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Case Report

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Successful Surgical Repair and Perioperative Management of 6-Month-Old With Total Anomalous Pulmonary Venous Return in a Developing Country: Considerations for the Treatment of Pulmonary Hypertension

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Abstract

Total anomalous pulmonary venous return (TAPVR) is a rare congenital cardiac defect, accounting for 1.5-3% of cases of congenital heart disease. With prenatal ultrasonography, the majority of these patients are diagnosed in utero with definitive surgery performed during the neonatal period. However, as prenatal screening may not be available in developing countries, patients may present in later infancy. We present successful surgical repair of a 6-month-old infant with TAPVR who presented for medical care at 5 months of age in Lima, Peru. The late presentation of such infants and the limited resources available for the treatment of elevated pulmonary vascular resistance may impact successful surgical correction of such defects. The perioperative care of such infants in developing countries is discussed and strategies for managing postoperative pulmonary hypertension is reviewed.

Keywords: Total anomalous pulmonary venous return; Congenital heart disease; Pulmonary hypertension

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Introduction

Total anomalous pulmonary venous return (TAPVR) is a rare congenital cardiac defect, accounting for 1.5-3% of cases of congenital heart disease (CHD) [1, 2]. TAPVR results from failure of the formation of a common pulmonary vein from the left atrium with persistent connection of the primitive pulmonary vascular plexus to the common cardinal and umbilico-vitelline veins [3, 4]. TAPVR can be classified based on the anatomic defect (level of pulmonary venous drainage) or physiologic effect. Anatomic variants include supracardiac (40-50%), intracardiac (15-20%), infracardiac (25-30%) or mixed type (5-10%) while physiologic consequences include obstructive or non-obstructive venous drainage [3, 4]. Obstruction, which results in severe derangements immediately after birth, is usually due to the external compression from surrounding structures or reduced caliber of the internal lumen due to pulmonary vein hypoplasia or stenosis [5]. Identifying the drainage sites and level of obstruction is important for determining the surgical approach. Diagnosis is usually achieved by echocardiography and cardiac catheterization [6]. With the advent of improved prenatal ultrasonography, the majority of patients are diagnosed in utero. Although prenatal screening with ultrasonography and postnatal neonatal screening with pulse oximetry is generally effective in identifying the defect; such screening may not be available or routine in developing countries [7, 8].

If not identified during the newborn period with such screening, the age at which patients become clinically symptomatic and present to the hospital depends on the presence or absence of obstruction and the existence of intra-cardiac or ex-

tra-cardiac shunts [9]. Clinical symptoms of congestive heart failure or hypoxemia, will not manifest until physiologic derangements occur related to obstruction of pulmonary venous return or the large left-to-right shunt. We report a 6-month-old infant with supracardiac TAPVR that presented in a developing country (Peru) at 5 months of age with the primary clinical symptoms of tachypnea and poor feeding. The late presentation of such infants is discussed and the perioperative challenges reviewed with emphasis on the prevention and treatment of elevated pulmonary vascular resistance in a developing country.

Case Report

The patient in this report was cared for during a cardiac surgery trip of Heart Care International (HCI) to El Instituto Nacional de Salud del Nino in Lima, Peru. HCI is a not-for-profit 501(c)(3) foundation based in Greenwich, Connecticut that has provided pediatric cardiology and cardiac surgery services in developing countries since 1994. HCI's goal is to not only provide primary cardiac surgical care, but also to train and educate host country health professionals. The majority of the equipment and supplies necessary for these surgical procedures is shipped into the country by HCI. Informed consent for surgery was obtained from the family and the HCI Board of Directors approved this report.

A 6-month-old, 5.5 kg former full-term male infant, who had been thriving and breastfeeding without difficulty, first presented for medical care at 5 months of age with new onset tachypnea and wheezing. During hospitalization for suspected pneumonia, a transthoracic echocardiogram was performed and revealed supracardiac TAPVR to an unobstructed confluence superior to the left atrium with a large atrial septal defect (ASD). In Peru, this cardiac lesion carries a very high mortality and rarely will children receive the option for surgical correction. This patient was scheduled for surgical repair as part of Heart Care International's twice annual pediatric cardiac surgical trip to Lima, Peru. On the day of surgery, a peripheral intravenous cannula (PIV) was placed to provide maintenance intravenous fluids and the patient was held *nil per os* for 6 h. He was transported to the operating room where routine American Society of Anesthesiologists' monitors were placed. Anesthesia was induced with fentanyl (5 µg/kg) and ketamine (1 mg/kg) and neuromuscular blockade provided by rocuronium (1 mg/kg). Following anesthetic induction, a nasogastric tube was inserted and sildenafil (2 mg/kg) was administered. Maintenance anesthesia included sevoflurane (inspired concentration of 1-3%) and fentanyl (total dose of 50 µg/kg). Endotracheal intubation was performed with a 3.5 mm cuffed endotracheal tube. A second PIV, a left radial arterial cannula, and a double lumen central venous catheter (internal jugular) were placed. Repair of the TAPVR was performed using the previously reported "closed-vein" technique for primary sutureless repair [10]. Cannulation of the aorta, superior *vena cava* (SVC), and inferior *vena cava* (IVC) was performed along with placement of a vent in the vertical vein. The systemic temperature was maintained between 28 - 32 °C. The venous confluence was exposed through the retracted ASD. The left atrial cuff was then sutured around the pulmonary confluence. Once this was complete, the confluence was opened and all four pulmonary venous orifices were identified. The vertical vein was ligated and the ASD was closed with an autologous pericardial patch. Prior to weaning from cardiopulmonary bypass (CPB), a loading dose of milrinone (25 µg/kg) was administered and an infusion started at 0.5 µg/kg/min. To maintain mean arterial pressure, an epinephrine infusion was initiated at 0.03 µg/kg/min. The patient was weaned from CPB without difficulty and heparin anticoagulation was reversed with protamine. Following weaning from CPB, mild hyperventilation ($PaCO_2$ 30-35 mm Hg) was maintained with an inspired oxygen concentration $\geq$ 0.6. The total CPB time was 99 min and aortic cross clamp time was 62 min. The patient was transported to the intensive care unit (ICU) with the endotracheal tube in place, receiving mechanical ventilation. Ongoing sedation was provided by continuous infusions of fentanyl and midazolam. The epinephrine infusion was discontinued on postoperative day (POD) 1 and the milrinone discontinued on POD 2. The patient's trachea was extubated on POD 2 and the inspired oxygen concentration weaned to room air on POD 5. An echocardiogram on POD 1 revealed no obstruction to flow, no gradients across the pulmonary veins, and good myocardial function. Sildenafil was continued via the NG tube every 6 h for 7 days. The patient was eating well without complications and was discharged home on POD 7.

Discussion

TAPVR typically presents in infancy with the clinical signs and symptoms dependent on the site of drainage of the pulmonary veins and the degree of obstruction. Infracardiac TAPVR, in which the pulmonary venous plexus drains into the sinus venosus below the diaphragm, almost always presents with an obstructed picture as the sinus venosus constricts shortly after birth. If not identified by routine ultrasonography during pregnancy or post-natal pulse oximetry screening, the supracardiac and intracardiac unobstructed variants of TAPVR can present later in life, manifesting symptoms related to the large left-to-right shunt with volume overload [11].

Infants with obstructed TAPVR appear critically ill, presenting at birth with marked cyanosis, tachypnea, dyspnea, hypoxemia, and metabolic acidosis. These children require urgent surgical repair [12]. In comparison, infants without obstruction, as was the case with our patient, may present later in infancy with signs and symptoms of congestive heart failure (tachypnea, poor feeding) related to volume overload and pulmonary over-circulation. Alternatively, signs and symptoms of pulmonary hypertension (PH) may develop if the pulmonary venous return becomes obstructed. The relatively late presentation of our patient at 5 months of life can be attributed to an unobstructed supracardiac TAPVR with a large unrestricted ASD allowing ample mixing at the atrial level and unimpeded pulmonary venous return.

When infants present later in life, several factors may complicate the perioperative care including ongoing failure to thrive, congestive heart failure, respiratory insufficiency, and

the potential for elevated pulmonary vascular resistance during the perioperative period especially following CPB when endothelial cell dysfunction may be present. The surgical technique used in our patient ("suture-less technique") is advantageous as it avoids the need for profound hypothermia and circulatory arrest with the potential for neurologic damage, limits postoperative bleeding, and has a decreased incidence of late restenosis which are particularly beneficial in a resource poor setting. Postoperatively, these patients are at a significant clinical risk for increased pulmonary vascular resistance and pulmonary hypertensive crisis [13, 14]. Given the vasoreactive effects of alveolar oxygen and arterial carbon dioxide ($PaCO_2$) on the pulmonary vasculature, simple maneuvers include mild hyperventilation and the delivery of a high inspired concentration of oxygen. Other perioperative factors that may increase pulmonary vascular resistance include acidosis, hypothermia, and the surgical stress response.

Medications that decrease systemic pressure by direct negative inotropic effects or systemic vasodilatation should be avoided as the precipitous decrease in systemic vascular resistance may result in rapid decompensation and perioperative cardiac arrest. The importance of such issues are exemplified by the increased incidence of perioperative cardiac arrest in infants with CHD especially those with PH [13-15]. Intense analgesia with the use of a high-dose opioid technique with synthetic opioids (fentanyl or sufentanil) effectively controls the hyper adrenergic stress response and may effectively blunt pulmonary vascular reactivity [16]. In order to maintain systemic pressure and avoid hypotension, anesthesia was induced with ketamine. Although previously postulated to be contraindicated in the setting of PH, recent data has demonstrated ketamine to be a safe and effective agent in this patient population as it maintains or increases systemic vascular resistance with little effect on PVR [17, 18]. A high-dose opioid technique with fentanyl was used intraoperatively with postoperative mechanical ventilation to optimize oxygenation and ventilation. Additionally, a postoperative fentanyl infusion was used to ensure adequate analgesia and sedation during the postoperative period during endotracheal intubation and mechanical ventilation.

Preexisting PH complicates the postoperative course in 2-7% of patients undergoing surgery for CHD [19-21]. Many of the episodes of PH can be effectively prevented by simple maneuvers of avoiding hypothermia, hypoxemia, acidosis, and agitation. Respiratory management plays a critical role in the management of PH. It is crucial to maintain adequate lung volumes and gas exchange while avoiding acidosis in the postoperative period when pulmonary edema, atelectasis, ventilation-perfusion mismatch, and bronchoconstriction may increase pulmonary vascular resistance (PVR). The maintenance of functional residual capacity (FRC) at baseline is crucial as either atelectasis or over-distention of alveoli can increase PVR. As such, positive end expiratory pressure should be titrated to maintain FRC. In our patient, sedation and ongoing ventilation were continued into the postoperative period to allow for the provision of intense analgesia and effective control of oxygenation and ventilation. PH may be exacerbated by airway instrumentation including tracheal suctioning [16, 22]. A rapid increase in PVR can lead to right heart failure with a decrease in right ventricular ejection and failure. In the absence of a patent foramen ovale or atrial septostomy, right heart failure leads to a decrease in pulmonary blood flow, decreased pulmonary venous return to the left atrium, decreased cardiac output, and cardiac arrest. Treatment strategies for PHC include the administration of 100% oxygen and hyperventilion to correct acidosis and provide a moderate degree of hypocarbia ($PaCO_2$ 25 - 30 mm Hg) [23]. Once the $PaCO_2$ is controlled, acidosis can be treated with the administration of sodium bicarbonate. Supplemental anesthesia can be administered especially if the crisis was precipitated by a noxious stimulus [24]. Cardiac output should be supported by the administration of fluid to increase preload and the use of inotropic agents as needed. Finally, various pharmacologic agents have been used for the treatment of PH including nitric oxide, phosphodiesterase inhibitors, prostacyclin analogues, and endothelin antagonists (Table 1) [25].

The time-honored and most commonly used pharmacologic therapy to treat or prevent postoperative PH following surgery for CHD remains inhaled nitric oxide (iNO) [26-28]. However, this agent may be not available in developing countries. NO is administered via inhalation, thereby limiting its systemic effects and preventing decreases in systemic arterial pressure. NO increases intracellular cyclic guanosine monophosphate (cGMP) causing smooth muscle relaxation and vasodilation. NO binds to hemoglobin and is inactivated. Because it is a selective pulmonary vasodilator, easy to administer, and has a rapid onset, inhaled NO has become the primary therapy for postoperative PH. Once formed, intracellular cGMP is metabolized by phosphodiesterase type 5 (PDE). PDE type 5 inhibitors increase cGMP levels by preventing their breakdown, leading to vasodilatory effects on the pulmonary vasculature. However, these medications are generally administered via the oral or intravenous route and hence also have significant effects on the systemic circulation. Sildenafil, the main PDE type 5 inhibitor can be administered via the oral or intravenous route [29-31]. Oral sildenafil has been shown to attenuate rebound PH after iNO withdrawal and shorten the time to extubation and the length of time that intensive care is needed [29]. More recently, an intravenous preparation has been introduced into clinical practice and shown to effectively control PH following surgery for CHD [31]. Although currently approved for use in adults with PH, sildenafil is used extensively off-label for the treatment of neonates, infants, and children with PH and may be used pre-emptively to mitigate pulmonary hypertensive crisis post-operatively as we attempted in this case. Despite such information, the United States Food and Drug Administration has recently cautioned against the long-term use of sildenafil in pediatric patients with PH due to an apparent increase in mortality during long-term therapy [32].

In an attempt to maximize pulmonary vasodilatation in this patient and to prevent PH, we used a combination of intravenous milrinone and enteral sildenafil. While both agents may impact systemic blood pressure, their vasodilatory effects on the pulmonary vasculature generally outweigh their systemic effects [33]. In the event of a decrease in systemic blood pressure, inotropic support may be required and vasopressin is considered the agent of choice to increase systemic blood

Table 1. Management of Perioperative Pulmonary Hypertensive Crisis

1. Correct hypoxemia and hypercarbia
2. Administer 100% oxygen
3. Hyperventilation
4. Maintain normothermia
5. Alkalization with the administration of sodium bicarbonate
6. Treat noxious stimuli by deepening the level of anesthesia or administering opioids such as fentanyl
7. After sedation and analgesia, provide neuromuscular blockade
8. Support cardiac output by administering fluid or inotropic agents
Vasopressin is preferable to adrenergic agents to increase mean arterial pressure without raising pulmonary artery pressure
9. Pharmacologic therapies
Nitric oxide
Increase intracellular cyclic GMP by inhibiting phosphodiesterase 5
Milrinone
Sildenafil (PR or NG)
Augment prostaglandin G_2 (prostacyclin) system (systemic or inhaled)
Epoprostenol (Flolan®)
Treprostinil (Remodulin®)
Inhibit endothelin system
Bosentan
Miscellaneous agents
Nesiritide
levosimendan

pressure. In a preliminary study of 15 pediatric patients with PH, the ratio of pulmonary-to-systemic vascular resistance decreased in three of five patients receiving phenylephrine, five of five patients receiving arginine vasopressin, and three of five patients receiving epinephrine [34]. In an effort to avoid the potential systemic effects of milrinone, investigational studies have reported its administration via aerosol, offering an alternative agent in settings where NO is unavailable [35, 36].

Prostaglandin I_2 (PGI_2) or prostacylin has recently seen increased use in the treatment of PH. PGI_2 stimulates the cAMP pathway to increase pulmonary vasodilation. These agents are available for systemic or inhalational administration. Children with PH show diminished PGI_2 synthase expression in lung vasculature, thus intravenous PGI_2 has become one of the standards of treatment of severe PH with right heart failure, showing improvements in long-term survival and quality of life. However, the intravenous route is generally used only for long-term therapy and not in the acute treatment or prevention of a PH crisis during the perioperative period. Although these agents have been shown to improve survival, their long-term administration may be cumbersome. Epoprostenol (Flolan®) requires continuous infusion without interruption via a central line, given its half life of 5 - 6 min. Treprostinil (Remodulin®) has a longer half-life (4 h) and is administered by continuous subcutaneous administration. The inhaled PGI_2 analog, iloprost (Ventavis®), on the other hand is administered as a nebulization at 3 - 4 h intervals, and has the advantage of causing selective pulmonary vasodilation without affecting systemic blood pressure [37-39]. Given their rapid responsiveness and limited systemic effects, these agents may have a role in the treatment of an acute PH crisis. Endothelin 1 is a potent vasoconstrictor with several receptor subtypes on vascular smooth muscle. Bosentan is the main endothelin receptor antagonist in use; however, other agents that provide more selective receptor antagonism have recently been introduced for clinical care [40]. Bosentan is administered orally, lowers pulmonary vascular resistance, and improves exercise tolerance with long-term administration. However, our experience has demonstrated that these agents (prostaglandin analogues and endothelin antagonists) are generally not available in developing countries.

In summary, we offer a potential clinical pathway for the management of TAPVR in developing countries where resources may be limited. In developing countries and in particular, on medical missions, the standard pharmacologic agents (nitric oxide, prostaglandin analogues, and bosentan) may not be available. In general, pharmacologic therapy of PH is limited to enteral sildenafil (PR or NG), intravenous milrinone, and intravenous vasopressin. Pre-trip planning must include consideration of agents and techniques to treat PH taking into account cost, ease of transport, long-term therapy, experience of the host country healthcare team, and specific customs regulations which may impact on drug availability. Given the late presentation our patient, perioperative care was compounded

by comorbid features of failure to thrive, chronic congestive heart failure from volume overload, and the potential for postoperative PH. Unfortunately, the majority of similar patients will die in the absence of the availability of appropriate medical management for PH and surgical expertise to treat the lesion. While it was fortuitous that Heart Care International was in the country at the time of presentation of this infant, the management of these patients is difficult in any country. Management of these patients is particularly difficult with limited pharmacologic agents and especially with the scarcity of advanced pharmacotherapies such as inhaled nitric oxide (Table 1). A thorough understanding of cardiopulmonary physiology including respiratory mechanics, acid-base interactions, pulmonary vascular reactivity, and cardiovascular physiology by a multidisciplinary team (cardiothoracic surgeons, intensivists, anesthesiologists, and cardiologists) will optimize patient outcomes and can be shared with colleagues in developing countries [41-44].

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