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Successful use of calcium channel blocker for management of arterio-venous malformations following Fontan procedure

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Brief Report

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Abstract

In diffuse forms of arteriovenous malformation following Fontan procedure, "classical" medical therapy, inhaled nitric oxide and sildenafil, may play a role, until re-direction of hepatic flow to pulmonary circulation cures it. However, in refractory cases, as reported in our 2-year-old patient, unusual medications such as calcium channel blockers can be tried and continued if patients respond adequately.

Pulmonary arteriovenous malformations are thin-walled pleural or sub-pleural vascular malformations.[1] They may be classified as simple, with a single artery feeding the malformation and a single draining vein, complex, with two or more feeding arteries and veins, or diffuse type, which is rare.[1] Pulmonary arteriovenous malformations following Glenn shunt in patients with single-ventricle physiology are a major cause of hypoxaemia and cyanosis. In addition, the management of such patients in the immediate postoperative period following the Fontan procedure remains challenging.

Case report

A 2-year-old girl born with hypoplastic left heart syndrome underwent stenting of the patent ductus arteriosus and bilateral artery banding at the age of 7 days and had a bidirectional Glenn shunt at the age of 9 months. She was admitted to our unit following Fontan procedure. During the past 8 months before surgery, she had become increasingly cyanotic, where her arterial oxygen saturation was 60% and her haemoglobin level was 22.8 g/dL.

Preoperative cardiac catheterisation showed low pulmonary arterial pressure (12 mmHg), and angiography revealed diffuse and rapid opacification of the lung parenchyma and of the pulmonary veins, consistent with arteriovenous malformations (Fig 1). The contrast opacification was particularly dense in the right lower lobe.

After a fenestrated (4 mm) extra-cardiac non-complicated Fontan procedure with an 18-mm conduit, she was admitted to the ICU and intubated on low-dose inotropic support, with milrinone at a dose of 0.5 mcg/kg/minute. She had low oxygen saturation (55–60%) that required the initiation of inhaled nitric oxide, at a concentration of 20 ppm. Saturation increased modestly to 70–75% and was well tolerated with no acidosis on blood gas analysis. She was extubated within 4 hours, on high-flow nasal cannula with 100% fraction of inhaled oxygen and 20 ppm nitric oxide. Milrinone was tapered and weaned off on day 2. Sildenafil was initiated on day 3 at 0.5 mg/kg/dose and was administered every 4 hours, whereas progressive weaning of inhaled nitric oxide was planned over the following 48 hours. However, nitric oxide could only be weaned down to 5 ppm. Over a period of 5 days, multiple trials to wean and stop the 5 ppm of nitric oxide were unsuccessful, with immediate severe decrease in oxygen saturation to 40% associated with acidosis, despite increasing sildenafil to 1 mg/kg/dose on day 8.

Because of the diffuse and severe form of the arteriovenous malformations, percutaneous transcatheter embolisation was not considered. Thus, medical management with calcium channel blockers was initiated on day 10. Amlodipine was started and the dose was increased progressively from 0.1 to 0.3 mg/kg/day. Oxygen saturation started to improve within 24 hours and increased progressively to reach 75–80% within 4 days. Nitric oxide could be weaned successfully. Non-invasive respiratory support and oxygen therapy were stopped on day 16. The patient was discharged home and followed up on a regular basis. Her oxygen saturation reached 95% within 3 months.

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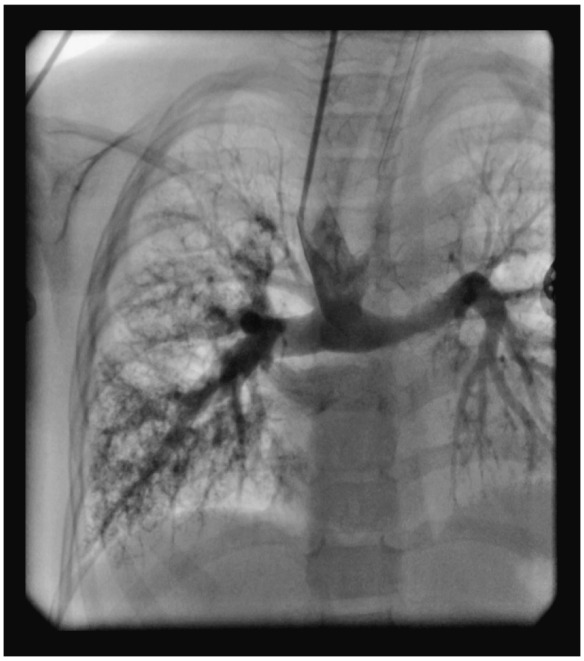

Figure 1. Cardiac catheterisation.

Discussion

The development of pulmonary arteriovenous malformations after the superior caval vein to pulmonary artery anastomosis (Glenn shunt) is a known complication and is associated with significant morbidity.[2] The role of the hepatic factor in the development of arteriovenous malformations following Glenn shunt has been extensively investigated. During Glenn procedure, if the antegrade pulmonary blood flow is completely interrupted, the lungs will receive flow exclusively from the superior caval vein, and the hepatic factor produced in the liver will not reach the pulmonary circulation. Thus, remodelling and dilatation of the pulmonary vasculature may be compromised and lead to the development of arteriovenous malformations. Arteriovenous malformations usually regress when the systemic venous blood flow from the liver and inferior caval vein is re-established after a Fontan procedure, or heart transplantation. This process can take days, weeks, or even months. Non-pulsatile pulmonary blood flow and chronic hypoxia have also been both incriminated in arteriovenous malformations after a Glenn shunt.[1–3]

Patients with small arteriovenous malformations with minimal right to left shunt may be asymptomatic. However, in advanced stages, arteriovenous malformations may present with profound hypoxaemia, cyanosis, cerebral embolisation, and brain abscesses.[1]

In presence of severe arteriovenous malformations, which cause significant arterial desaturation following a Fontan procedure, several therapeutic options have been reported.[4–6] Percutaneous or surgical interruption of individual arteriovenous malformations has been described when the vessels were large and accessible, and lobectomy has been reported for localised arteriovenous malformations.[7] However, when arteriovenous malformations are small and diffuse, only medical treatment is available.

Inhaled nitric oxide has been described as an effective rescue treatment, mainly in the acute postoperative period, with significant improvement in arterial saturation.

Phosphodiesterase-5 inhibitor, sildenafil, is commonly used to wean inhaled nitric oxide and is continued until resolution of the arteriovenous malformations following Fontan procedure and restoration of the hepatic blood flow into the pulmonary circulation. Its use has been well described in the literature as a complementary and alternative therapy to inhaled nitric oxide for the treatment of hypoxaemia resulting from arteriovenous malformations following Fontan procedure.[5,6]

In our patient, serial trials of nitric oxide cessation were attempted after initiation of high-dose sildenafil failed and were associated with severe hypoxaemia and acidosis. As the patient responded to nitric oxide, calcium channel blockers were introduced with the hypothesis that it would dilate the pulmonary arterioles and divert blood flow away from the arteriovenous malformations, into the normal capillaries. The role of calcium channel blockers in the treatment of pulmonary hypertension has not been clearly established, and its use is limited to responders to nitric oxide. Amlodipine, a dihydropyridine, acts by binding to the L-type calcium channels in the heart and vascular smooth muscles. It also enhances endogenous nitric oxide formation and increases its half-life through antioxidative properties.[8] Sands et al[9] have described the unusual but successful use of nifedipine in two patients with arteriovenous fistulas, one with Osler–Rendu–Weber syndrome and another with congenital dyskeratosis.

We hypothesise that calcium channel blockers, in comparison with sildenafil, may have preferential action on normal pulmonary vasculature rather than on the abnormal arteriovenous malformations, thus reducing the amount of the diverted blood through the shunts.

To our knowledge, this is the first reported case of the successful use of amlodipine, after failure of high-dose sildenafil, in weaning inhaled nitric oxide.

Conclusion

Pulmonary arteriovenous malformations following Glenn shunt continue to be a cause of considerable morbidity and a major cause of profound hypoxaemia complicating Fontan procedure. In diffuse forms, medical therapy may play a role. Inhaled nitric oxide in the early postoperative period and bridging to oral sildenafil could be an effective treatment modality for postoperative hypoxaemia, until re-direction of hepatic flow to pulmonary circulation cures the arteriovenous malformations. However, in refractory cases, unusual medications such as calcium channel blockers can be tried and continued if patients respond adequately.

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Conflicts of interest. None.

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