Pulmonary hypertension in pediatric heart transplantation

Robert E. Shaddy*

*Present address: Cardiology, Suite 1500, Primary Children’s Medical Center, 100 North Medical Drive, Salt Lake City, UT 84113, USA. Tel.: +1-801-588-2600; fax: +1-801-588-2612.

Abstract

Pulmonary hypertension can pose a significant problem in the management of children with congestive heart failure. Assessment of pulmonary artery anatomy, pressures and (when possible) pulmonary vascular resistance is critically important in the evaluation of these children when they are under consideration for heart transplantation. Severe, fixed elevation of the pulmonary vascular resistance is a contraindication to heart transplantation because of concerns of acute post-transplant donor right ventricular failure. However, even modest degrees of pulmonary hypertension can complicate the post-operative management of pediatric heart transplant recipients. This review will provide information regarding the recognition, diagnosis, and pre-operative and post-operative management of pulmonary hypertension in patients under consideration for heart transplantation. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Many single center and multicenter studies assessing risk factors for heart transplantation have found pre-transplant pulmonary hypertension to be a significant risk factor for early or late mortality after heart transplantation [1–9]. Pulmonary hypertension can be evaluated in several ways including pulmonary artery pressures, pulmonary vascular resistance, and transpulmonary gradients. In addition, it has long been known that not only are baseline values of these measurements important, but response to vasodilators or other interventions may be equally or even more important. Furthermore, in some children with complex congenital heart disease, it is virtually impossible to calculate accurate measurements of pulmonary artery pressures and resistances because of anatomic constraints. This review will provide information regarding the recognition, diagnosis, and pre-operative and post-operative management of pulmonary hypertension in patients under consideration for heart transplantation.

2. Pre-transplant evaluation

Assessment of pulmonary artery anatomy, pressures and (when possible) pulmonary vascular resistance is critically important in the evaluation of children and adults under consideration for heart transplantation. Severe, fixed elevation of the pulmonary vascular resistance is a contraindication to heart transplantation because of concerns of acute post-transplant donor right ventricular failure. In pediatric and adult heart transplantation both elevated transpulmonary pressure gradient (the difference between mean pulmonary artery pressure and mean left atrial or pulmonary capillary wedge pressure) and elevated pulmonary vascular resistance have been identified as risk factors for early mortality after heart transplantation [10–12]. A recent multi-institutional analysis of risk factors for mortality in children > 1
year of age at the time of transplantation did not find elevated pulmonary vascular resistance to be a risk factor [13]. However, the most likely reason for this is that the current selection criteria exclude those patients with significantly elevated non-reactive pulmonary vascular resistance [14].

The etiology of the pulmonary hypertension varies. In some patients with severe left or systemic ventricular dysfunction, left atrial hypertension may be the cause. In this situation, patients with left atrial hypertension may have an elevated pulmonary vascular resistance because the cardiac index is low, the pulmonary vasculature is constricted, or there is fixed pulmonary vascular disease with a reduction in recruitable lung vessels [15]. Since significant variation in the degree of pulmonary hypertension (both positive and negative) can occur over time, it is important to monitor the degree of pulmonary hypertension serially [16,17]. Although this is generally followed serially by cardiac catheterization, echocardiography may also be useful for determining the need for and timing of repeat right heart catheterizations for assessing the progress of pulmonary hypertension [18]. Preoperative assessment of patients with pulmonary hypertension then is directed toward increasing cardiac output with drugs such as dobutamine or enoximone, or combining vasodilation and an increase in cardiac output with drugs such as nitroprusside, prostaglandins, nitroglycerin, isosorbide dinitrate, and milrinone. Previous studies have compared the effects of various pharmacologic agents in determining reversibility of pulmonary hypertension in patients undergoing evaluation for heart transplantation. Early reports demonstrated the efficacy of prolonged therapy with amrinone in reducing pulmonary hypertension and allowing for safe orthotopic heart transplantation [19,20]. Pre-transplant response of pulmonary vascular resistance to intravenous nitroprusside or nitroglycerin has been shown to be predictive of post-transplant pulmonary vascular resistance [12,21–23], although some have argued that it is not predictive of long-term outcome [24]. One study demonstrated similar beneficial effects of intravenous nitroglycerin and isosorbide dinitrate [25]. Some investigators have argued that prostaglandin E₁ is superior to nitroglycerin or nitroprusside in the pre-transplant evaluation of pulmonary vasoreactivity in adults with chronic heart failure [26]. Prostaglandin E₁ has also been used more chronically in adults with pulmonary hypertension awaiting heart transplantation in order to lower pulmonary vascular resistance [27]. Bolus milrinone has also been found to be safe and effective in assessing reversibility of pulmonary hypertension in adults [28]. One study compared the effects of nitroglycerin, nitroprusside, prostaglandin E₁, dobutamine, and enoximone in adults [29]. In this study, all drugs tested significantly increased cardiac output and decreased pulmonary vascular resistance. All drugs but dobutamine significantly lowered systemic and pulmonary artery pressures and wedge pressure. However, only prostaglandin E₁ significantly decreased transpulmonary pressure gradient. From this, the authors recommended that prostaglandin E₁ be considered to test reactivity in patients with severe pulmonary hypertension who are initially unresponsive to nitroglycerin or nitroprusside.

More recently, inhaled nitric oxide has been studied and employed to test for reactivity in patients with pulmonary hypertension under consideration for heart transplantation. Nitric oxide is a potent pulmonary vasodilator with minimal systemic effects. It appears to be more beneficial in those patients with elevated left atrial pressure (>15 mmHg) than in those with lower left atrial pressures [15]. One study compared the effects of different doses of inhaled nitric oxide with the intravenous vasodilators, sodium nitroprusside and prostacyclin [30]. In this study, pulmonary capillary wedge pressure actually increased and transpulmonary pressure gradient and pulmonary vascular resistance decreased with 20 ppm inhaled nitric oxide, with no further changes noted with higher doses of nitric oxide. In addition, the pulmonary/systemic vascular resistance ratio was only decreased by nitric oxide and not by the other vasodilators (Fig. 1). Inhaled prostacyclin has also been studied in the pre-transplant evaluation of adults with pulmonary hypertension and induces a selective pulmonary vasodilation that is comparable to nitric oxide [31]. The impact of undersizing or oversizing of donor hearts on survival in heart transplant recipients is controversial [32]. Although some early studies suggested that oversized donors in heart transplant recipients with pulmonary hypertension may be beneficial, more recent data suggests that oversizing donors does not appear to have a positive impact on survival in this situation [33–35].

Children outside of the neonatal period with a transpulmonary gradient >15–20 mmHg, or an indexed pulmonary vascular resistance >6 units with maximal vasodilation are usually not considered suitable candidates for heart transplantation alone. However, there are reports of children undergoing successful orthotopic heart transplantation with much higher pulmonary vascular resistances [14,36–39]. Pre-transplant pharmacologic interventions with oxygen, dobutamine, nitroprusside, amrinone, PGE₁, and inhaled nitric oxide have been shown to be predictive of post-transplant pulmonary vascular resistance in children [15,40]. Administration of these agents during right heart catheterization demonstrates the degree of acute reactivity of the pulmonary vasculature. However, in those with inadequate acute responses to
Fig. 1. Mean pulmonary artery (MPAP) and pulmonary capillary wedge (PCWP) pressures, systemic (SVR) and pulmonary (PVR) vascular resistances, PVR/SVR ratio, and transpulmonary pressure gradient (TPG), for basal state (C), nitric oxide (NO), inhalation with 20 ppm, sodium nitroprusside (SNP) infusion, and prostacyclin (PGI₂) infusion. Data presented are mean ± standard error of the mean. Statistical significance is shown for NO, SNP, and PGI₂ compared to basal state. *P < 0.05; **P < 0.01. Reproduced with permission from Kieler-Jensen et al. [30].

these agents, administration of these or other agents for a prolonged period of time (e.g. days to weeks) with repeat right heart catheterization may be necessary before seeing a beneficial effect. Gajarski et al. found that assessment of pulmonary vascular reactivity with PGE₁ may be a more important predictor of good outcome than absolute resistance indices [41]. In this study, there was also a higher incidence of post-transplant arrhythmias in those patients with elevated pulmonary vascular resistance index compared to those with normal pulmonary vascular resistance index. Inhaled nitric oxide in children has also been shown to be effective in assessing pulmonary vasoreactivity [15]. In one study, children with high left atrial pressures (> 15 mmHg) had a better response to 80 ppm nitric oxide than those with low left atrial pressure. In this study, three patients with Shone’s complex and high left atrial pressure actually showed an increase in left atrial pressure with nitric oxide, but also a concomitant decrease in pulmonary vascular resistance. This may be due to the effects of an increase in cardiac output and thus an increased left atrial pressure because of mitral stenosis, or noncompliance of the left atrium or left ventricle [15].

Special circumstances may exist whereby elevated pulmonary artery pressures may not be amenable to assessment using the usual pharmacologic interventions. Some patients with complex congenital heart disease, many of whom have undergone multiple surgeries, may have stenosed, hypoplastic, discontinuous or even atretic pulmonary arteries [3,42–44]. In this setting, it may be very difficult or even impossible to accurately assess pulmonary vascular resistance, and other factors such as transpulmonary gradients may be more predictive of outcome [3]. In newborns with ductal-dependent systemic perfusion, some degree of pulmonary hypertension invariably exists, but generally this is considered reversible for several months after birth [45]. Some of these infants may have restrictive interatrial communications that can be a significant risk factor for death after transplantation [45,46]. Children with restrictive cardiomyopathies also appear to be at increased risk for the development of severe, irreversible pulmonary hypertension [47]. These patients require close follow-up of changes in pulmonary vascular resistance if they are to be acceptable heart transplant candidates. Pulmonary emboli can also complicate the clinical course of patients with heart failure and can result in pulmonary hypertension [48,49]. Close follow-up of children with pulmonary hypertension who may someday require heart transplantation is mandatory in order not to allow the pulmonary hypertension to progress to the point where heart transplantation is no longer an option. Indeed, one possible indication for heart transplantation in children with severe heart disease not otherwise under consideration for transplantation is evidence of a progressive rise in pulmonary vascular resistance that would be expected to preclude transplantation at a later date.

3. Post-operative management

Post-transplant pulmonary hypertension has long been recognized as a serious and potentially fatal complication secondary to right-sided heart failure [50]. Although unusual etiologies such as acquired cor
riatriatum or selective right ventricular graft failure may occur [51], the etiology is usually secondary to pre-transplant pulmonary hypertension that has not resolved. In this setting, the donor right ventricle responds to the abnormal recipient pulmonary circulatory dynamics by developing early dilation and tricuspid regurgitation that may persist despite resolution of pulmonary hypertension [52]. Autopsy studies of short-term pediatric heart transplant survivors have shown pulmonary vasculopathy involving arteries, veins, and lymphatics [53]. Some degree of right ventricular failure is common in patients with pre-transplant pulmonary hypertension and usual lasts for three to five days. By five to seven days the right ventricle usually begins to improve, and by the pulmonary vascular resistance usually falls, and most can be weaned from mechanical or pharmacologic support. Hemodynamic parameters such as right sided filling pressures and functional right ventricular assessment with echocardiography can be used to follow the course of right ventricular recovery and direct appropriate weaning from supportive measures. Many of the pharmacologic interventions used to determine pulmonary vascular reactivity before heart transplant have been found to be effective in the post-transplant management of these patients. For instance, prostaglandin E$_1$ has long been known to be effective in treating pulmonary hypertension after heart transplantation [54–58]. Some investigators have used simultaneous infusion of norepinephrine into the left atrial catheter to avoid systemic hypotensive effects of prostaglandin E$_1$ [56]. Other agents that have been found effective for the treatment of post-transplant pulmonary hypertension include prostacyclin, nitroprusside, enoximone, and alkalinization [57–60]. Inhaled nitric oxide has gained in popularity as an effective and selective treatment for post-transplant pulmonary hypertension [30,57,61,62]. Right heart failure may be so severe that ECMO or right heart mechanical assist are required to support the circulation [63–66]. When moderate–severe right ventricular failure is present in the early post-transplant period, early or aggressive weaning of inotropic support, ECMO, or ventilation can lead to catastrophic right ventricular decompensation and cardiovascular collapse. Often, the higher the pre-transplant pulmonary vascular resistance, the more substantial the post-transplant reduction in pulmonary vascular resistance that occurs [34]. Some have argued that prophylactic therapy of pulmonary hypertension in infants and children after heart transplantation may be warranted to reduce the occurrence of transitional pulmonary hypertension and to prevent the development of post-transplant right ventricular failure [58]. Fortunately, long-term pulmonary hypertension after successful orthotopic heart transplantation is uncommon. Some infants with ductal-dependent systemic circulation (e.g. hypoplastic left heart syndrome) receive inhaled nitrogen supplementation before heart transplantation in order to optimize systemic blood flow. Although there have been theoretical concerns of long-term pulmonary hypertension in these patients, there appear to be no measured adverse effects on pulmonary vascular resistance in this group of patients [67].

In conclusion, children with congestive heart failure under consideration for heart transplantation require careful assessment of pulmonary artery pressures and resistances. In those with pulmonary hypertension, their reactivity to pharmacologic interventions must be tested. For those with acceptable pulmonary artery pressures and resistances, heart transplantation can be undertaken, although with careful monitoring and treatment of post-transplant pulmonary hypertension.

References


