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EDITORIAL

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To inhale or to nebulize: Treating the pulmonary vascular bed post-operatively in children with congenital heart disease

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Controlling the pulmonary vascular bed is key to the early management of infants with congenital heart disease (CHD) who have potential for excessive pulmonary blood flow or obstruction to blood egress from the lungs. Timing of surgical management has evolved to ensure that the hemodynamic consequences of excessive pulmonary blood flow or pulmonary venous hypertension do not translate into irreversible elevation of pulmonary vascular resistance through remodeling of the pulmonary vascular bed, characterized by smooth muscle cell hypertrophy, pulmonary vasoconstriction and impaired endothelium-dependent pulmonary vasodilation. However, even with appropriately timed surgery, the pulmonary vascular bed remains reactive to cardiopulmonary bypass, which precipitates activation of a systemic inflammatory response with associated endothelial cell injury and inhibition of nitric oxide (NO) production and increase in endothelin levels [1]. The post-operative response may vary from clinically irrelevant elevation in right ventricular pressures to pulmonary hypertensive (PH) crises characterized by abrupt pulmonary vasoconstriction leading to hypotension, hypoxia and associated with increased mortality [2]. High-risk pre-operative anatomic subtypes as well as preventative post-operative strategies for those at risk have been defined [2], and as a consequence the incidence of PH crises have declined significantly from over 30% in the 1980's to less than 1% in contemporary series [3], although this may vary depending on the definitions and treatment protocols used. Mortality, however associated with severe post-operative PH remains high at approximately 10% [3]. Inhaled NO (iNO), mediates selective pulmonary vasodilation by stimulating production of cGMP and both retrospective [4], and randomized trials [5] have demonstrated fewer post-operative pulmonary hypertensive crises and significant decreases in mortality, although these results have not been substantiated by a systematic review [6]. Nearly all studies however have demonstrated efficacy in reducing elevated pulmonary artery pressures in the post-operative infant undergoing surgery for CHD and consequently iNO has become the standard therapy for post-operative PH in this setting. Timing of introduction of iNO may vary between institutions with some employing an early post-operative "prophylactic" approach in those at risk and others reserving iNO for those with proven severe post-operative PH. Concerns have been raised however regarding potential for oxidation of hemoglobin to methemoglobin by iNO. This may lead to reduced oxygen carrying capacity of hemoglobin as methemoglobin in unable to reversibly bind oxygen and levels over 10% in infants have been associated with cyanosis. Rebound PH has also been described with rapid weaning due to a down-regulation of endogenous NO production [7]. For these reasons comparable alternative therapies for PH in the post-operative CHD patient have been sought. Iloprost is an analog of prostacyclin, which through a cAMP dependent pathway leads to decreased levels of cytosolic calcium and selective pulmonary vasorelaxation. Previous studies assessing iloprost in CHD patients with post-operative PH have demonstrated effective reduction in mean

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pulmonary artery pressures [8], however previous comparative studies with iNO have not suggested superior efficacy of one agent over the other in reducing post-operative pulmonary pressures [9, 10].

In this edition of the journal, Kirbas et al. [11], report on the randomized use of iNO versus nebulized iloprost in 16 children (mean age of 36 months) with severe PH undergoing intracardiac repair of CHD. All patients were deemed to have PH as defined by pulmonary artery to aortic pressure ratios > 0.7 although it is not clear whether this definition was applied pre- or post-operatively. Only patients > 24 months underwent pre-operative catheterization and indexed pulmonary resistances were not reported. Both agents were commenced immediately after cardiopulmonary bypass. iNO was administered at 20 parts per million with nebulized iloprost dosage of 0.5 μg/kg every 90 min mirroring doses used in previous studies [10]. In similar cohorts of patients both agents produced significant reductions in pulmonary artery pressures and pulmonary artery to systemic pressure ratios over the 3 days of monitoring. Cardiac output increased significantly in both groups but mirroring previous studies, superior efficacy of either agent over the other was not demonstrated with respect to any of the measured variables. No PH crises were reported in either group with no significant adverse effects seen in either cohort.

This study confirms previous reports suggesting comparable efficacy of both agents in treating post-operative PH. The paper provides a template on how to identify and approach high-risk patients, and highlights optimal peri- and post-operative strategies to limit the impact of cardiac surgery on the pulmonary vascular bed. Both filling pressures and pulmonary arterial and systemic pressures should be continuously monitored to herald acute elevations in pulmonary vascular resistance so that pulmonary hypertensive crises may be dealt with quickly. As to which agent should be used, we are probably no wiser than before and it appears to come down to a matter of choice. Both agents are delivered locally with less systemic effects than intravenous agents. It is true that iNO requires a somewhat complicated delivery system, however many units have mastered this technique and it may be that the optimal approach is the one that is established. Certainly switching from one agent to another without a clear understanding of dosing and delivery is not advised. Both agents may be used simultaneously however this has not demonstrated increased potency over either substance alone [9]. Other issues relating to cost are not to be underestimated with reports suggesting daily administration of iNO is 20 times more expensive than inhaled iloprost [8]. In a unit performing 300 open-heart surgeries a year, with 5% of these patients deemed to be high-risk requiring an average of 3 days post-operative therapy, this would equate to an extra 100,000 USD per annum! Other issues relating to potential risks with iNO including methemoglobinemia, and rebound PH as discussed above also need to be considered. Issues plaguing iloprost use in idiopathic pulmonary arterial hypertension such as inconvenient dosing schedules and potential for bronchoconstriction are not relevant to the acute care of intubated post-operative children. And so we are left with a choice based not on efficacy but on cost and convenience. If further larger studies corroborate the existing data, it may be hard to justify the extra cost involved in persisting with iNO.

Conflict of interest: none declared

References

1. Komai H, Adatia IT, Elliott MJ, de Leval MR, Haworth SG. Increased plasma levels of endothelin-1 after cardiopulmonary bypass in patients with pulmonary hypertension and congenital heart disease. J Thorac Cardiovasc Surg, 1993; 106: 473–478.
2. Bando K, Turrentine MW, Sharp TG et al. Pulmonary hypertension after operations for congenital heart disease: Analysis of risk factors and management. J Thorac Cardiovasc Surg, 1996; 112: 1600–1607.
3. Lindberg L, Olsson AK, Jögi P, Jonmarker C. How common is severe pulmonary hypertension after pediatric cardiac surgery? J Thorac Cardiovasc Surg, 2002; 123: 1155–1163.
4. Miller OI, Tang SF, Keech A et al. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: A randomised double-blind study. Lancet, 2000; 356: 1464–1469.
5. Journois D, Baufreton C, Mauriat P et al. Effects of inhaled nitric oxide administration on early postoperative mortality in patients operated for correction of atrioventricular canal defects. Chest, 2005;128: 3537–3544.
6. Bizzarro M, Gross I. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database Syst Rev, 2005; 4: CD005055.
7. Miller OI, Tang SF, Keech A, Celermajer DS. Rebound pulmonary hypertension on withdrawal from inhaled nitric oxide. Lancet, 1995; 346: 51–52.
8. Limsuwan A, Wanitkul S, Khosithset A, Attanavanich S, Samankatiwat P. Aerosolized iloprost for postoperative pulmonary hypertensive crisis in children with congenital heart disease. Int J Cardiol, 2008;129:333–338.
9. Rimensberger PC, Spahr-Schopfer I, Berner M et al. Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: Vasodilator capacity and cellular mechanisms. Circulation, 2001; 103: 544–548.
10. Loukanov T, Bucsenez D, Springer W et al. Comparison of inhaled nitric oxide with aerosolized iloprost for treatment of pulmonary hypertension in children after cardiopulmonary bypass surgery. Clin Res Cardiol, 2011; 100: 595–602.
11. Kirbas A, Yalcin Y, Tanrikulu N, Gurer O, Isik O. Comparison of inhaled nitric oxide and aerosolized iloprost in pulmonary hypertension in children with congenital heart surgery. Cardiol J, 2012; 19: 387–394.