Use of sildenafil and nitric oxide in the management of hypoxemia owing to pulmonary arteriovenous fistulas after total cavopulmonary connection

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Hypoxemia after total cavopulmonary connection is a predictable outcome in children with pulmonary arteriovenous fistulas (PAVF). Fontan completion is often performed earlier than routine in these children with a view to recruiting hepatic venous blood, which contains hepatic factor. This has an antiangiogenic effect and is associated with regression of PAVF in the medium term. Before this occurs, hypoxemia may develop, and the purpose of this report is to highlight the time frame over which hypoxemia may develop and the utility of inhaled nitric oxide and orally administered pulmonary vasodilators. We present the case histories of 2 children with PAVF who underwent total cavopulmonary connection. Both patients had significant postoperative hypoxemia associated with the presence of PAVF. Pulmonary vasodilatation occurring as a result of anesthetic agents and vasodilating infusions in the immediate postoperative period may delay the onset of hypoxemia, which may respond dramatically to inhaled nitric oxide. Sildenafil was used in both patients with normalization of systemic oxygen saturations over the short term and therapy was later ceased. Although not proven by the cases presented, we suggest that the benefit derived from sildenafil relates to vasodilatation of resistance vessels within the pulmonary parenchyma, which diminishes flow through PAVF, increasing systemic oxygenation until regression of PAVF, induced by hepatic factor, can take place.

Clinical Summaries

PATIENT 1. This child was born at 33 weeks with mitral atresia, ventricular septal defect, hypoplastic left ventricle, and aortic coarctation. Her condition was stabilized on a prostaglandin infusion and initial palliation included pulmonary artery banding with coarctation repair through a left thoracotomy. Atrial septectomy was performed at 2 months of age, and a bidirectional superior cavopulmonary con-

nection and Damus–Kaye–Stansel connection were performed at 6 months of age.

At 41 months of age, the patient was clinically cyanosed. Cardiac catheterization demonstrated PAVF with right and left pulmonary venous saturations of 82% and 89% and low pulmonary vascular resistance. An 18-mm nonfenestrated extracardiac conduit was placed with the use of cardiopulmonary bypass, and oxygen saturation at the end of the procedure was 98% (Figure 1). During the immediate postoperative period, the patient remained well oxygenated and in hemodynamically stable condition. She was extubated on the first and discharged from intensive care on the third postoperative day. Between postoperative days 4 and 5, the patient had several transient periods of desaturation with readings between 36% and 69% despite supplemental oxygen. This was attributed to the presence of PAVF that had been identified preoperatively. Sildenafil was commenced on day 7, at 2 mg every 6 hours, and increased to 7 mg every 6 hours on day 9 owing to further episodes of desaturation. The patient's oxygen saturation gradually rose over several days, and she was discharged on day 11, receiving 10 mg sildenafil 3 times daily. Eight months after the procedure, the patient is well with arterial oxygen saturations of 97%. Sildenafil has been ceased although the patient continues to receive diuretics and angiotensin-converting enzyme inhibitors.

PATIENT 2. The second patient was born at term with double-inlet left ventricle, L-transposition of the great arteries, and aortic coarctation with a hypoplastic transverse arch. A modified Norwood procedure with a right ventricle–pulmonary artery conduit was performed with creation of a superior cavopulmonary connection at 4 months.

At cardiac catheterization before Fontan completion, systemic saturations were 65% and moderate PAVF were evident on pulmonary arterial injection. Pulmonary venous saturations were 92% and pulmonary vascular resistance was low. A 16-mm extracardiac nonfenestrated Fontan procedure was performed with cardiopulmonary bypass. Initial oxygen saturations of 70% improved to 87% with high-flow oxygen (Figure 1).

On return to the intensive care unit, inhaled nitric oxide was briefly trialed in an attempt to elevate oxygen saturations, which were then 80% to 85%, without significant benefit and was ceased. There was a period of hypotension and junctional rhythm necessitating a low-dose epinephrine infusion and pacing; however, saturations remained stable and the child was extubated with saturations of around 80%. Significant desaturation occurred on postoperative day 5, necessitating reintubation, and nitric oxide was again trialed with significant benefit to oxygenation. This improvement could not be explained only by improved ventilation/perfusion matching. The diagnosis of PAVF was confirmed on cardiac catheterization on day 5 (representative image, Figure 2). Sildenafil was commenced on day 7 at a dose of 5 mg every 6 hours. This dose was increased to

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Figure 1. Oxygen saturations in patients 1 (A) and 2 (B). ICU, Intensive care unit; CPB, cardiopulmonary bypass; iNO, inhaled nitric oxide.

7.5 mg every 6 hours, and the patient was successfully weaned from inhaled nitric oxide and extubated on day 11. The patient was discharged receiving 6.5 mg of sildenafil 3 times daily, which was ceased 11 months after the operation. At 14 months the patient is well, arterial oxygen saturation is 95% on room air, and the child takes only aspirin.

Discussion

This report establishes the utility of sildenafil, an orally administered agent that reduces pulmonary vascular resistance, in treatment of children with hypoxemia owing to PAVF after completion of cavopulmonary connection. Sildenafil may facilitate weaning from ventilation with acceptable oxygenation. Increasing pulmonary

Figure 2. A, Preoperative angiogram in patient 1, with injection into the right internal jugular vein through the superior cavopulmonary anastomosis, with contrast in both pulmonary arteries. Note early return of contrast through arteriovenous fistulae into pulmonary veins, filling the common atrium from the right side (outlined). B, Postoperative angiogram in patient 2, with injection into the left pulmonary artery. Note early return of contrast via arteriovenous fistulas, into the pulmonary veins, outlining the common atrium (outlined).

vascular resistance in the days after operation may be associated with worsening of hypoxemia. In our experience, sildenafil is of use during this later period, even if use of inhaled nitric oxide in the early postoperative period is not associated with benefit.

PAVF are a considerable cause of morbidity in the cohort of children undergoing staged palliation before definitive total cavopulmonary connection. They occur in up to 25% of patients undergoing these procedures. Their development may be related to the absence of “hepatic factor” in the hepatic venous effluent in the pulmonary circulation that occurs after isolation of the lungs after superior cavopulmonary connection.¹

Two earlier reports have described the use of inhaled nitric oxide to correct critical hypoxemia owing to PAVF after staged cavopulmonary connection.^{2,3} Nitric oxide lowers resistance in vascular beds associated with well-ventilated parts of the lung, the effect of which is more pronounced after cardiopulmonary bypass.⁴ This may increase flow through physiologic right-to-left pathways, diverting flow away from abnormal PAVF pathways. Nitric oxide causes smooth muscle relaxation by increasing cyclic guanosine monophosphate levels through the actions of guanylate cyclase. Systemic vasodilators including angiotensin-converting enzyme inhibitors and systemic vasodilators do not provide significant pulmonary vasodilatation and in some cases may worsen intrapulmonary shunting. Neither was used during the acute phases of the cases described.

Sildenafil may provide both an alternative and complementary therapy in this setting. Sildenafil prevents the breakdown of cyclic guanosine monophosphate by inhibiting phosphodiesterase.⁵ Hence, it can produce pulmonary vasodilatation independent of

nitric oxide and may potentiate the effects of inhaled nitric oxide on the pulmonary vasculature.

In children known to have PAVF, the development of hypoxemia may be effectively treated with sildenafil. In those with large PAVF, treatment may be indicated before the onset of severe hypoxemia, which may manifest as pulmonary vascular resistance rises in the days after cardiopulmonary bypass. We suggest that the benefit derived from sildenafil relates to vasodilatation of the native pulmonary bed, providing a lower resistance pathway than that offered by the PAVF. Over the weeks to months after completion of the Fontan circulation, PAVF are likely to regress as a result of hepatic factor now reaching the pulmonary circulation, and sildenafil is no longer required.

References

1. Duncan BW, Desai S. Pulmonary arteriovenous malformations after cavopulmonary anastomosis. *Ann Thorac Surg.* 2003;76:1759-66.
2. Urcelay GE, Borzutzky AJ, Becker PA, Castillo ME. Nitric oxide in pulmonary arteriovenous malformations and Fontan procedure. *Ann Thorac Surg.* 2005;80:338-40.
3. Hofer A, Pusch M, Haizinger B, Mair R, Gitter R, Gombotz H. Successful management of severe life-threatening hypoxemia due to pulmonary arteriovenous malformation. *Anesthesiology.* 2002;97:1313-5.
4. Wessel DL. Inhaled nitric oxide for the treatment of pulmonary hypertension before and after cardiopulmonary bypass. *Crit Care Med.* 1993; 21(Suppl):S344-5.
5. Michelakis E, Tymchak W, Lien D, Webster L, Hashimoto K, Archer S. Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. *Circulation.* 2002;105:2398-403.