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Early postoperative care of patients with pulmonary hypertension associated with congenital cardiac disease

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THE FUNCTIONAL AND STRUCTURAL STATE OF THE pulmonary vascular bed plays a pivotal role in the presentation and outcome of the child with congenital cardiovascular disease. It is in the immediate postoperative period that the child is most vulnerable to a sudden or sustained increase in pulmonary vascular resistance. Following surgery for congenital cardiac disease, pulmonary vascular reactivity is heightened, and vasospastic stimuluses may result in sudden increases in pulmonary arterial pressure and resistance, resulting in acute right-sided cardiac failure, tricuspid regurgitation, systemic hypotension, myocardial ischaemia, and increased resistance in the airways. These episodes, called pulmonary hypertensive crises, may be lethal events. Mildly stimulating events can precipitate similar crises, and the crises tend to last longer and cluster.[1,2]

The pathophysiology of such events is complex, and incompletely understood by the analysis or measurement of a single vasoactive mediator. Postoperative pulmonary hypertension represents a complex interplay between the preoperative condition of the patient, particularly age at repair, type of lesion, and presence of a syndrome, and the inevitable disruption in the environment of hormones and vasoactive peptides that results from cardiac surgery. Important contributors to the milieu of enhanced vasoconstriction are cardiopulmonary bypass, hypothermia, and circulatory arrest. Residual cardiac lesions, and the sequels of the response to stress, hypoxia, and metabolic and respiratory acidosis, may all contribute additional imbalances favouring pulmonary vasoconstriction. Postoperative sequels such as right and left ventricular and atrioventricular valvar dysfunction will be important in determining how well the postoperative elevation in pulmonary vascular resistance is tolerated. Currently, dysfunction of endothelial cells, present preoperatively and exacerbated by perioperative influences, is considered a unifying hypothesis to account for many postoperative sequels.[3–5] Improvements in surgical and perioperative technique, however, and perhaps most importantly the trend towards performing surgical repair early, has resulted in a marked decrease in the incidence of symptomatic postoperative pulmonary hypertension in countries with privileged patterns of referral. The incidence of postoperative pulmonary hypertensive events decreased from 31% in the period from 1980 through 1984, to 6.8% before the routine use of inhaled nitric oxide.[6] Series reflective of contemporary practice suggest that pulmonary hypertension complicates 2.0% of patients undergoing congenital cardiac surgery, with crises occurring in 0.75%.[7] The mortality in those suffering a crisis, nonetheless, remains high, at 20%, and pulmonary vascular disease is identified as a major contributor to length of stay in hospital, and the need for prolonged mechanical ventilation.[6–9]

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Predicting risk factors for symptomatic postoperative pulmonary hypertension

It is difficult to predict which patients will experience pulmonary hypertensive crises, or right ventricular failure with low cardiac output postoperatively. Patients who experience crises usually have reactive pulmonary vascular beds. Patients dying from pulmonary arterial hypertensive crises have increased muscularization of the small pulmonary arterioles without changes of irreversible pulmonary vascular disease.[1] Patients who undergo surgical repair with fixed elevations of pulmonary vascular resistance may not experience crises, but are at risk of right ventricular failure, especially if there is postoperative deterioration of atrioventricular valvar regurgitation and right ventricular function. Most patients with lesions produced by increased arterial flow to the lungs at high pressure but low pulmonary vascular resistance will not require postoperative therapy for pulmonary arterial hypertension.[7] There is, therefore, considerable value in attempting to select high-risk patients for special monitoring, or even prophylactic therapy. Stratification of risk is mainly clinical, because lung biopsy and cardiac catheterization are not performed routinely prior to cardiac surgery. Patients with clinical or echocardiographic signs of an elevated pulmonary vascular resistance may benefit from preoperative cardiac catheterization to assess risk and operability. Preoperative lung biopsy alone has a limited capacity to define operability compared with haemodynamic assessments. Patients with extracardiac syndromes, especially Down's syndrome, seem to be at increased risk of pulmonary hypertensive events.[7] Patients with pulmonary venous or left atrial hypertension, whether following pulmonary venous surgery or from abnormalities of the left heart such as hypoplasia, mitral regurgitation, or stenosis, have extremely reactive pulmonary vasculature. In general, for all lesions, early repair appears to confer benefit on postoperative pulmonary vascular complications. This applies to those with common arterial trunk, atrioventricular septal defect, ventricular septal defect, and transposition with ventricular septal defect.[7,10,11] Patients with aortic origin of a pulmonary artery, common arterial trunk, and functionally univentricular lesions with unrestrictive pulmonary blood flow have markedly reactive pulmonary vascular beds in the postoperative period, especially if intervention is delayed beyond the age of 2 months.[10,12] All patients with problematic postoperative pulmonary hypertension should undergo investigation to exclude residual or overlooked left-to-right intracardiac shunts. In general, there is consensus that early repair of uncomplicated left to right shunt lesions in the first 6 months of life reduces the risk of postoperative pulmonary hypertension in patients with high-risk diagnoses. Thus a profile of a high-risk patient might be a 14-month-old child with Down's syndrome, an unbalanced atrioventricular septal defect, but not sufficiently unbalanced to preclude biventricular repair. At preoperative cardiac catheterization, the pulmonary vascular resistance index is calculated at 6.0 Wood units $\cdot$ m^2. The patient is reactive to inhaled nitric oxide and hyperoxia. The lowest pulmonary vascular resistance index is 1.5 Wood units $\cdot$ m^2, with a shunt of more than 5 to 1 from left to right. The child undergoes repair, and postoperatively there is insufficiency and stenosis of the newly reconstructed left atrioventricular valve, and regurgitation across the right atrioventricular valve.

The use of pulmonary arterial catheters

If it is difficult to predict who will develop symptomatic postoperative pulmonary hypertension, the question may be asked whether all patients should have a pulmonary arterial catheter inserted to monitor pulmonary arterial pressure. The use of pulmonary arterial lines is associated with low morbidity, particularly when used in an institution experienced in their management. The adverse event associated with short-term insertion of such lines is the risk of bleeding after removal, especially in the presence of elevated pulmonary arterial and right ventricular pressures.[13] The risk may be mitigated by placing the line through the right atrium, or the muscular right ventricular infundibulum. The incidence of symptomatic pulmonary arterial hypertension, however, is now so low that it may no longer be justified to place a line in all patients undergoing repair of high pressure or high flow lesions, or both. Pulmonary arterial lines focus the attention of caregivers on the pulmonary arterial pressure. This may, paradoxically, delay progress through the cardiac intensive care unit, as there is a tendency to react to each fluctuation in pulmonary arterial pressure. For the evaluation of new postoperative therapies, nonetheless, whether specific for the pulmonary vasculature or otherwise, pulmonary arterial lines are essential to provide data on cardiac output, as well as for the calculation of pulmonary vascular resistance. Often the decision to place a pulmonary arterial line is made by necessity in the operating room in presence of elevated pulmonary arterial pressures, with mean pressures greater than 25 mmHg or more than 50 to 60% of systemic pressure, or if there is the need for specific

pulmonary vasodilator therapy to separate from cardiopulmonary bypass. Echocardiography accurately predicts right ventricular and pulmonary arterial pressures through interrogation of the velocities of tricuspid regurgitation and pulmonary insufficiency. Imaging of the right ventricle and evaluation of potential residual lesions is also useful. Echocardiographic assessment in the sick unstable postoperative patient with limited windows, nonetheless, is operator-dependant, and while echocardiographic assessment is extremely valuable, it may not be feasible in off-hours or during a crisis. After the crisis has resolved, pulmonary arterial pressures may be misleadingly normal. Right ventricular pressure may not predict pulmonary arterial pressure if there is obstruction of the right ventricular outflow tract, or in the right or left pulmonary arteries. Echocardiography, together with monitoring of mixed venous saturations and central venous pressures, nonetheless, are powerful tools in the assessment of pulmonary hypertensive patients. The use of small implantable devices that monitor pulmonary arterial pressure have not been used extensively in this population. If the patient is at risk for sustained pulmonary hypertension, and prolonged postoperative therapy is likely, these devices may have a place in monitoring.

The management of postoperative pulmonary hypertension

There are no clear measurements of pulmonary arterial pressure or pulmonary vascular resistance that indicate a need for postoperative therapy. Consensus would indicate that patients with postoperative pulmonary hypertension with mean arterial pressures greater than 25 mmHg, or more than 50 to 60% of systemic pressure, associated with signs of low cardiac output or its surrogates, are concerning and indicative of the need to consider specific therapy. Prevention of pulmonary hypertensive crises is a worthy goal of treatment, but elusive because of the difficulty in predicting who will suffer a crisis, along with the rarity of crises in contemporary practice.

Management of symptomatic pulmonary hypertension involves avoiding or mitigating vasoconstrictive triggers, and the use of pulmonary vascular specific therapies. It has been observed that pulmonary hypertensive crises may be triggered by stressful stimuluses, including tracheal suctioning, pain, and anxiety. The use of fentanyl at high doses to suppress the response to stress in neonates undergoing surgery has been established in randomized controlled studies.[14,15] It has become common practice to use continuous infusions of fentanly combined with muscular relaxation through the first postoperative night. Supplemental doses of fentanyl prior to endotracheal suctioning will suppress the pulmonary vasoconstrictor response providing suction is performed without causing hypoxia or hypercarbia.

Hypoxia is a potent pulmonary vasoconstrictor, and should be avoided in high-risk patients. There is less evidence to suggest that hyperoxia is as potent a vasodilator as in the preoperative patient. Mechanical ventilation with high concentrations of oxygen for prolonged periods should be avoided. Avoiding hypoxia is extremely important, and ventilation with supplemental oxygen is used often to prevent triggering pulmonary vasoconstriction. Acidosis, whether respiratory or metabolic, is a powerful vasoconstrictor, and alkalosis is as effective a pulmonary vasodilator as inhaled nitric oxide.[16,17] Hyperventilation, or the infusion of sodium bicarbonate, is an extremely useful strategy in the immediate management of pulmonary hypertensive crises while more specific strategies are put in place. There are, however, drawbacks to prolonged induction of therapeutic alkalosis. The disadvantages of prolonged high mechanical ventilator settings include pulmonary barotraumas, and reduction of cardiac output, especially in the face of poor right ventricular function. Infusions of sodium bicarbonate decrease cardiac output and cerebral blood flow and increase central venous pressure and systemic vascular resistance. Avoiding acidosis is as important as avoiding hypoxia to prevent pulmonary vasoconstriction, and most would advocate a pH of greater than 7.4 in patients at risk, or 7.5 in refractory pulmonary arterial hypertension. In patients with a surgically created right-to-left "pop off" and hypoxemia, some would advocate adjusting the haemoglobin to a level commensurate with systemic arterial saturations of oxygen.

Inhaled nitric oxide has become the accepted therapy for postoperative pulmonary arterial hypertension. Its advantages include the ease of delivery, minimal side effect profile, and specificity for the pulmonary vascular bed. Nitric oxide is derived from endothelial cells, and activates guanylate cyclase to cause vascular vasodilation through a mechanism dependent on cyclic guanosine monophosphate. Nitric oxide is inactivated rapidly by haemoglobin. If inhaled, it causes selective pulmonary vasodilation because of rapid inactivation by haemoglobin before transit through the pulmonary vascular bed. Thus, unlike non-specific pulmonary vasodilators, nitric oxide decreases the intrapulmonary shunt fraction, and will often improve systemic arterial oxygenation.

When inhaled, nitric oxide has been shown in many studies to be an effective pulmonary vasodilator

in postoperative patients with congenital cardiac disease.[3,16,18–22] The doses have ranged from 2–80 parts per million.[19] There does not appear to be any clear benefit from doses in excess of 10–20 parts per million for routine use. It is often forgotten that the measured levels represent the concentration at the proximal endotracheal tube, and may not reflect the dose delivered to the alveolus. Side effects, such as methaemoglobinemia, are rare with doses less than 80 parts per million even for prolonged periods. It is prudent, however, to measure levels of methaemoglobin daily while nitric oxide is administered. Commercially available devices for delivery, and use of ventilators without mechanical bellows, have reduced concerns with nitric dioxide and issues surrounding gas scavenging.[23,24] Thus, inhaled nitric oxide may reduce mortality after repair of atrioventricular septal defects.[22] In a randomised double blind controlled trial, treatment with nitric oxide reduced pulmonary arterial hypertensive crises and shortened the time to reach criterions for extubation. The number of days requiring ventilation, however, were not significantly different, perhaps in view of the prolonged protocol used for weaning to avoid rebound pulmonary hypertension.[25] Another randomized and controlled study failed to show an advantage when nitric oxide was used against a background of presumably hyperoxic alkalosis.[26]

Rebound pulmonary hypertension has been described upon rapid withdrawal of nitric oxide, or withdrawal prior to resolution of pulmonary vascular constriction.[27,28] Rebound may result in considerable hemodynamic instability, ventilatory difficulty, and hypoxia. It requires reinstitution of inhaled nitric oxide, or adjunctive therapies such as hyperoxic alkalosis. The effects can be minimized by slow weaning, in particular the last 5 parts per million. The need, however, for prolonged inhalation of nitric oxide may delay tracheal extubation, and transition to oral or intermittently inhaled pulmonary vasodilators may be considered at this point in therapy. A randomized controlled blinded study has demonstrated that oral sildenafil, an inhibitor of type 5 phosphodiesterase, given at 0.3 to 0.5 mg/kg, results in abolition of rebound, and facilitates shorter times to extubation and in intensive care.[29] This strategy also may be useful in transitioning patients to chronic therapy.[30] Despite attention to adjunctive measures, and the use of inhaled nitric oxide, there are patients whose pulmonary arterial hypertension is refractory to therapy. Sildenafil given intravenously or orally, and inhaled iloprost and intravenous prostacyclin, may be used to augment an insufficient pulmonary vasodilatory response to inhaled nitric oxide.

Drugs, which augment cardiac output as well as dilate the pulmonary vascular bed, such as milrinone, levosimendan, and nesiritide may be useful adjuncts providing the patient is tolerant of systemic vasodilation. Vasopressin is a pulmonary vasodilator and systemic vasoconstrictor, and may be useful in the management of systemic hypotension associated with pulmonary hypertension. Strategies to prevent pulmonary hypertension postoperatively by initiating therapies prior to or during cardiopulmonary bypass such as citrulline to augment nitric oxide production, sildenafil to increase cyclic guanosine monophosphate levels, or endothelin receptor antagonists to diminish the effects of elevated endothelin 1 levels, are promising ideas and potentially fruitful areas of research.[31,32]

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