CARDIOPULMONARY BYPASS, MYOCARDIAL MANAGEMENT, AND SUPPORT TECHNIQUES

EFFECTIVE CONTROL OF REFRACTORY PULMONARY HYPERTENSION AFTER CARDIAC OPERATIONS

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Objectives: Inhaled nitric oxide is a promising therapy to control pulmonary hypertension. However, pulmonary hypertension caused by valvular heart disease is often refractory to inhaled nitric oxide. The objective of this study was to determine whether the combination of inhaled nitric oxide plus dipyridamole will cause a response in patients with pulmonary hypertension undergoing cardiac operations who had not responded to inhaled nitric oxide alone. **Methods:** Responses in 10 patients (62 ± 7 years) with pulmonary hypertension caused by aortic or mitral valvular disease (mean pulmonary artery pressure, ≥ 30 mm Hg) were studied in the operating room after valve replacement. The effect of inhaled nitric oxide alone (40 ppm) on pulmonary vascular resistance, mean pulmonary artery pressure, cardiac output, and mean arterial pressure was determined. Inhaled nitric oxide administration was then stopped and patients were given dipyridamole (0.2 mg/kg intravenously); the effect of inhaled nitric oxide plus dipyridamole was then examined. **Results:** Dipyridamole effected a response in patients who had not responded to nitric oxide. Pulmonary vascular resistance and mean pulmonary artery pressure were significantly reduced and cardiac output was increased without change in mean arterial pressure. **Conclusions:** Patients with refractory pulmonary hypertension in whom inhaled nitric oxide alone fails to cause a response may respond to combined therapy of inhaled nitric oxide plus dipyridamole. This therapy may be particularly valuable in patients with dysfunction of the right side of the heart as a result of pulmonary hypertension because of its effective lowering of right ventricular afterload. (J Thorac Cardiovasc Surg 1997;113:363-70)

Increased pulmonary vascular resistance (PVR) may greatly complicate the perioperative treatment of patients undergoing cardiac operations. Because PVR is the primary clinical determinant of

right ventricular afterload, increased PVR may result in right ventricular afterload mismatch, compromising cardiac output. Pharmacologic agents that are currently used as pulmonary vasodilators typically produce vasodilation of both the systemic and pulmonary circulations. Such nonselective vasodilation may be hazardous in patients with increased PVR¹; significant hypotension may result if the degree of systemic vasodilation exceeds that of the pulmonary vasodilation.

Inhaled nitric oxide (NO) is a promising therapy to control pulmonary hypertension.² It has been shown to produce a significant reduction in both pulmonary arterial pressure and PVR without reducing systemic arterial pressure or systemic vascular resistance in patients after cardiac operation. It may therefore be clinically valuable as a "selective" pulmonary vasodilator in patients undergoing car-

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diac operation.³ Mechanistically, inhaled NO lowers PVR by stimulating guanylate cyclase in pulmonary vascular smooth muscle to produce guanosine 3',5'-cyclic guanosine monophosphate (cGMP), which in turn produces vascular smooth muscle relaxation by mechanisms that are yet unclear.⁴ The net concentration of cGMP within pulmonary vascular smooth muscle is determined by the balance of its production by guanylate cyclase and degradation by phosphodiesterase.

In patients undergoing cardiac operations who have pulmonary hypertension, the hypertension frequently is a result of valvular heart disease. Valvular heart disease produces remodeling of the pulmonary vascular bed, which in turn may reduce the effectiveness of NO in lowering PVR.² In patients in whom pulmonary hypertension does not respond to inhaled NO, we hypothesized that the effectiveness of inhaled NO could be increased with the use of a two-pronged approach: (1) stimulating cGMP production with inhaled NO and (2) preventing the breakdown of cGMP by inhibiting the enzyme responsible for its degradation, phosphodiesterase. The purpose of this study was to determine whether the combination of stimulating cGMP production (inhaled NO) plus preventing cGMP breakdown by phosphodiesterase inhibition (dipyridamole) will cause a response in patients with pulmonary hypertension undergoing cardiac operation in whom inhaled NO alone had failed to cause a response.

The results of this study demonstrate that this two-pronged approach may be an effective strategy to control pulmonary hypertension in patients undergoing cardiac operations.

Methods

This protocol was approved by the Human Subjects Review Committee of the University of Colorado Health Sciences Center and the Research and Development Committee, Human Subjects Subcommittee of the Denver Veterans Affairs Medical Center. Informed consent was obtained from each participant.

Administration of inhaled NO. Inhaled NO was supplied in tanks of 2200 ppm (Scott Medical Products, Plumsteadville, Pa.) and was administered into the inspiratory arm of the anesthesia breathing circuit. The concentration of inhaled NO was continuously monitored at a location just proximal to the endotracheal tube by chemoluminescence (chemoluminescence monitor model 42H, Thermo Environmental Instruments Inc., Franklin, Mass.). The exhalation limb of the breathing circuit was likewise continuously monitored by chemoluminescence for NO₂ and NO_x (toxic higher oxides of NO).

Protocol for data collection. Ten patients (62 ± 7 years) with pulmonary hypertension caused by aortic or

mitral valvular disease (mean pulmonary artery pressure ≥ 30 mm Hg) underwent study in the operating room after valve replacement. Patients received preoperative medication consisting of morphine sulfate 0.1 mg/kg and scopolamine 0.4 mg intramuscularly 1 hour before arrival in the operating room. Ongoing drug therapy for concomitant medical problems was continued as deemed appropriate by the attending anesthesiologist.

Monitoring in each patient was done with a five-lead electrocardiogram, a radial arterial line, and a pulmonary artery thermodilution oximetric catheter (Abbot Laboratories, Chicago, Ill.) introduced through the right internal jugular vein. To accurately measure pulmonary venous outflow pressure (left atrial pressure) for determination of PVR, a left atrial pressure monitoring catheter was introduced into the left atrium via the right superior pulmonary vein after the patient had been weaned from cardiopulmonary bypass. The left atrial pressure catheter was subsequently removed after completion of data collection and before chest closure. The anesthetic technique consisted of a high-dose narcotic (fentanyl) and relaxant (vecuronium) technique supplemented with intravenous midazolam. Inhalational anesthetic agents were administered only during cardiopulmonary bypass.

Data were collected in the operating room beginning approximately 20 minutes after completion of cardiopulmonary bypass but before chest closure. After weaning from bypass and after protamine administration, all patients were in hemodynamically stable condition and demonstrated normal coagulation. No patients required cardiac pacing, antiarrhythmic therapy, or inotropic or vasoactive drug administration. No inhalational anesthetics were administered after the time of cessation of cardiopulmonary bypass or during the period of data collection.

The protocol for collection of data proceeded as follows: tidal volume was set at approximately 10 ml/kg and respiratory rate adjusted to establish an arterial carbon dioxide tension (Pco₂) of approximately 40 mm Hg and an arterial pH of approximately 7.40.⁵ To avoid changes in pulmonary hemodynamics caused by changes in ventilatory patterns, ventilator settings were subsequently not altered during the study period. Fraction of inspired oxygen was maintained at a mean of 0.97 (range 0.94 to 0.99) and no patient had the application of positive end-expiratory pressure at any point during the study period. Arterial oxygen tension (Po₂) was therefore maintained at greater than 250 mm Hg throughout the study period to avoid any influence of hypoxemia on pulmonary vascular tone. Arterial and mixed venous blood gas samples were obtained at each point of data collection. The hemodynamic variables measured and recorded were heart rate, systemic mean arterial blood pressure, mean pulmonary arterial pressure, central venous pressure, left atrial pressure, and thermodilution cardiac output (mean of three values). These allowed mathematical derivation of pulmonary and systemic vascular resistance, cardiac index, right ventricular stroke work index, and transpulmonary gradient.

After placement of the left atrial pressure line and with the patient in a hemodynamic steady-state condition, baseline hemodynamic variables were determined. Then

40 ppm of NO was added to the ventilatory circuit. After 10 minutes of administration of inhaled NO, 40 ppm, hemodynamic variables were determined. The inhaled NO administration was then stopped, and hemodynamic variables determined. Dipyridamole (Boehringer, Richfield, Conn.) (0.2 mg/kg intravenously) was then slowly administered. After measurement of hemodynamic variables, 40 ppm of NO was again added to the ventilatory circuit. After 10 minutes, hemodynamic variables were measured and inhaled NO administration was then stopped. After 10 minutes, hemodynamic data after administration of inhaled NO were collected. The left atrial pressure line was then removed under direct vision and its insertion site in the right superior pulmonary vein was determined to be hemostatic. Methemoglobin level was determined before and after data collection.

Statistical analysis. Statistical analyses were done with a MacIntosh Quadra 650 computer (Apple Computer, Inc., Cupertino, Calif.) and StatView software (Brain Power, Inc., Calabasas, Calif.). Data are presented as mean plus or minus 1 standard error of the mean. Statistical evaluation used standard analysis of variance in conjunction with the Student-Newman-Keuls multiple comparisons procedure. At *p* value of less than 0.05 was accepted as statistically significant.

Results

The study population comprised 10 patients, and subject demographics are listed in Table I. All patients had a history of cigarette smoking; however, none demonstrated clinical or radiographic evidence of significant chronic pulmonary disease.

Table II lists the arterial and mixed venous blood gas values along with the hemodynamic variables determined at each point of data collection. There were no changes in values of arterial pH, arterial PO_2 , or arterial PCO_2 throughout the study period. Likewise there were no significant changes in heart rate, central venous pressure, or left atrial pressure throughout the period of data collection. Methemoglobin concentration was 2.1 ± 0.1 before NO administration and was unchanged after inhaled NO administration.

No hemodynamic effects were noted with either inhaled NO alone or dipyridamole alone (Table II). However, the combination of inhaled NO and dipyridamole produced a significant reduction in transpulmonary gradient (Table II) and mean pulmonary artery pressure without a change in mean systemic arterial pressure (Fig. 1). This reduction in pulmonary arterial pressure resulted in a significant increase in cardiac output (Table II) and a significant reduction in PVR (Fig. 2). The calculated systemic vascular resistance also was lower because cardiac output increased without a change in mean systemic arterial pressure (Table II). However, be-

Table I. Patient demographics

No. of patients	10
Age (yr)	62 ± 7
Aortic crossclamp time (min)	96 ± 13
Cardiopulmonary bypass time (min)	129 ± 16
Tidal volume (cc/kg)	10
Respiratory rate (breaths/min)	11

Values are mean plus or minus the standard error of the mean.

cause the ratio of pulmonary-to-systemic vascular resistance fell, it would appear that the vasodilating action of inhaled NO plus dipyridamole is preferential to the pulmonary circulation (Table II).

Discussion

The results of this study demonstrate that a two-pronged approach of stimulating cGMP production with inhaled NO and preventing the breakdown of cGMP by inhibiting the enzyme responsible for its degradation, phosphodiesterase, effects a response in patients with pulmonary hypertension undergoing cardiac operation in whom inhaled NO alone had failed to cause a response.

As in the present study, most adult patients undergoing cardiac operation who have pulmonary hypertension have this pulmonary hypertension as a result of mitral or aortic valvular disease. At least three pathophysiologic mechanisms contribute to the pulmonary hypertension seen in long-standing aortic or mitral valvular disease: (1) increased left atrial pressure transmitted on a retrograde basis into the arterial circulation, (2) vascular remodeling of the pulmonary vasculature in response to chronic obstruction to pulmonary venous drainage ("fixed component"), and (3) pulmonary arterial vasoconstriction ("reactive component").⁶ Once the elevated left atrial pressure is relieved by valve replacement, the increased PVR does not immediately return to the normal range; several days to weeks may be required. The pulmonary vasoconstrictive effects of cardiopulmonary bypass are well recognized, and patients with chronic pulmonary vascular structural changes may have an exaggerated response to vasoconstricting agonists. The results of the present study suggest that the "reactive" component of the increased PVR in such patients may be modulated with a combination therapy that increases cGMP production (inhaled NO) and prevents cGMP breakdown (dipyridamole).

Patients undergoing cardiac operation provided a unique opportunity to examine the influence of inhaled NO on PVR. A homogeneous group of

Table II. Hemodynamic data

	<i>Before</i>	<i>NO alone</i>	<i>Dipyridamole alone</i>	<i>NO plus dipyridamole</i>	<i>After</i>
Temperature (°C)	36.2 ± 0.5	36.2 ± 0.5	36.2 ± 0.5	36.0 ± 0.5	36.0 ± 0.5
Hemoglobin (gm/dl)	8.7 ± 0.5	8.7 ± 0.5	8.4 ± 0.5	8.5 ± 0.5	8.3 ± 0.5
Arterial pH	7.44 ± 0.03	7.41 ± 0.03	7.43 ± 0.03	7.46 ± 0.03	7.42 ± 0.03
Arterial PO ₂ (mm Hg)	276 ± 37	265 ± 29	297 ± 35	278 ± 21	264 ± 33
Arterial PCO ₂ (mm Hg)	35 ± 3	38 ± 3	32 ± 3	33 ± 3	33 ± 3
Venous pH	7.33 ± 0.01	7.32 ± 0.01	7.31 ± 0.01	7.37 ± 0.01	7.33 ± 0.01
Venous PO ₂ (mm Hg)	37 ± 2	36 ± 2	36 ± 2	39 ± 2	35 ± 2
Venous PCO ₂ (mm Hg)	45 ± 4	46 ± 4	46 ± 4	44 ± 4	45 ± 4
Heart rate (min ⁻¹)	96 ± 7	94 ± 7	98 ± 6	95 ± 4	95 ± 9
CVP (mm Hg)	9 ± 2	10 ± 3	10 ± 3	10 ± 2	9 ± 1
LAP (mm Hg)	11 ± 2	11 ± 2	10 ± 2	10 ± 2	9 ± 2
MPAP (mm Hg)	39 ± 3	40 ± 4	39 ± 3	29 ± 3*	38 ± 3
TPG (mm Hg)	28 ± 3	29 ± 3	29 ± 3	19 ± 3*	27 ± 3
Cardiac output (L/min)	3.6 ± 0.4	3.5 ± 0.4	3.6 ± 0.5	5.4 ± 0.4*	3.7 ± 0.4
MAP (mm Hg)	72 ± 4	71 ± 4	70 ± 5	70 ± 5	71 ± 5
SVR (dynes/sec/cm ⁵)	1400 ± 40	1395 ± 50	1333 ± 40	890 ± 40*	1340 ± 40
PVR/SVR ratio	0.44 ± 0.04	0.48 ± 0.06	0.47 ± 0.06	0.3 ± 0.04*	0.44 ± 0.04

Values are mean plus or minus the standard error of the mean. *Venous*, Mixed venous; *CVP*, central venous pressure; *LAP*, left atrial pressure; *MAP*, mean arterial pressure; *MPAP*, mean pulmonary artery pressure; *TPG*, transpulmonary gradient; *SVR*, systemic vascular resistance.

**p* = 0.04 versus "Before" and "After" values.

patients could be studied: patients undergoing valve replacement. Control of many variables that affect PVR was available in this group of patients. Surgical access allowed accurate measurement of pulmonary venous outflow pressure (left atrial pressure) for calculation of PVR.⁷ The patient who was anesthetized and receiving mechanical ventilation allowed for maintenance of a constant rate of ventilation and tidal volume to avoid mechanical alterations of PVR.⁸ Furthermore, arterial PO₂ could be well controlled and changes in acid-base status avoided.^{6,9}

In our protocol, a standard cardiac anesthetic technique was used. Intravenous anesthetic agents were administered only before cardiopulmonary bypass and inhalational anesthetic agents were not administered after cessation of cardiopulmonary bypass until after the period of data collection. Therefore any influence of anesthesia on PVR was assumed to have been held constant during the period of data collection. Although the anesthetic technique may or may not influence the response of the pulmonary vasculature to inhaled NO, the influence was held constant during the period of data collection. In addition, to optimize clinical relevance patients were examined early after operation.

The present study was designed to examine the acute effects of inhaled NO administration. Therefore one may not draw conclusions regarding the effects of prolonged exposure. NO is a potentially toxic gas: inhalation of greater than 1000 ppm has

been shown to cause acute lung injury in laboratory animals.¹⁰ In human beings, NO is believed to cause silo filler's disease.¹¹ Therefore prolonged administration of inhaled NO requires chemoluminescence monitoring to accurately measure the concentration of inhaled NO and to measure the exhaled concentration of its toxic metabolite, nitrogen dioxide (NO₂). Blood samples are also required to measure the level of methemoglobin concentration.² During the brief administration of inhaled NO in the present study, there were no changes in level of NO₂ or methemoglobin. Despite these potential toxicities, prolonged administration of inhaled NO to patients with adult respiratory distress syndrome in concentrations up to 80 ppm and for durations up to 53 days have not been found to produce lung toxicity.¹² Nonetheless, a trial of inhaled NO has been reported to precipitate pulmonary edema in a patient with stable heart failure.¹³ Of particular concern in patients undergoing cardiac operations is the possibility that inhaled NO may depress myocardial contractility. Although no changes in cardiac output were found with inhaled NO in the present study, further investigation is required to determine the influence of inhaled NO on cardiac function.

Pulmonary vascular tone is assumed to be closely related to intracellular levels of pulmonary vascular smooth muscle cGMP. Because phosphodiesterase activity determines the catabolic rate of cGMP, other investigators have targeted phosphodiesterase inhibition as a therapeutic strategy by which to lower

Fig. 1. The combination of inhaled NO plus dipyridamole produced a significant reduction in mean pulmonary arterial pressure without change in mean systemic arterial pressure. Values are mean plus or minus standard error of the mean. * $p = 0.03$ versus "Before" and "After" values.

pulmonary vascular tone.^{14, 15} In the present study, dipyridamole was used to inhibit phosphodiesterase activity; no hemodynamic effects were observed after administration of dipyridamole alone. In the present study, only the combination of increased cGMP production (inhaled NO) and inhibition of cGMP breakdown (dipyridamole) produced a marked reduction in PVR and pulmonary arterial pressure. The results of the present study may reflect the fact that patients were studied very early after cardiopulmonary bypass. However, we have previously reported that patients undergoing aorto-coronary bypass did respond to inhaled NO immediately after cardiopulmonary bypass,³ which suggests a significance in the response to inhaled NO among patients with pulmonary hypertension caused by valvular heart disease.

In mammalian tissues, at least seven isoforms of phosphodiesterase have been identified. Phosphodiesterase type V is specific for the breakdown of cGMP.¹⁶ Although dipyridamole is a clinically available, potent inhibitor of phosphodiesterase type V, its actions are somewhat nonspecific. For example, dipyridamole inhibits isoforms of phosphodiesterase other than type V. The possibility therefore exists

Fig. 2. The combination of inhaled NO plus dipyridamole produced a significant reduction in PVR and an associated significant increase in cardiac output. Values are mean plus or minus standard error of the mean. * $p = 0.02$ versus "Before" and "After" values.

that some of the hemodynamic changes noted in the present study were attributable to inhibition of isoforms of phosphodiesterase involved in adenosine 3',5'-cyclic adenosine monophosphate metabolism; 3',5'-cyclic adenosine monophosphate-mediated pathways are also important in the control of pulmonary vascular smooth muscle tone.^{17, 18} In addition, dipyridamole prevents adenosine reuptake by endothelial and red blood cells,¹⁹ thereby potentiating the local actions of adenosine. Because adenosine has been shown to produce selective pulmonary vasodilation in patients undergoing cardiac operation,^{20, 21} one may not exclude some contribution of adenosine to the hemodynamic effects noted

in the present study. Nonetheless, the results of the present study demonstrated hemodynamic effects only when the combination of inhaled NO and dipyridamole was used.

In summary, the combination of dipyridamole and inhaled NO was effective in producing pulmonary vasorelaxation in patients undergoing cardiac operations in whom inhaled NO alone was ineffective in lowering pulmonary arterial pressure and PVR. We conclude that such a two-pronged strategy of stimulating cGMP production (inhaled NO) and preventing its breakdown (dipyridamole) may offer effective control of refractory pulmonary hypertension in patients undergoing cardiac operations.

REFERENCES

1. Packer M, Greenberg B, Massie B, Dash H. Deleterious effects of hydralazine in patients with pulmonary hypertension. *N Engl J Med* 1982;306:1326-31.
2. Fullerton DA, McIntyre RC Jr. Inhaled nitric oxide: therapeutic applications in cardiothoracic surgery. *Ann Thorac Surg* 1996;61:1865-4.
3. Fullerton DA, Jones SD, Jaggars J, Piedalue F, Grover FL, McIntyre RC Jr. Effective control of pulmonary vascular resistance with inhaled nitric oxide following cardiac operation. *J Thorac Cardiovasc Surg* 1996;111:753-63.
4. Rapport RM, Draznin MB, Murad R. Sodium nitroprusside-induced protein phosphorylation in intact rat aorta is mimicked by 8-bromo cyclic GMP. *Proc Natl Acad Sci U S A* 1982;79:6470-4.
5. Fullerton DA, Kirson LE, St. Cyr JA, Kinnard T, Whitman GJR. Influence of hydrogen ion concentration versus carbon dioxide tension on pulmonary vascular resistance after cardiac operation. *J Thorac Cardiovasc Surg* 1993;106:528-36.
6. Grossman W, Alpert JS, Braunwald E. Pulmonary hypertension. In: Braunwald E, ed. *Heart disease: a textbook of cardiovascular medicine*. 2nd ed. Philadelphia: WB Saunders, 1984:830-1.
7. Morris AH, Chapman RH, Gardner RN. Frequency of technical problems encountered in the measurement of pulmonary artery wedge pressure. *Crit Care Med* 1984;12:164-70.
8. Fishman AP. Pulmonary circulation. In: AP Fishman, ed. *Handbook of physiology: the respiratory system*. Vol. 1. Bethesda, Maryland: American Physiologic Society, 1985:93-165.
9. Fullerton DA, Kirson LE, St. Cyr JA, Albert JD, Whitman GJR. The influence of respiratory acid-base status on adult pulmonary vascular resistance before and after cardiopulmonary bypass. *Chest* 1993;93:1091-5.
10. Stavert DM, Lehnert BE. Nitric oxide and nitrogen dioxide as inducers of acute pulmonary injury when inhaled at relatively high concentrations for brief periods. *Inhal Toxicol* 1990;2:53-67.
11. Zapol WM, Hurford WE. Inhaled nitric oxide in the adult respiratory distress syndrome and other lung diseases. *New Horiz* 1993;1:638-50.
12. Rossaint R, Falke K, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993;328:399-405.
13. Bocchi EA, Bacal F, Auler JOC, de Carvalho MJ, Bellotti G, Pileggi F. Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. *Am J Cardiol* 1994;74:70-4.
14. 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.
15. Cohen AH, Hanson K, Morris K, et al. Inhibition of cyclic 3',5'-guanosine monophosphate-specific phosphodiesterase selectively vasodilates the pulmonary circulation in chronically hypoxic rats. *J Clin Invest* 1996;97:172-9.
16. Schoeffer P, Lugnier C, Demesy-Waeldele F, Stodet JC. Role of cyclic AMP and cyclic GMP phosphodiesterases in the control of cyclic nucleotide levels and smooth muscle tone in rat isolated aorta. *Biochem Pharmacol* 1987;36:3965-72.
17. Fullerton DA, Hahn AR, Banerjee A, Harken AH. Pulmonary vascular smooth muscle relaxation by cGMP- versus cAMP-mediated mechanisms. *J Surg Res* 1994;57:259-63.
18. Fullerton DA, Agrafojo J, McIntyre RC Jr. Pulmonary vascular smooth muscle relaxation by cAMP-mediated mechanisms. *J Surg Res* 1996;61:444-8.
19. Roos H, Pflieger K. Kinetics of adenosine uptake by erythrocytes and the influence of dipyridamole. *Mol Pharmacol* 1972;8:417-25.
20. Fullerton DA, Jones SD, Grover FL, McIntyre RC Jr. Adenosine effectively controls pulmonary hypertension following cardiac surgery. *Ann Thorac Surg* 1996;61:1118-24.
21. Fullerton DA, Kirson LE, Jones SD, McIntyre RC Jr. Adenosine is a selective pulmonary vasodilator in cardiac surgical patients. *Chest* 1996;109:41-6.

Discussion

Dr. R. Scott Mitchell (*Stanford, Calif.*). Dr. Fullerton has presented the results of a beautiful study demonstrating a relatively selective effect on secondary pulmonary hypertension with augmentation of the supply of cGMP, a very potent smooth muscle relaxant, by administration of inhaled NO and simultaneous inhibition of its degradation. This group has been able to produce a relatively selective effect on the pulmonary vasculature. Although there were some lesser effects on the systemic vascular resistance, these were more than compensated for by increased cardiac output. The investigation is a straightforward yet elegant one with each patient serving as his or her own control. One caveat is that this is not really severe pulmonary hypertension with mean pulmonary artery pressures averaging only about 38 or 39 mm Hg and the pulmonary hypertension was termed refractory only because it failed to respond initially to inhaled NO. That leads to my first question. Do the authors think that this failure to respond to inhaled NO alone had any relationship to the altitude in Denver and the known pulmonary hypertensive effect of chronic hypoxia?

Dr. Fullerton. That is a good question, and I do not know the answer. Among patients who are ambulatory and breathing room air in Denver, the normal mean pulmonary arterial blood pressure has been studied in the catheterization laboratory at the University of Colorado and it is 22 mm Hg, a little bit higher than it is at sea level.

The patients who undergo study in a protocol such as this are, of course, receiving mechanical ventilation and the inspired oxygen fraction among these patients is substantially higher than it is on room air. In most of the patients the inspired oxygen fraction approaches 90%. So, acknowledging that the barometric pressure in this sort of thing is different, I suspect that altitude probably plays little role. It may, however, play a role in the condition of the pulmonary circulation in these patients before they undergo operation. It is clear, particularly in the pediatric population, that patients who live at elevations even higher than Denver, between 6000 and 9000 feet, will have severe pulmonary hypertension that is particularly difficult to control in the perioperative period. It may be variable. This problem is one that is difficult to study, however.

Dr. Mitchell. We have not used inhaled NO as the first line of therapy for pulmonary hypertension, and I would like to hear how these patients fared later in the operative course as regards conventional therapy, such as infused nitroglycerin or sodium nitroprusside.

Dr. Fullerton. To be eligible for the study these patients could not require inotropic support or require other vasoactive agents, so this is a group of patients with significant pulmonary hypertension, yet in whom it seems to be compensated for from a hemodynamic standpoint. We do not believe it would be appropriate to study other patients. These patients all left the hospital with pulmonary arterial pressures that were approximately a mean of 40 mm Hg, which is about twice the normal value for the local control group.

Dr. Mitchell. Last, although such patients were obviously not included in this study, do you have any information for us as to patients in whom weaning from cardiopulmonary bypass failed, who have pulmonary hypertension and right ventricular failure? Have you tried this combination of dipyridamole and NO for those patients?

Dr. Fullerton. We have, and I think it is fair to say the results are anecdotal. In that sort of situation there are so many variables that have an impact on the data that I believe it is difficult to conclude whether the treatment works under those circumstances. I will say that we have a similar protocol in which we use this combination in patients with adult respiratory distress syndrome, and the results are quite different. I think that the patients in whom weaning from cardiopulmonary bypass fails are somewhat similar to those in the adult respiratory distress syndrome group in the sense that protracted cardiopulmonary bypass induces significant lung injury. Something about the injured lung causes its response to be different, and in those situations we think our combined therapy has worked a couple of times. Why it has or has not is hard to know.

Dr. Edward D. Verrier (Seattle, Wash.). I have two brief questions. The more common scenario, at least in our practice, is not the one in which a patient with a mean pressure of 40 mm Hg can be weaned from cardiopulmonary bypass without receiving some inotropes and the combination of a phosphodiesterase inhibitor as an inotrope. Could you comment once again as to whether there is going to be some efficacy in that?

The second, related question is that inhaled NO to date is not widely available. It is still on protocol. When we

need it, we have to go to the neonatal intensive care unit and beg the neonatologist to borrow some. What is the status of inhaled NO for general use in its relationship to the Food and Drug Administration?

Dr. Fullerton. In regard to your first question, faced with the situation that you described, and if you desire to use phosphodiesterase inhibition, it probably makes more sense to use an agent like milrinone. In that situation, the augmented contractility that would be offered is probably needed, and it may or may not be synergistic in that situation, but my advice would be not to use dipyridamole but instead to use milrinone. I would caution you, however, that milrinone has been studied by our group in the laboratory, but other groups have demonstrated in human beings that the actions of milrinone seem to be more pronounced in the systemic circulation. All of us who have used milrinone have more than once seen an example of that: as soon as the drug administration starts there is a significant drop in blood pressure because the systemic circulation opens up more than the pulmonary circulation, which in that setting may be the rate-limiting step, and flow and cardiac output are unable to compensate and maintain blood pressure. Nonetheless, that would be my recommendation.

I can tell you that our results in patients with adult respiratory distress syndrome with use of this sort of a protocol to modulate PVR have suggested that it will not work in patients with adult respiratory distress syndrome, so there is something different about this group of patients as opposed to the adult respiratory distress syndrome group.

NO is considered an experimental agent by the Food and Drug Administration. The distribution varies by geography, but there are probably 100 centers across the country that have it available to them. To use it you must have an investigational new drug number from the Food and Drug Administration, which can be obtained. Call the Food and Drug Administration and ask how you get one. The real up-front cost associated with using it is about \$40,000. You must have a chemiluminescence monitor, so a lot of places that have called us inquiring about how to prepare to use NO have been held up by this capital investment. If and when it will be used liberally is unknown.

Dr. Joseph Bavaria (Philadelphia, Pa.). We have been using NO quite a bit recently and are initiating prospective studies. I do not think there is any way our institution could be blinded to its use because the NO canisters are so huge.

I would like to ask the authors about the application of this in lung transplantation. Recently, we have been trying to operate on our patients with primary pulmonary hypertension without using bypass if possible, and we have been successful with use of a combination of prostaglandin E₁ and inhaled NO. We have not used the authors' two-pronged strategy, which I find intriguing. I would like your comments about the use of this drug in standard lung transplantation, as well as in something more experimental such as I just mentioned.

Dr. Fullerton. Parallel to the study that was presented by Dr. Bavaria at this meeting, several authors have presented data to suggest that donation of the NO moiety during the period of reperfusion may well attenuate the lung injury that is inherent in lung transplantation. We

have not used that strategy clinically, and we have not needed to. When a lung transplantation goes sour it goes sour very quickly and very notably. I believe that we have used NO in one or two of our lung transplant recipients, and in one of them it was clearly life saving. That was a patient who had severe lung injury, and most of the time we do not use that.

We have been routinely using cardiopulmonary bypass for the pulmonary hypertensive group, so I cannot comment on your other question.

Dr. Gregory Misbach (*Redlands, Calif.*). There may be some who already use dipyridamole in the preoperative period for its antiplatelet effect. Can you give us any comparison of oral and intravenous dosages and time courses such that by changing the preoperative dosage there might be some benefit in the ways that you have described?

Dr. Fullerton. That is an interesting strategy. I would caution you about the use of the oral dose and comparing the oral dose with the intravenous dose. Early on we learned that if this drug is administered too rapidly, it will cause hypotension. The hypotension is transient, but it is something that should be avoided. In our protocol we spend approximately 12 to 14 minutes infusing the dose of dipyridamole. Wondering whether, if a little was good, a lot would be better, on occasion we have given up to 0.6 mg/kg and we have found that this routinely produces hypotension. In patients who are receiving dipyridamole preoperatively I

really do not know how that might relate. It is an interesting thought, but I really cannot comment on that.

Dr. Richard G. Fosburg (*De Mar, Calif.*). I would like to bring up a historical note for some of the membership. Dr. Fullerton was the 1990 Samson resident prize winner and serves as an example for the candidates for the 1996 resident prize. He is also a credible component of our program.

Appendix

Hemodynamic formulas used are as follows:

1. PVR ($\text{dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$) =

$$\frac{\text{Mean pulmonary artery pressure} - \text{left atrial pressure}}{\text{Cardiac output}} \times 80$$

2. Systemic vascular resistance ($\text{dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$) =

$$\frac{\text{Mean arterial pressure} - \text{Central venous pressure}}{\text{Cardiac output}} \times 80$$

3. Transpulmonary gradient (mm Hg) =

$$(\text{Mean pulmonary arterial pressure}) - (\text{Left atrial pressure})$$