Perioperative Management of Pediatric Pulmonary Hypertension

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Perioperative management of patients with pulmonary hypertension or those at risk for increased pulmonary vascular reactivity should focus on supporting the patient through the vulnerable period of physiologic derangements surrounding surgery, including acute alterations in pulmonary blood flow, altered pulmonary endothelial function following cardiopulmonary bypass, invasive mechanical ventilation, and adaptation to new hemodynamics following correction or palliation of congenital heart disease lesions. These patients require careful attention to each step of perioperative management by teams experienced in the care of pediatric patients with pulmonary hypertension. This article will focus on preoperative evaluation, pulmonary hypertensive crises, general principles of perioperative management, and specific pulmonary vasodilator therapies.

PREOPERATIVE EVALUATION

Pulmonary hypertension (PH) is present in 2% to 7% of patients undergoing congenital cardiac surgery,[1] and is an important risk factor for adverse events in noncardiac surgical procedures. Thus, PH must be carefully considered as part of the preoperative anesthesia evaluation. The current American Heart Association (AHA)/American Thoracic Society (ATS) guidelines for pediatric PH emphasize that thorough preoperative evaluation, including consultation with cardiac anesthesia and judicious plans for appropriate postprocedural monitoring are recommended for pediatric patients with PH undergoing surgical or procedural interventions (Table 1).[2] A retrospective review of 156 pediatric PH patients undergoing 256 noncardiac surgeries and catheterizations found that death or pulmonary hypertensive crisis (PHC) occurred in 4.5% of patients (5% of cardiac catheterizations and 2.7% of all procedures).[3]

Preoperative planning includes consideration of appropriate postoperative monitoring. This is particularly important for patients with PH undergoing noncardiac surgery. We recommend that a cardiac anesthesia team manage such patients intraoperatively and that pediatric PH service consults are performed pre- and postoperatively. These patients require special attention to intraoperative management given their physiology, including special attention to operative events such as patient positioning, pneumoperitoneum, and diaphragmatic compression that may be poorly tolerated in the patient with PH.[4]

PULMONARY HYPERTENSIVE CRISES

The main focus of intra- and postoperative management in patients with abnormal pulmonary vascular tone is avoiding PHCs. These are defined by a sudden increase in pulmonary artery pressure (PAP) such that the ratio of PAP to systemic arterial pressure exceeds 0.75. This is accompanied by a rise in central venous pressure of 20% or more, a decrease in systemic mean arterial pressure of 20% or more, a decrease in systemic oxygen saturation below 90%, and associated evidence of low cardiac output syndrome.[5] The sudden rise in PAP typically leads to increased right ventricular (RV) end-diastolic pressure and increased right atrial pressure. PHCs can lead to acute RV failure and systemic hypotension. PHCs are often accompanied by bronchoconstriction that complicates ventilation.[6] Although echocardiography can be challenging during an acute PHC, it may be particularly useful in postoperative patients to identify residual shunts, additional cardiac lesions, RV outflow tract or anatomic pulmonary arterial (PA) obstruction, or atrioventricular valve dysfunction. Additionally, echocardiography can be helpful to quantify RV performance and interventricular septal position and to evaluate for compromised left ventricular (LV) diastolic filling.

The diagnosis of PHC is significantly aided by the presence of a PA catheter to directly measure PAP. Otherwise, the diagnosis is clinical and is often imprecise or delayed. As the incidence

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of PHC has declined, the routine use of PA catheters has declined. However, their use is associated with low morbidity in postoperative monitoring of children, in contrast to their use in adult or general intensive care units (ICUs).[7] Although the use of PA catheters in low-risk patients may delay ICU stay and overall recovery, PA monitoring in high-risk patients may aid in rapid diagnosis of PHC and determining response to therapies.

Incidence of postoperative PHC is decreasing. Several factors contribute to this decreased incidence, including performing corrective surgery for congenital lesions at a younger age, better surgical technique, changes in cardiopulmonary bypass practice, and pulmonary hypertensive therapies.[8-11] Still, PHC occurs in 0.75% to 4% of patients[1] and remains a condition with important morbidity and mortality. Mortality following a PHC was as high as 50% in older studies, but is 20% in contemporary series.[12] Despite their decreasing incidence, PHCs account for a significant portion of postoperative mortality following cardiac surgery, as high as 8% of 30-day mortality following repair of total anomalous pulmonary connection.[13]

Risk factors for PHC following cardiac surgery include the age of the patient, the type of lesion, and abnormalities in pulmonary vascular development in patients with congenital heart disease (CHD). High-risk lesions for PHC postoperatively include those with systemic PAPs: truncus arteriosus or aortic origin of PA, and those with left atrial or pulmonary venous hypertension, including obstructed total anomalous pulmonary venous return and hypoplastic left heart syndrome with intact atrial septum.[14,15] Risk of PHC after repair for these lesions increases if repair is delayed beyond the neonatal period. Importantly, PHC can occur despite a technically successful surgical repair. General principles governing those patients at high risk for postoperative PHC include patients with labile pulmonary vascular tone or decreased pulmonary vascular cross-sectional area due to developmental hypoplasia of the pulmonary vasculature. Further, the RV in patients who previously had significant shunting is particularly vulnerable for failure postoperatively after shunt closure due to loss of "pop-off" with right-to-left shunting. Recognizing these risks preoperatively will lead to appropriately aggressive intervention to prevent and treat PHCs should they occur. Such aggressive intervention is imperative, as incompletely treated crises herald clustering and longer duration of subsequent PHC.[5,6]

POST-CARDIOPULMONARY BYPASS PHYSIOLOGY AND PHC

Following cardiopulmonary bypass, patients are at particular risk for life-threatening PHC. Endothelial cell dysfunction is exacerbated by cardiopulmonary bypass, cardioplegic arrest, and hypothermia.[11,16] Although exposure of blood to artificial membranes causes an inflammatory response, this alone does not account for endothelial dysfunction post bypass.[17,18] In postoperative PH, it is difficult to distinguish among causative physiologic insults, including cardiopulmonary bypass, circulatory arrest, and hypothermia. However, improved operative techniques including decreased duration of cardiopulmonary bypass, modified ultrafiltration, and myocardial protection strategies have together significantly decreased incidence of postoperative PH. In contrast to extensive investigations aimed at preserving myocardial function, there has been little focus on preservation of pulmonary vascular function during cardiopulmonary bypass. Blood flow from the vasa vasorum via the bronchial circulation prevents infarction of the pulmonary vasculature during cardiopulmonary bypass, but is inadequate to prevent endothelial dysfunction.[16,19] Following separation from cardiopulmonary bypass, reperfusion injury may further damage the endothelium.

GENERAL PRINCIPLES OF PERIOPERATIVE MANAGEMENT

Pulmonary hypertensive crises may be provoked by acidosis, agitation, pain, hypoxia, or tracheal suctioning. Thus, both the cardiac anesthesiologist and the cardiac intensivist must meticulously manage these patients during the perioperative period to avoid provoking PHC. Principles of management for these patients are routed in best practices for any patient undergoing surgery, but the reactive pulmonary vascular bed in at-risk patients will be particularly unforgiving of physiologic derangements that are otherwise transiently well tolerated.

Respiratory management in these patients must first be focused on achieving adequate lung volumes. Titrating ventilator management to maintain functional residual capacity is especially crucial in patients at risk for PHC, as both underventilation and overdistension will be poorly tolerated.[20] Additionally, gas exchange must be carefully managed to avoid acidosis. Animal studies have demonstrated that a decrease in pH from 7.4 to 7.3 leads to a 23% increase in pulmonary vascular resistance (PVR) in lambs with PH.[21] Even mild hypoxia can precipitate a PHC, due to exaggerated hypoxic pulmonary vasoconstriction. Similarly, given effects on PVR, both pulmonary edema and atelectasis should be avoided if possible. Postoperative patients are at particularly high risk of respiratory derangements, as alveolar edema, ventilation/perfusion mismatch, and bronchoconstriction have been all been demonstrated following cardiac surgery.[22,23] Should PHC occur, brief hyperventilation and concomitant sodium bicarbonate administration can be utilized to raise pH immediately,[24] but this strategy should be used with care due to the risk for lung injury. Further, this should be avoided as long-term management owing to the effects of alkalosis of decreasing cerebral blood flow and raising systemic vascular resistance (SVR).

In addition to judicious ventilator management, the perioperative teams caring for patients with PH must have a comprehensive plan for sedation and analgesia. As noted, pain, anxiety, and agitation can each provoke a PHC. Thus, a preemptive plan to avoid such events is crucial for postoperative care of the patient at risk for PHC. In neonates, high-dose fentanyl has been specifically demonstrated to attenuate the stress response to surgery.[25,26] For all high-risk patients, continuous fentanyl and muscle

relaxants should be part of the routine management on the first postoperative night. Special attention by both nursing and respiratory therapist staff is needed during endotracheal suctioning, as this may trigger a PHC; patients may require premedication with fentanyl prior to tracheal suctioning. Adequate analgesia and anxiolysis in high-risk patients requires careful attention of the entire medical care team, and goals for deep sedation (State Behavioral Scale -1 to -2) during the first postoperative day should be clearly communicated by the ICU physician. However, the side effects of systemic hypotension and decreased cardiac output from sedative agents, especially benzodiazepines, need to be considered and judicious titration of continuous infusions of short-acting agents is preferable.

SPECIFIC THERAPIES

The ideal vasoactive agent to treat PHC would be one that maximizes pulmonary vasodilation, minimizes systemic hypotension, augments RV function, and increases cardiac output. Currently, there is not one single drug that satisfies all requirements, but these ideals should govern choice of pharmacologic intervention. In patients whose pulmonary vascular beds are responsive, inhaled pulmonary vasodilator therapies lower PVR without concomitant lowering of SVR, and such agents are thus mainstays of PHC therapy.

For this reason, the AHA/ATS pediatric PH guidelines recommend inhaled nitric oxide (iNO) as a first-line agent in treating and preventing perioperative PHC.[2] At low doses, iNO improves ventilation/perfusion matching, decreases the intrapulmonary shunt fraction, and often increases the systemic arterial saturation.[27] Further, a randomized controlled trial using iNO in the postoperative period after CHD surgery demonstrated decreased time to meet criteria for extubation and decreased incidence of PHC.[28] Moreover, iNO use postoperatively is associated with decreased mortality after repair of atrioventricular septal defects.[29] A number of prospective studies and case series have demonstrated benefits of iNO therapy in pediatric patients with PH postoperatively.[11,30-33] The abrupt withdrawal of iNO therapy or discontinuation of its use before resolution of pulmonary vascular reactivity is associated with rebound PH and may precipitate a PHC. A randomized, controlled, blinded study has demonstrated that the phosphodiesterase type 5 (PDE-5) inhibitor sildenafil abolishes rebound with iNO withdrawal and facilitates shorter times to extubation and decreased ICU length of stay.[34] Dipyridamole is also effective at diminishing rebound.[35]

An alternative to iNO therapy is inhaled prostacyclin analogue treatment. Inhaled iloprost is an equally effective pulmonary vasodilator compared with iNO in children with CHD and PHC.[36,37] An adult, randomized, crossover trial demonstrated inhaled prostacyclin was as efficacious as iNO,[38] but the analogous study has not yet been performed in pediatrics. Further, inhaled prostacyclins may be useful adjunctive agents in patients without adequate pulmonary vasodilation to iNO therapy. Caution is warranted with inhaled iloprost administration as it may worsen reactive airway symptoms.[39]

In addition to its use in preventing rebound PH with iNO cessation, sildenafil has been demonstrated to be useful as a stand-alone pulmonary vasodilator. Intravenous sildenafil in a double-blind, placebo-controlled trial has been shown to reduce PAP and shorten time to extubation and ICU stay without adverse events in children after cardiac surgery.[12] Compared with iNO, sildenafil has a greater pulmonary vasodilatory response but increased intrapulmonary shunt in postoperative cardiac patients.[40] However, this increase in intrapulmonary shunt was not associated with impaired oxygenation in these patients. Sildenafil, either enterally or intravenously delivered, should be used cautiously if concomitant nitrovasodilators and other phosphodiesterase inhibitors are being used (such as milrinone) because profound systemic hypotension may occur.

In addition to pulmonary vasodilators, other vasoactive agents are useful adjuncts to support and recover the patient with PHC. "Inodilator" drugs—milrinone, levosimendan, and nesiritide—are both inotropic and lusitropic agents as well as pulmonary and systemic vasodilators. These may be useful adjuncts to specific pulmonary vasodilator therapy if the patient does not develop systemic hypotension.[41,42] In particular, these drugs must be used with caution in patients who may have elevated RV pressures, as systemic hypotension puts them at risk for coronary ischemia. Vasopressin is a pulmonary vasodilator and systemic vasoconstrictor, which may have a place in the treatment of systemic hypotension associated with PH.[43,44] Vasopressin may be particularly useful in RV failure without LV dysfunction; increased afterload on the left ventricle may restore interventricular septal position (shift rightward) and result in more favorable LV and RV geometry. Additionally, increased systemic pressure will limit RV coronary ischemia.

MECHANICAL SUPPORT AND SURGICAL STRATEGIES

In patients unresponsive to vasodilator therapies, other options may be considered such as flap valve closure of the shunt or postoperative creation of a right-to-left shunt to permit transient right-to-left shunting and RV decompression. In high-risk patients, especially after cardiac transplantation with an unprepared donor right ventricle, it is judicious to prepare preoperatively for temporary mechanical support for the right ventricle as a postoperative bridge to recovery.[45-47]

CONCLUSION

Perioperative management of the pediatric patient with PH or the patient at risk for increased pulmonary vascular reactivity requires careful preoperative planning and a comprehensive and meticulous approach to sedation, analgesia, mechanical ventilation, pulmonary vasodilation, and vasoactive medications. This strategy is best executed with cardiac anesthesiologist and pediatric cardiac intensivists experienced in the perioperative management of patients with PH, in consultation with a pediatric PH expert. Perioperative management is focused on preventing and treating PHCs, which may lead to acute and fatal RV failure. PHC may best be prevented by surgical considerations

Table 1. Preoperative Anesthesia Evaluation	
Recommendations From the AHA/ATS Guidelines on Pediatric PH[2]	
Careful preoperative planning, consultation with cardiac anesthesia, and plans for appropriate postprocedural monitoring are recommended for pediatric patients undergoing surgery or other interventions	Class I; Level of Evidence C
Elective surgery for patients with pediatric PH should be performed at hospitals with expertise in PH and in consultation with the pediatric PH service and anesthesiologists with experience in the perioperative management of children with PH	Class I; Level of Evidence C
General postoperative strategies for avoiding PHC, including avoidance of hypoxia, agitation, and acidosis, should be used in children at high risk for PHCs	Class I; Level of Evidence B
Induction of alkalosis can be useful for treatment of PHCs	Class IIa; Level of Evidence B
Administration of opiates, sedatives, and muscle relaxants is recommended for reducing postoperative stress response and the risk for or severity of PHCs	Class I; Level of Evidence B
In addition to conventional postoperative care, iNO and/or inhaled PGI_2 should be used as the initial therapy for PHCs and failure of the right side of the heart	Class I; Level of Evidence B
Sildenafil should be prescribed to prevent rebound PH in patients who have evidence of a sustained increase in PAP on withdrawal of iNO and require reinstitution of iNO despite gradual weaning of iNO dose	Class I; Level of Evidence B
In patients with PHCs, inotropic/pressor therapy should be used to avoid RV ischemia caused by systemic hypotension	Class I; Level of Evidence B
Mechanical cardiopulmonary support should be provided in refractory cases	Class I; Level of Evidence B

including early intervention, judicious strategies for cardiopulmonary bypass and ultrafiltration, and consideration of valved septal defect closure in selected high-risk patients. In the ICU, medical management to prevent PHC centers on avoiding hypoxia, acidosis, pain, and agitation. Some patients clearly benefit from pulmonary vasodilators, including iNO, inhaled prostacyclins, and PDE-5 inhibition. Finally, the critical care and cardiology teams caring for patients with PH postoperatively must have a low threshold to investigate for residual or overlooked cardiac lesions that must be addressed in a timely fashion. Patients with PHC and RV failure refractory to medical management may require mechanical support with extracorporeal or implantable devices. Over the past several decades, postoperative mortality due to PHC has declined markedly, but perioperative management of pediatric patients with PH remains a clinically challenging enterprise requiring careful attention of all members of the health care team.

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