Inhaled Nitric Oxide for Acute Right-Ventricular Dysfunction After Extrapleural Pneumonectomy

Evans R Fernández-Pérez MD, Mark T Keegan MRCPI, and Barry A Harrison FANZCA FRACP

Increased pulmonary vascular pressure and decreased right-ventricular performance may occur following pneumonectomy. Inhaled nitric oxide decreases right-ventricular afterload and improves cardiac index by selectively decreasing pulmonary vascular resistance without causing systemic hypotension. We report the use of inhaled nitric oxide in a patient with acute right-ventricular dysfunction after extrapleural pneumonectomy. *Key words: pulmonary vascular pressure, ventricle, pneumonectomy, inhaled nitric oxide, afterload, cardiac index, pulmonary vascular resistance, hypotension.* [Respir Care 2006;51(10):1172–1176.

Introduction

Malignant pleural mesothelioma is associated with a high mortality rate.[1] Extrapleural pneumonectomy, which, in addition to pneumonectomy, involves extensive resection of lymph nodes, pericardium, diaphragm, and chest wall, offers potential for cure. Hemodynamic complications associated with pneumonectomy are still a major problem.[2–4] The literature has consistently shown acute right-ventricular dysfunction to be an important risk factor for early postoperative morbidity.[5–7] Postoperative acute right-ventricular dysfunction can be minimized by prompt diagnosis and optimizing right-ventricular work by selectively decreasing pulmonary vascular resistance. This report discusses the pathophysiology and the role of inhaled nitric oxide (INO) in the treatment of acute right-ventricular dysfunction after extrapleural pneumonectomy.

Case Summary

A 41-year-old woman presented with a malignant pleural mesothelioma. Five months of gemcitabine and cisplatin chemotherapy led to tumor shrinkage. She had a history of non-Hodgkin's lymphoma, treated 20 years previously with chemotherapy and radiotherapy to the chest. A stent had been placed in the left subclavian vein, because of an occlusion secondary to extrinsic compression by mesothelioma. Transthoracic echocardiogram showed normal left and right ventricular function, with normal right-ventricular and pulmonary-artery pressures (Fig. 1A). Pulmonary function testing showed only a mild restrictive defect. Imaging techniques showed the tumor to be resectable, and the patient underwent a left thoracotomy. Because of pleural, pericardial, and chest-wall involvement, an extrapleural pneumonectomy was performed. The surgery lasted 6 h, and the estimated blood loss was 700 mL, which was replaced with a combination of crystalloid and colloid. Despite intraoperative episodes of hypotension related to hypovolemia and great-vessel compression, the patient was extubated following completion of the procedure.

Her postoperative electrocardiogram showed post-pericardiectomy changes, without evidence of myocardial ischemia. She was transferred to a monitored intermediate-care area. Anticoagulation with warfarin was begun on the third postoperative day, because of the presence of the left subclavian stent. On postoperative day 9 the patient developed progressive dyspnea. A chest radiograph showed a large left hydrothorax. A left chest tube was inserted, which drained 1,700 mL of serosanguinous fluid. Despite initial relief, 4 h later the patient became increasingly short of breath and subsequently became unresponsive. Cardiopulmonary resuscitation was started for pulseless electrical activity arrest. The patient was intubated and ventilated, and responded to chest compressions, intravenous fluids, and pressor medications,

Evans R Fernández-Pérez MD is affiliated with the Division of Pulmonary and Critical Care Medicine; Mark T Keegan MRCPI is affiliated with the Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota. Barry A Harrison FANZCA FRACP is affiliated with the Department of Anesthesiology, Mayo Clinic College of Medicine, Jacksonville, Florida.

Correspondence: Mark T Keegan MRCPI, Department of Anesthesiology, Mayo Clinic College of Medicine, Charlton 1145, 200 First Street SW, Rochester MN 55095. E-mail: keegan.mark@mayo.edu.

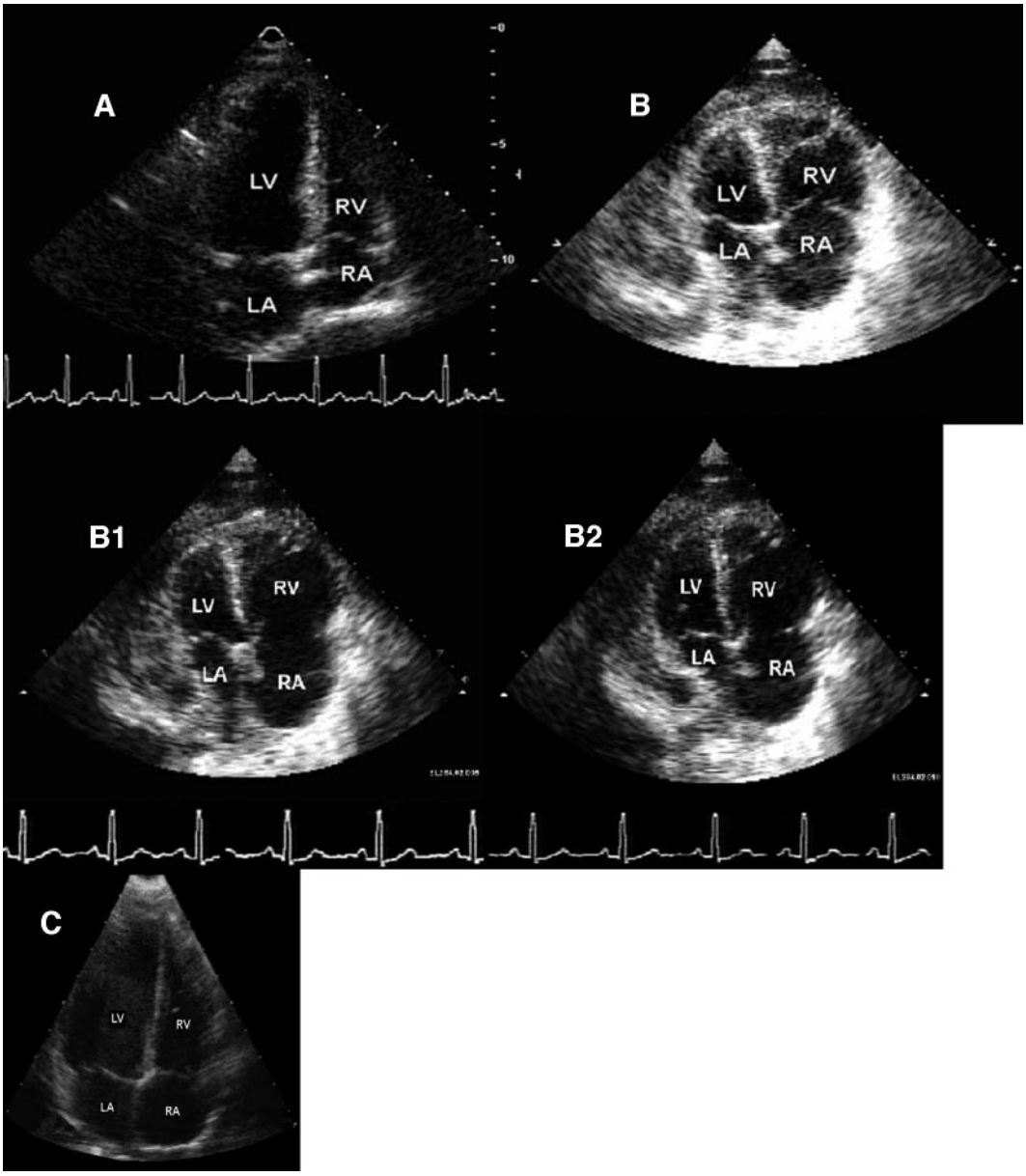

Fig. 1. Four-chamber view from a two-dimensional transthoracic echocardiogram. A: Normal right-heart chamber dimensions (prior to surgery). B: Marked enlargement of the right atrium and ventricle, with alteration of the right-ventricle shape, which is also hypokinetic. B1: End-systole image. B2: End-diastole image. C: Echocardiogram after discharge. RA = right atrium. LA = left atrium. RV = right ventricle. LV = left ventricle.

including epinephrine. After transfer to the intensive care unit, arterial and pulmonary-artery catheters were inserted. The pulmonary-artery catheter showed high pulmonary vascular resistance and low cardiac index. An epinephrine infusion was used to maintain blood pressure as volume was being administered. Four units of packed red blood cells were administered for a hemoglobin concentration of 6 mg/dL, and 4 units of fresh frozen plasma, for an international normalized ratio of 2.6. A chest radiograph showed a clear right lung and small left-sided pleural effusion (Fig. 2). Myocardial enzymes and electrocardiogram did not indicate myocardial infarction.

An emergency transthoracic echocardiogram showed the right heart to be massively enlarged, with marked reduction in right-ventricular systolic function (Fig. 1B). The entire right-ventricular wall was akinetic. The right atrium was also enlarged. The tricuspid signal was so diffuse that right-ventricular pressure could not be measured. There was no left-ventricular or other valvular abnormality, and, in fact, the left ventricle was hyperdynamic. There was no evidence of a patent foramen ovale. Because of the right-ventricular dysfunction, we started INO (at 20 ppm) to decrease the right-ventricular afterload. Pulmonary vascular resistance decreased

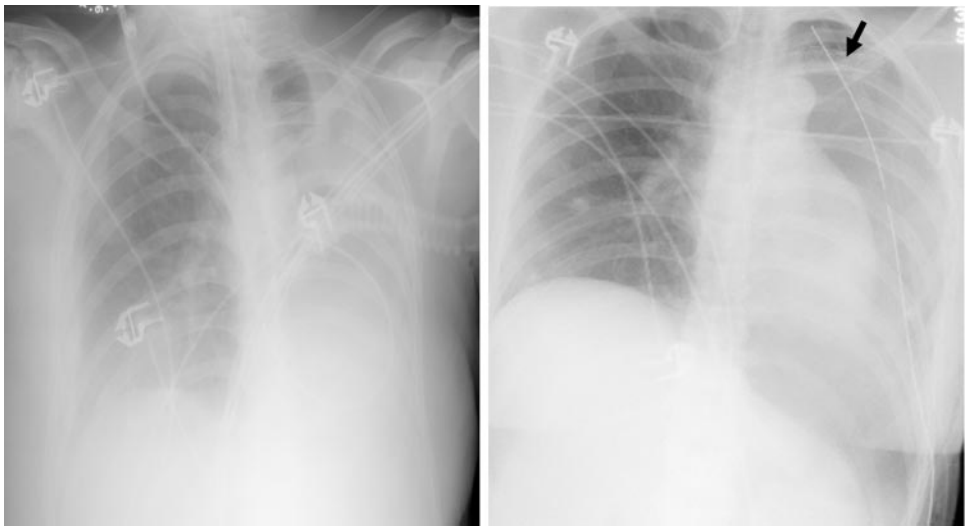

Fig. 2. Chest radiograph showing left-lung opacification (pneumonectomy), before (left) and after (right) left-chest-tube placement. The arrow points to a left-subclavian-vein stent.

Table 1. Changes in Hemodynamic Data Before and After Administration of INO

	Immediately before INO	After 20 min of INO	After 12 h of INO	After 24 h of INO	After 32 h of INO
F_{IO_2}	0.7	0.7	0.6	0.5	0.4
P_{aO_2} (mm Hg)	190	250	268	205	180
HR (beats/min)	106	105	109	106	106
CVP (mm Hg)	10	11	7	8	10
Mean PAP (mm Hg)	24	24	20	19	23
MAP (mm Hg)	83	74	70	77	80
Cardiac index (L/min/m^2)	0.94	1.55	2.64	2.97	2.27
SVI (mL/m^2)	7	13	24.2	28	22
SVRI (dyn · s · cm^{-5} · m^{-2})	3,283	3,256	1,907	1,855	2,360
PVRI (dyn · s · cm^{-5} · m^{-2})	593	258	121	108	70
INO (ppm)	0	20	20	20	10
Epinephrine (μg/kg/min)	0.24	0.14	0.08	0.05	0
Dopamine (μg/kg/min)	0	2.1	2.1	2.1	2
Dobutamine (μg/kg/min)	0	2.1	8	8	5

F_{IO_2} = fraction of inspired oxygen
P_{aO_2} = partial pressure of oxygen
HR = heart rate
CVP = central venous pressure
PAP = pulmonary artery pressure
MAP = mean arterial blood pressure
SVI = stroke volume index
SVRI = systemic vascular resistance index
PVRI = pulmonary vascular resistance index
INO = inhaled nitric oxide

and cardiac index increased with INO. Intravenous dobutamine was also initiated to increase right-ventricular function. The epinephrine infusion that had been started on arrival to the intensive care unit was continued, for inotropic and pressor effects.

Table 1 shows the initial response to INO and the progressive improvement in the patient's hemodynamics. The patient was weaned from the epinephrine infusion over the next 24 h, and the INO was discontinued approximately 60 h after initiation. Other pressor medications were weaned over the course of the next few days. A thoracic duct leak, pericardial and pleural effusions, and respiratory failure ultimately requiring tracheostomy further complicated the patient's course, but she eventually left the hospital approximately 6 weeks after the surgery. A transthoracic echocardiogram performed 3 weeks after her cardiac arrest showed normal right-ventricular size and function (see Fig. 1C).

Discussion

Acute right-ventricular dysfunction results from right-ventricle infarction[8] and/or increase in right-ventricular af-

terload.[9] Compared to the left heart, the right heart is at increased risk of failure in response to an increase in afterload.[10] The right ventricle is anatomically adapted for the generation of a sustained low-pressure perfusion, which is possible because of the low resistance and high compliance of the pulmonary vascular bed.[11] Increased right-ventricular afterload prolongs the isovolumetric contraction phase and ejection time and augments wall-tension and myocardial oxygen consumption.[11,12] Acute right-ventricular dilation, with a resultant shift of the intraventricular septum, causing compression of the left ventricle, results in a decrease in left-ventricular end-diastolic volume. Eventually, left-ventricular failure will result because of ventricular interdependence.[13,14]

The post-pneumonectomy state plays an important role in the etiology of right-ventricular failure when a patient is hypovolemic. After a pneumonectomy, the right heart is dysfunctional. This dysfunction, thought to be due to increased afterload, worsens in the first 3 postoperative days.[15] In an animal model of hemorrhagic shock, the post-pneumonectomy state led to higher mortality than in animals without pulmonary resection. The higher mortality was due to right-ventricular dysfunction and increased pulmonary vascular resistance.[16] In our patient, hypovolemia (caused by the removal of serosanguinous fluid from the left chest) coupled with mediastinal shift that may have kinked the great vessels, causing right-ventricular dysfunction, led to acute right-heart failure and cardiac arrest.

Treatment of acute right-heart syndrome consists of optimizing preload in an attempt to maximize forward flow out of the right ventricle,[17] to support the function of the right ventricle and decrease right-ventricular afterload. In the operating room, percutaneous cardiopulmonary bypass[18] has been used to provide mechanical support to the right ventricle. Additionally, inotropic agents, such as dobutamine[19,20] and milrinone,[21] may be useful in the support of the failing right heart. In an animal model of acute right-heart failure and hypotension, norepinephrine increased right-ventricular blood flow and contractility while decreasing pulmonary vascular resistance.[22,23]

INO is a selective pulmonary vasodilator.[24] The pulmonary vascular relaxant action of this compound results from binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine monophosphate,[25,26] which reduces intracellular calcium concentration in vascular smooth muscle and leads to vasodilation. INO decreases pulmonary vascular resistance, offloading and improving the right-ventricular stroke work.

INO has been approved by the United States Food and Drug Administration for the treatment of hypoxic respiratory failure with associated pulmonary hypertension of the term and near-term newborn.[27] Although there is no compelling data to justify advocating INO for other indications, a European expert panel identified a variety of medical conditions in which INO is a reasonable rescue treatment in patients with severe acute pulmonary hypertension and/or severe refractory arterial hypoxemia.[28] In fact, INO has been effective in "off-label" treatment of right-ventricular dysfunction.[29–34] In the case of a patient with idiopathic pulmonary fibrosis who developed severe right-ventricular failure following a perioperative cardiac arrest, INO improved oxygenation and hemodynamic variables, and the patient survived.[35] When administered to hemodynamically stable patients with acute respiratory distress syndrome, INO reduced right-ventricular end-diastolic volume and increased right-ventricular ejection fraction and mixed venous oxygen saturation.[36,37]

Bhorade et al reported the use of INO in 26 patients in the intensive care unit with acute right-heart failure with subsequent increase in cardiac output and stroke volume related to decreases in pulmonary vascular pressure and resistance.[38]

In a retrospective review, a group of 17 post-cardiac-surgery patients with pulmonary hypertension treated with INO showed a significant decrease in pulmonary-artery pressure and improvement in right-ventricular work.[39] Similarly, INO has proven useful in the management of patients with chronic obstructive pulmonary disease and pulmonary hypertension,[40] pulmonary embolism,[41] post-pneumonectomy pulmonary edema,[42] and post-traumatic pneumonectomy.[43]

In conclusion, the influence of a pneumonectomy on the development of acute right-ventricular failure, especially in the setting of hypovolemia, is important and challenging. As an addition to conventional medical and surgical support of the right ventricle, the use of INO to reduce right-ventricular afterload is based on sound scientific principles and might be helpful in the management of patients with acute right-ventricular failure after pneumonectomy.

REFERENCES

1. Ribak J, Selikoff IJ. Survival of asbestos insulation workers with mesothelioma. Br J Ind Med 1992;49(10):732–735.
2. Harpole DH, Liptay MJ, DeCamp MM Jr, Mentzer SJ, Swanson SJ, Sugarbaker DJ. Prospective analysis of pneumonectomy: risk factors for major morbidity and cardiac dysrhythmias. Ann Thorac Surg 1996;61(3):977–982.
3. Sugarbaker DJ, Jaklitsch MT, Bueno R, Richards W, Lukanich J, Mentzer SJ, et al. Prevention, early detection, and management of complications after 328 consecutive extrapleural pneumonectomies. J Thorac Cardiovasc Surg 2004;128(1):138–146.
4. Tanita T, Hoshikawa Y, Tabata T, Noda M, Handa M, Kubo H, et al. Functional evaluations for pulmonary resection for lung cancer in octogenarians: investigation from postoperative complications. Jpn J Thorac Cardiovasc Surg 1999;47(6):253–261.
5. Alvarez JM, Panda RK, Newman MA, Slinger P, Deslauriers J, Ferguson M. Postpneumonectomy pulmonary edema. J Cardiothorac Vasc Anesth 2003;17(3):388–395.
6. Kowalewski J, Brocki M, Dryjanski T, Kapron K, Barcikowski S. Right ventricular morphology and function after pulmonary resection. Eur J Cardiothorac Surg 1999;15(4):444–448.

7. Reed CE, Spinale FG, Crawford FA Jr. Effect of pulmonary resection on right ventricular function. Ann Thorac Surg 1992;53(4):578–582.
8. Kinch JW, Ryan TJ. Right ventricular infarction. N Engl J Med 1994;330(17):1211–1217.
9. Romand JA, Donald FA, Suter PM. Acute right ventricular failure, pathophysiology and treatment. Monaldi Arch Chest Dis 1995;50(2): 129–133.
10. Hurford WE, Zapol WM. The right ventricle and critical illness: a review of anatomy, physiology, and clinical evaluation of its function. Intensive Care Med 1988;14 Suppl 2:448–457.
11. Mebazaa A, Karpati P, Renaud E, Algotsson L. Acute right ventricular failure–from pathophysiology to new treatments. Intensive Care Med 2004;30(2):185–196.
12. Brooks H, Kirk ES, Vokonas PS, Urschel CW, Sonnenblick EH. Performance of the right ventricle under stress: relation to right coronary flow. J Clin Invest 1971;50(10):2176–2183.
13. Brunet F, Dhainaut JF, Devaux JY, Huyghebaert MF, Villemant D, Monsallier JF. Right ventricular performance in patients with acute respiratory failure. Intensive Care Med 1988;14 Suppl 2:474–477.
14. Sibbald WJ, Driedger AA. Right ventricular function in acute disease states: pathophysiologic considerations. Crit Care Med 1983; 11(5):339–345.
15. Okada M, Okada M, Ishii N, Yamashita C, Sugimoto T, Okada K, et al. Right ventricular ejection fraction in the preoperative risk evaluation of candidates for pulmonary resection. J Thorac Cardiovasc Surg 1996;112(2):364–370.
16. Cryer HG, Mavroudis C, Yu J, Roberts AM, Cue JI, Richardson JD, Polk HC Jr. Shock, transfusion, and pneumonectomy: death is due to right heart failure and increased pulmonary vascular resistance. Ann Surg 1990;212(2):197–201.
17. Goldstein JA, Barzilai B, Rosamond TL, Eisenberg PR, Jaffe AS. Determinants of hemodynamic compromise with severe right ventricular infarction. Circulation 1990;82(2):359–368.
18. Yokota K, Yasukawa T, Kimura M, Fujita Y, Sari A. Right heart failure in the setting of hemorrhagic shock after pneumonectomy: successful treatment with percutaneous cardiopulmonary bypass. Anesth Analg 1997;85(6):1268–1271.
19. Ferrario M, Poli A, Previtali M, Lanzarini L, Fetiveau R, Diotallevi P, et al. Hemodynamics of volume loading compared with dobutamine in severe right ventricular infarction. Am J Cardiol 1994; 74(4):329–333.
20. Meyer RJ, Kern KB, Berg RA, Hilwig RW, Ewy GA. Post-resuscitation right ventricular dysfunction: delineation and treatment with dobutamine. Resuscitation 2002;55(2):187–191.
21. Haraldsson Å, Kieler-Jensen N, Ricksten S-E. The additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in postcardiac surgical patients with pulmonary hypertension. Anesth Analg 2001;93(6):1439–1445.
22. Vlahakes GJ, Turley K, Hoffman JI. The pathophysiology of failure in acute right ventricular hypertension: hemodynamic and biochemical correlations. Circulation 1981;63(1):87–95.
23. Salisbury PF. Coronary artery pressure and strength of right ventricular contraction. Circ Res 1955;3(6):633–638.
24. Ichinose F, Roberts JD Jr, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. Circulation 2004;109(25):3106–3111.
25. Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991;43(2):109–142.
26. Gaston B, Drazen JM, Loscalzo J, Stamler JS. The biology of nitrogen oxides in the airways. Am J Respir Crit Care Med 1994;149(2 Pt 1):538–551.
27. American Academy of Pediatrics. Committee on Fetus and Newborn. Use of inhaled nitric oxide. Pediatrics 2000;106(2 Pt 1):344–345.
28. Germann P, Braschi A, Della Rocca G, Dinh-Xuan AT, Falke K, Frostell C, et al. Inhaled nitric oxide therapy in adults: European expert recommendations. Intensive Care Med 2005;31(8):1029–1041.
29. Kadosaki M, Kawamura T, Oyama K, Nara N, Wei J, Mori N. Usefulness of nitric oxide treatment for pulmonary hypertensive infants during cardiac anesthesia. Anesthesiology 2002;96(4):835–840.
30. Argenziano M, Choudhri AF, Moazami N, Rose EA, Smith CR, Levin HR, et al. Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. Ann Thorac Surg 1998;65(2):340–345.
31. Goldman AP, Delius RE, Deanfield JE, Macrae DJ. Nitric oxide is superior to prostacyclin for pulmonary hypertension after cardiac operations. Ann Thorac Surg 1995;60(2):300–305;discussion 306.
32. Solina AR, Ginsberg SH, Papp D, Pantin EJ, Denny J, Ghandivel I, Krause TJ. Response to nitric oxide during adult cardiac surgery. J Invest Surg 2002;15(1):5–14.
33. Inglessis I, Shin JT, Lepore JJ, Palacios IF, Zapol WM, Bloch KD, Semigran MJ. Hemodynamic effects of inhaled nitric oxide in right ventricular myocardial infarction and cardiogenic shock. J Am Coll Cardiol 2004;44(4):793–798.
34. Mathisen DJ, Kuo EY, Hahn C, Moncure AC, Wain JC, Grillo HC, et al. Inhaled nitric oxide for adult respiratory distress syndrome after pulmonary resection. Ann Thorac Surg 1998;66(6):1894–1902.
35. King R, Esmail M, Mahon S, Dingley J, Dwyer S. Use of nitric oxide for decompensated right ventricular failure and circulatory shock after cardiac arrest. Br J Anaesth 2000;85(3):628–631.
36. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 1993;328(6):399–405.
37. Fierobe L, Brunet F, Dhainaut JF, Monchi M, Belghith M, Mira JP, et al. Effect of inhaled nitric oxide on right ventricular function in adult respiratory distress syndrome. Am J Respir Crit Care Med 1995;151(5):1414–1419.
38. Bhorade S, Christenson J, O'Connor M, Lavoie A, Pohlman A, Hall JB. Response to inhaled nitric oxide in patients with acute right heart syndrome. Am J Respir Crit Care Med 1999;159(2):571–579.
39. Maxey TS, Smith CD, Kern JA, Tribble CG, Jones DR, Kron IL, Crosby IK. Beneficial effects of inhaled nitric oxide in adult cardiac surgical patients. Ann Thorac Surg 2002;73(2):529–532; discussion 532–533.
40. Adnot S, Kouyoumdjian C, Defouilloy C, Andrivet P, Sediame S, Herigault R, Fratacci MD. Hemodynamic and gas exchange responses to infusion of acetylcholine and inhalation of nitric oxide in patients with chronic obstructive lung disease and pulmonary hypertension. Am Rev Respir Dis 1993;148(2):310–316.
41. Imanaka H, Miyano H, Takeuchi M, Kumon K, Ando M. Effects of nitric oxide inhalation after pulmonary thromboendarterectomy for chronic pulmonary thromboembolism. Chest 2000;118(1):39–46.
42. Rabkin DG, Sladen RN, DeMango A, Steinglass KM, Goldstein DJ. Nitric oxide for the treatment of postpneumonectomy pulmonary edema. Ann Thorac Surg 2001;72(1):272–274.
43. Nurozler F, Argenziano M, Ginsburg ME. Nitric oxide usage after posttraumatic pneumonectomy. Ann Thorac Surg 2001;71(1):364–366.