsella JP, Clarke WR, Abman SH.* Effects of dipyridamole and inhaled nitric oxide in pediatric patients with pulmonary hypertension. Am J Respir Crit Care Med 1998; 158: 1388–95.

4 *Kinsella JP, Torielli F, Ziegler JW, Ivy DD, Abman SH.* Dipyridamole augmentation of response to nitric oxide (Letter). Lancet 1995; 346: 647–8.

5 *Van Obbergh LJ, Charbonneau M, Blaise G* Combination of inhaled nitric oxide with i.v nitroglycerin or with a prostacyclin analogue in the treatment of experimental pulmonary hypertension. Br J Anaesth 1996; 77: 227–31.

6 *O'Hare R, McLoughlin C, Milligan K, McNamee D, Sidhu H.* Anaesthesia for Caesarean section in the presence of severe primary pulmonary hypertension. Br J Anaesth 1998; 81: 790–2.

7 *Haworth SG* Pulmonary vascular remodelling in neonatal pulmonary hypertension. Chest 1988; 93: 133S–8S.

8 *Gaine SP, Rubin LJ.* Primary pulmonary hypertension. Lancet 1998; 352: 719–25.

9 *Fullerton DA, Jaggers J, Piedalue F, Grover FL, McIntyre RC Jr.* Effective control of refractory pulmonary hypertension after cardiac operations. J Thorac Cardiovasc Surg 1997; 113: 363–8.

10 *Thomas MK, Francis SH, Corbin JD.* Characterization of a purified bovine lung cGMP-binding cGMP phosphodiesterase. J Biol Chem 1990; 265: 14964–70.

11 *Hoehn T, Krause M, Hentschel R.* High-frequency ventilation augments the effect of inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Eur Respir J 1998; 11: 234–8.

12 *Berner M, Beghetti M, Ricou B, Rouge JC, Prêtre R, Friedli B.* Relief of severe pulmonary hypertension after closure of a large ventricular septal defect using low dose inhaled nitric oxide. Intensive Care Med 1993; 19: 75–7.

13 *Troncy E, Collet J-P, Shapiro S, et al.* Inhaled nitric oxide in acute respiratory distress syndrome. A pilot randomized controlled study. Am J Respir Crit Care Med 1998; 157: 1483–8.

14 *Fullerton DA, Jones SD, Jaggers J, Piedalue F, Grover FL, McIntyre RC Jr.* Effective control of pulmonary vascular resistance with inhaled nitric oxide after cardiac operation. J Thorac Cardiovasc Surg 1996; 111: 753–63.

15 *Cortigiani L, Baroni M, Picano E, et al.* Acute hemodynamic effects of endogenous adenosine in patients with chronic heart failure. Am Heart J 1998; 136: 37–42.

16 *Ziegler JW, Ivy DD, Fox JJ, Kinsella JP, Clarke WR, Abman SH.* Dipyridamole, a cGMP phosphodiesterase inhibitor, causes pulmonary vasodilation in the ovine fetus. Am J Physiol 1995; 269: H473–9.

17 *Salvemini D, Pistelli A, Vane J.* Conversion of glyceryl trinitrate to nitric oxide in tolerant and non-tolerant smooth muscle and endothelial cells. Br J Pharmacol 1993; 108: 162–9.

18 *Troncy E, Jacob E, Peres da Silva E, et al.* Comparison of the effect of inhaled nitric oxide and intravenous nitroglycerine on hypoxia-induced pulmonary hypertension in pig. Eur J Anaesthesiol 1996; 13: 521–9.

19 *Paulus WJ, Vantrimpont PJ, Shan AM.* Acute effects of nitric oxide on left ventricular relaxation and diastolic distensibility in humans. Assessment by bicoronary sodium nitroprusside infusion. Circulation 1994; 89: 2070–8.