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Anesthesiology
2000; 92:1827-9
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Sildenafil Can Increase the Response to Inhaled Nitric Oxide

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INHALED nitric oxide (NO) reduces pulmonary artery pressure and increases arterial oxygen tension (P_{aO_2}) in many patients with pulmonary hypertension^{1,2} and acute respiratory failure.³ Not all patients, however, manifest an equally effective response,⁴ and investigators have sought to enhance the physiologic effects of inhaled NO.⁵ One possible strategy is to increase the availability of cyclic guanosine monophosphate (cGMP), an intracellular messenger of NO, by blocking its degradation by cGMP-specific phosphodiesterase (PDE-5). Dipyridamole, a PDE-5 inhibitor, has been used in combination with inhaled NO to decrease pulmonary artery pressure in patients with pulmonary hypertension of various etiologies.^{6,7} However, the results of these small series have been inconsistent, possibly because of the multiple pharmacologic actions of this drug.⁷

Sildenafil is a newer PDE-5 inhibitor used in the management of erectile dysfunction⁸ that acts by increasing the local availability of endogenous NO. Sildenafil has a higher PDE-5 selectivity than dipyridamole and a predict-

able gastrointestinal absorption,⁹ which make it an attractive complement to inhaled NO for the management of acute pulmonary hypertension in critically ill patients. Rather than simply adding the effect of a second vasodilator, sildenafil may enhance the selective pulmonary vasodilator effect of inhaled NO by making more messenger cGMP available locally. For example, the administration of sildenafil was recently reported to attenuate the acute pulmonary hypertension associated with the withdrawal of inhaled NO in two infants treated for pulmonary hypertension.¹⁰

We report the case of a patient with severe hypoxemia caused by pulmonary hypertension and venous blood shunting through a patent foramen ovale (PFO) that was reversed using inhaled NO in association with systemic sildenafil administration.

Case Report

A 52-yr-old woman with severe interstitial pulmonary fibrosis, Crohn disease, and previous pulmonary thromboembolism developed acute respiratory failure while being evaluated for a living related-donor lung transplant. The likely cause of her exacerbation was infectious. Chest radiograms showed her chronic diffuse pattern of pulmonary infiltrates and a new parenchymal consolidation at the right lung base. Gram stains of bronchial secretions showed abundant neutrophils without predominant organisms. She was administered broad-spectrum antibiotics, her trachea was intubated, and mechanical ventilation was begun. A norepinephrine infusion (1-3 $\mu\text{g}/\text{min}$) was used to treat hypotension. Pulmonary artery (PA) catheterization revealed a mean PA pressure of 50 mmHg, a cardiac output of 4.8 l/min with a stroke volume of 47 ml, a pulmonary artery occlusion pressure of 14 mmHg, and a central venous pressure of 9 mmHg. An echocardiogram showed normal left ventricular function, mild right ventricular (RV) dilation, mild tricuspid regurgitation, and a PFO. The latter was not present in a study performed a year earlier, when the systolic RV pressure had been estimated at 41 mmHg. To confirm the presence of a hemodynamically significant shunt, an indocyanine dilution study was performed, which showed a pattern of early dye recirculation compatible with a right-to-left intracardiac shunt (fig. 1).¹¹ NO inhalation was considered in an attempt to decrease the PA pressure and reverse blood flow through the PFO, unload the RV, improve P_{aO_2} , and stabilize the patient sufficiently to perform an urgent lung transplant. Based on our ongoing experience with the use of PDE-5 inhibitors in investigational protocols of inhaled NO in patients with the acute respiratory distress syndrome (Food and Drug Administration IND # 54,973), we elected to administer inhaled NO in conjunction with oral sildenafil. Written informed consent was obtained.

This article is featured in "This Month in Anesthesiology."
Please see this issue of ANESTHESIOLOGY, page 5A.

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Received from the Departments of Anesthesia and Critical Care, Respiratory Care Services, and the Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. Submitted for publication October 8, 1999. Accepted for publication January 18, 1999. Supported in part by a Clinical Research Starter Grant from the Foundation for Anesthesia Education and Research/Ohmeda Inc., American Society of Anesthesiologists, Rochester, Minnesota (to Dr. Bigatello).

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Key words: Acute pulmonary hypertension; hypoxemia; patent foramen ovale; phosphodiesterase inhibitors; pulmonary vasodilators.

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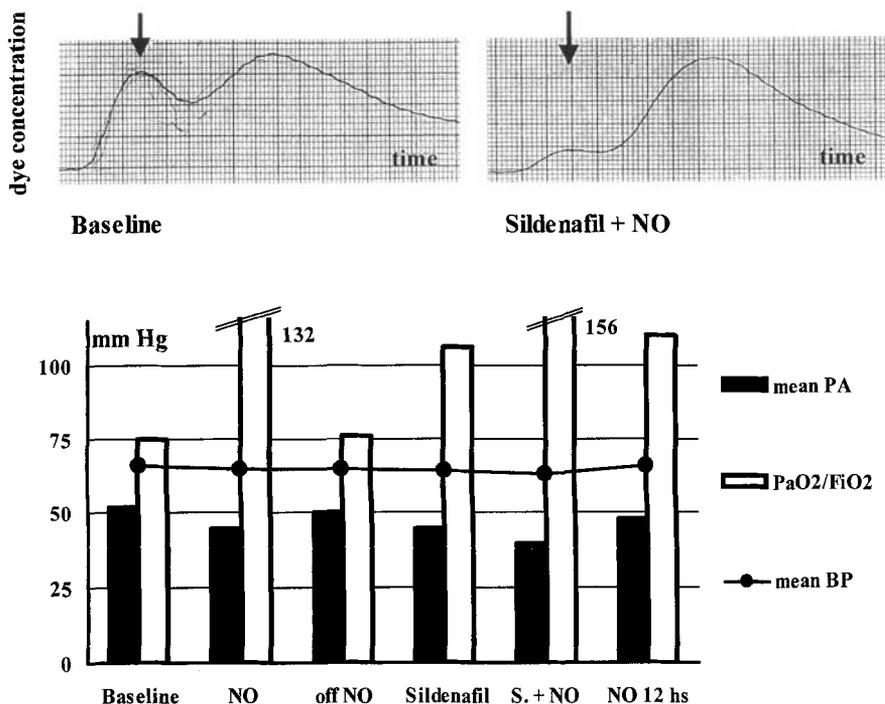


Fig. 1. Hemodynamic and respiratory effects of inhaled 5-ppm NO and 25-mg oral sildenafil. The two top panels are indocyanine green dilution curves documenting a reduction of intracardiac shunt following the administration of NO and sildenafil. The arrows indicate the early dye recirculation peak caused by a right-to-left shunt. BP = systemic blood pressure; NO = nitric oxide; PA = pulmonary artery.

The effects of inhaled NO and sildenafil on the pulmonary circulation and gas exchange are illustrated in figure 1. Inhaled NO (5 ppm) rapidly decreased mean PA pressure from 52 to 44 mmHg, without affecting systemic blood pressure. After discontinuation of NO, the PA pressure returned to baseline values. Sildenafil, 25 mg, was then administered *via* the nasogastric tube and decreased PA pressure to a similar extent as inhaled NO alone. Inhaled NO, resumed 30 min after sildenafil administration, further decreased mean PA pressure to 40 mmHg. A repeated indocyanine green dilution study showed a marked reduction of the early dye recirculation, indicating a substantial resolution of the right-to-left intracardiac shunt (fig. 1). The Pa_{O₂} increased by 76% with NO alone, by 40% with sildenafil alone, and by 112% with sildenafil + NO. The calculated venous admixture decreased from 51% at baseline to 37% with NO, to 44% with sildenafil alone, and to 34% with sildenafil + NO. Plasma sildenafil concentration measured by high-performance liquid chromatography was undetectable at baseline, 5.5 ng/ml at 15 min, and 7.7 ng/ml at 30 min after administration of the drug. Inhaled NO was continued, and a second dose of sildenafil was administered 12 h later. The patient, however, continued to deteriorate because of worsening lung infection and progression of her parenchymal infiltrates. Ten days later, she was removed from the transplant list and allowed to die.

Discussion

Despite the ultimately dismal outcome, this case has important implications. Although the favorable effect of inhaled NO in patients with pulmonary hypertension and intracardiac shunts is known,¹² the impact on patient outcome is uncertain. As with other clinical indications for NO treatment, it may be desirable to potentiate and prolong the

physiologic effects of NO inhalation. In this case, we were able to temporarily enhance the action of NO with the administration of a PDE-5 inhibitor. Sildenafil was rapidly absorbed by the gastrointestinal tract of a critically ill patient. The initial hemodynamic effect of 25 mg sildenafil (50–25% of the dose recommended for the management of erectile dysfunction) occurred within 15 min of administration. Plasma concentrations were as low as 10% of those reported after 50 mg to 100 mg of sildenafil administration to stable patients.⁹ This finding complements the observation of Atz and Wessel,¹⁰ who, without measuring sildenafil levels, demonstrated an increased plasma concentration of cGMP after the administration of a sildenafil dose equivalent to approximately 50% of the recommended adult dose.

The vasodilator effect of a small dose of sildenafil showed a mild selectivity for the pulmonary circulation because it decreased pulmonary artery pressure without affecting systemic blood pressure or worsening the intrapulmonary shunt or the Pa_{O₂}. This pattern of “dose-limited” pulmonary selectivity has been observed with other systemic vasodilators, such as prostacyclin,¹³ which is currently used in the management of pulmonary hypertension. The potential advantage of using a selective PDE-5 inhibitor instead of systemic vasodilators in conjunction with NO is that the PDE-5 inhibitor might enhance the local selectivity provided by inhaled NO. Our observation in this patient supports this hypothesis, as shown by

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the significant reduction of the venous admixture caused by the combination of inhaled NO and sildenafil. Decreasing pulmonary vascular resistance in the presence of extracardiac shunts often increases the fraction of blood shunted and worsens the Pa_{O_2} , as observed with prostacyclin.¹³ However, in the presence of an intracardiac shunt, decreasing pulmonary vascular resistance may increase nonshunting output and flow, because the resistance through the intracardiac defect is largely unaffected by the vasodilator. The decrease of the degree of oxygen shunting that was observed in this patient after the administration of sildenafil (fig. 1) can be explained on this basis. These findings should not be extrapolated to patients with hypoxemia from intrapulmonary shunting (e.g., acute respiratory distress syndrome) where sildenafil might increase shunting and worsen the Pa_{O_2} .

Our observation suggests that small doses of sildenafil may be a useful adjunct to inhaled NO in the management of pulmonary hypertension and hypoxemia associated with a reversible right-to-left cardiac shunt. Although its use was safe in this patient, caution should always be used when administering this potent vasodilator in a critically ill patient. The ongoing administration of systemic nitrovasodilators, such as nitroglycerin and sodium nitroprusside, should be considered an absolute contraindication to the use of sildenafil. Increased selectivity for pulmonary circulation might be achieved by testing lower doses of sildenafil or by nebulized administration.

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