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Adverse Hemodynamic Effects Observed with Inhaled Nitric Oxide After Surgical Repair of Total Anomalous Pulmonary Venous Return

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Abstract. The following is a case report of a 1-month-old patient who developed adverse hemodynamic sequelae during the use of nitric oxide (NO) in the postoperative period for pulmonary hypertension after correction of total anomalous pulmonary venous return. At the time of diagnosis, the patient had evidence of systemic right ventricular pressures estimated by continuous-wave Doppler. He was sedated and paralyzed for hyperventilation in preparation for surgery and underwent pulmonary vein confluence to left atrial anastomosis. Postoperative pulmonary hypertension was managed by hyperventilation, sedation, and paralysis until a sudden onset of systemic-level pulmonary pressure required NO therapy. Satisfactory results were obtained in minutes, but a rebound pulmonary hypertension occurred with concomitant systemic hypertension and no radiographic changes. We suspected left atrial hypertension secondary to a sudden increase in pulmonary blood flow to an noncompliant left ventricle. Discontinuation of NO resulted in stabilization of the hemodynamic profile of the patient and he continued to be managed with paralysis, hyperventilation, and sedation. Based on this experience we suggest that NO should be used with caution in patients with obstructive lesions at the atrial level prior to surgery (mitral valve stenosis and cor triatriatum) or in patients with a poorly compliant left ventricle (cardiomyopathy and left ventricular dysfunction). These entities are unable to tolerate a sudden increase in pulmonary blood return thus creating paradoxical pulmonary hypertension.

Key words: Nitric oxide — Pulmonary hypertension — Complications — Total anomalous venous connection

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Total anomalous pulmonary venous return (TAPVR) is a congenital heart defect that accounts for 1% of all congenital cardiac defects and can be associated with pulmonary hypertension secondary to obstruction to the pulmonary venous return. The pulmonary artery smooth muscle in TAPVR can be hypertrophied; its hyperreactivity is thought to be responsible for the acute rises in pulmonary vascular resistance following corrective surgery. Pulmonary hypertension contributes significantly to postoperative morbidity and death and is usually managed with sedation/paralysis, hyperventilation/hyperoxia, and inotropic support [5, 8].

Current data support the use of inhaled nitric oxide (NO) in the treatment of pulmonary hypertension [4, 9]. We report a case in which inhaled NO was intended to treat pulmonary hypertension following surgical correction of TAPVR but resulted in unexpected paradoxical pulmonary hypertension, most likely secondary to poor left heart compliance and excessive pulmonary blood flow.

Case Report

MR is a 1-month-old white male born to a 39-year-old G2P1 mother via an uncomplicated normal spontaneous vaginal delivery with a birth weight of 3560 g. He was admitted to the cardiac intensive car unit with a 2-day history of intermittent cyanosis and progressive respiratory distress.

Initial laboratory data showed capillary blood gases as follows: pH, 7.20; pCO_2, 55 Torr; pO_2, 11 Torr; and base deficit, −7.4 mEq/Lt. Further workup demonstrated a hemoglobin of 7.7 mg/dl, hematocrit of 23.2%, a platelet count of 88,000/UL, and a white blood cell count of 12,300 cells/μl. Antibiotic therapy with ampicillin and cefotaxime was administered for presumed sepsis. The chest roentgenogram showed diffuse interstitial edema with a normal cardiac silhouette. The electrocardiogram demonstrated right ventricular hypertrophy. The echocardiogram revealed the diagnosis of mixed TAPVR (three pulmonary

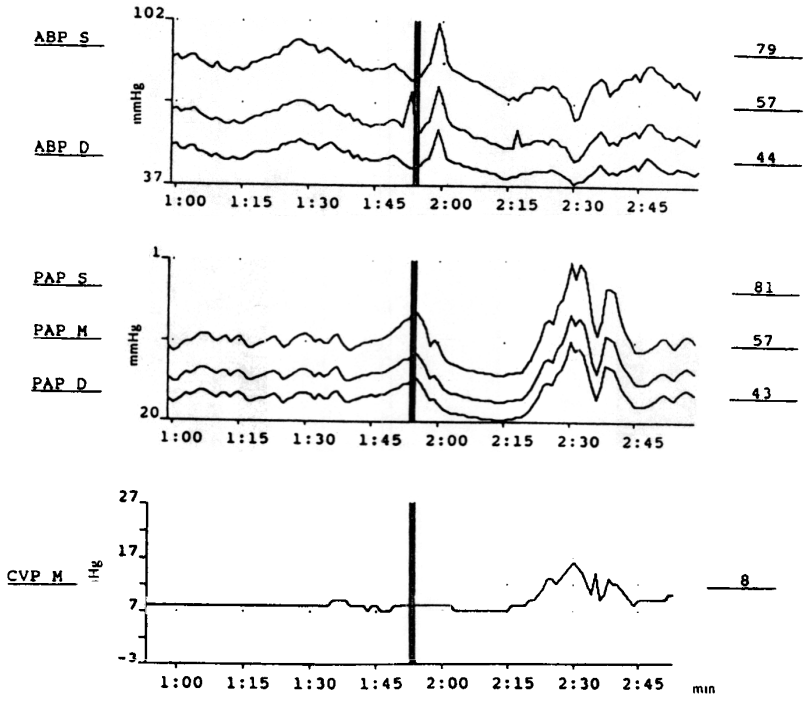

Fig. 1. Variation in systolic (*S*), mean (*M*), and diastolic (*D*), arterial blood pressure (*ABP*), pulmonary artery pressure (*PAP*), and central venous pressure (*CVP*) before, during, and after inhaled NO (see text for descriptions). The *solid bar* represents initiation of inhaled NO treatment.

veins draining infradiaphragmatically into the portal system, and the remaining upper left pulmonary vein draining into the innominate vein); in addition, there was evidence of right heart dilatation, tricuspid regurgitation, and systemic right ventricular pressure (estimated by continuous-wave Doppler).

The patient was sedated with fentanyl at 7 μg/kg/hr and paralyzed with vecuronium at 0.6 mg/hr; he was also mechanically ventilated with the following ventilatory settings: FiO_2, 1.0; IMV, 50 per minute; PIP, 30 cm; and PEEP, 5 cm. In addition, furosemide (0.4 mg/hr), dopamine (10 μg/kg/min), and prostaglandin (0.02 μg/kg/min) were also administered.

The patient underwent corrective surgery with pulmonary vein confluence to left atrial anastomosis; the left upper pulmonary vein was left intact. Immediately following surgery, the patient remained hemodynamically stable, supported with epinephrine (0.05 μg/kg/min) and dopamine (7.5 μg/kg/min). During the first 36 hours following surgery, the pulmonary artery pressure ranged between one half and three quarters of systemic pressure, and the patient was managed with sedation, paralysis, and hyperventilation (with an arterial CO_2 of 24–30 Torr).

At about 36 hours in the postoperative period, the patient developed sudden onset systemic-level pulmonary pressure with concomitant systemic hypotension (Fig. 1); NO therapy at 80 ppm was promptly begun. Prior to NO therapy, arterial blood gas showed the following: pH, 7.47; $paCO_2$, 26 Torr; paO_2, 83 Torr; and a base deficit equivalent to −2.6 mEq/L. During the ensuing 15 minutes, both a decrease in the pulmonary artery pressure and an improvement in systemic pressure were observed. Arterial blood gas showed no significant changes in pH or $paCO_2$, but paO_2 increased to 364 Torr.

These favorable changes were followed by an unexpected rise in pulmonary pressure (during a period of 15 minutes) that exceeded systemic-level pressure. This "rebound" pulmonary hypertension occurred with concomitant systemic hypotension and central venous pressure elevation to 16 mmHg. This phenomenon was not associated with any change in the administration of NO delivery or in the chest roentgenogram. Therapy with NO was discontinued based on the rationale that this latter episode of pulmonary hypertension may have been caused by left atrial hypertension secondary to a sudden increase in pulmonary blood flow into a noncompliant left atrium and ventricle.

The suspension of NO therapy resulted in stabilization of the patient's hemodynamic profile. The patient remained in sedation/paralysis, hyperventilation, and inotropic support for an additional 3 days. The remaining hospital course was uneventful and he was discharged 18 days after surgery on oral furosemide.

Discussion

Pulmonary hypertension is one of the leading causes of death and morbidity in children after cardiac surgery and is associated with preoperative intrinsic pulmonary vascular abnormality [4]. This abnormal pulmonary vascular endothelium is further damaged by cardiopulmonary bypass. Vasodilators such as nitroprusside, tolazoline, or prostaglandin/prostacyclin can be effective in treating pulmonary hypertension but have unfavorable sequelae, such as increased intrapulmonary right-to-left shunting (as a result of indiscriminate vasodilatation of pulmonary vessels) and systemic hypotension.

Current therapy for postoperative pulmonary hyper-

tension includes the use of NO, a biologic diatomic molecule produced in the endothelium from L-arginine by the enzyme NO synthetase. Nitric oxide, previously known as endothelial-derived relaxing factor, stimulates guanylate cyclase to form cGMP, which in turn causes relaxation of the vascular smooth muscle by decreasing the concentration of free calcium in the smooth muscle cytosol [1, 11]. Once inhaled, NO acts exclusively on the adjacent alveolar unit and is rapidly inactivated by hemoglobin, thus avoiding systemic hypotension. In addition, since NO manifests its effects in better ventilated regions of the lung, it selectively dilates only the pulmonary vessels in these areas, thus maximizing ventilation/perfusion matching. For these reasons, NO is thought to be superior to conventional vasodilating agents.

Previous reports on the use of inhaled NO did not disclose adverse hemodynamic profile in patients [4, 9]. In our patient, the initial response to NO was a significant decrease in pulmonary artery pressure with an increase in arterial oxygen content, indicating improved pulmonary blood flow. The subsequent paradoxical pulmonary hypertension was not caused by alteration in the administration of NO or by the extrinsic factors (such as atelectasis or pneumothorax). We speculated that NO induced a pulmonary hypertensive crisis by acutely increasing pulmonary blood flow and therefore preload into a relatively noncompliant left atrium and ventricle. The left atrium in TAPVR, due to failure of inclusion of the common pulmonary veins during embryological development, is 50% of the expected size; although surgical repair improves the capacity of the left atrium, its compliance remains relatively impaired [6]. With the administration of inhaled NO, the increase in pulmonary venous return resulted in left atrial hypertension and subsequent reflex pulmonary venous and arterial vasoconstriction.

In addition to TAPVR after surgery, there are other pathophysiologic states in which NO therapy and an increase in pulmonary blood flow could be detrimental, including (1) left atrial obstructive lesions (such as mitral stenosis or supramitral ring) prior to relief of obstruction and (2) left ventricular dysfunction and/or dilated cardiomyopathy with decreased ventricular compliance and suboptimal diastolic function [2, 10]. These patients may not tolerate an acute increase in preload to the left atrium or ventricle and therefore could develop an abrupt increase in left atrial pulmonary arterial pressures and pulmonary edema.

In summary, while inhaled NO has been found to be of benefit in the treatment of pulmonary hypertension in children with congenital heart disease, paradoxical pulmonary hypertension can occur in certain pathophysiologic states as a result of this therapy.

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