

Management of pediatric cardiac transplantation candidates with pulmonary hypertension and high pulmonary vascular resistance

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ABSTRACT

Background and objectives. Right ventricular failure is an important cause of mortality and morbidity after orthotopic heart transplantation (OHT). The right ventricle of the donor may fail to accommodate to the high pulmonary vascular resistance (PVR) of the recipient. Pulmonary hypertension (PH) due to chronic heart failure with $PVRi > 4$ Wood units.m², transpulmonary gradient > 15 mmHg adversely affect the outcome of OHT. In this study we aimed to evaluate management strategies in our pediatric cardiac transplantation candidates with PH and high PVR prior to OHT.

Method. Twenty-six cardiac transplantation candidates (age: 10.2 ± 4.6 , 1-17 years) underwent cardiac catheterization for the determination of PVR and pulmonary arterial pressure. They were admitted to the hospital and received 1-3 days of intravenous (IV) vasodilator therapy; 0.5-3 µg/kg/min nitroglycerin and/or 0.5-3 µg/kg/min nitroprusside, 5-15 µg/kg/min dobutamin and/or dopamin to keep systolic blood pressure above 80 mmHg.

Results. Thirteen patients had dilated cardiomyopathy (CMP), 11 had restrictive CMP, one had hypertrophic CMP and one had congenital heart disease (CHD). Nineteen of the 26 patients underwent OHT.

Mean pulmonary arterial pressure of the patients ranged between 11 and 82 mmHg (30.4 ± 16 mmHg) and $PVRi$ between 0.41-21.4 Wood units.m² (5.3 ± 5.7). Nine patients had $PVRi$ above 4 Wood units.m². Six of these patients had IV treatment for longer than three days and some received specific anti-PH treatment. Eventually they underwent a pulmonary vasoreactivity test with IV iloprost and six had $PVRi < 4$ Wood units.m². Five of them underwent OHT.

Conclusion. Cardiac transplantation candidates with PH and high PVR should be evaluated after conditioning with vasodilator and inotropic treatment. Specific treatment for PH and vasoreactivity testing may help selected patients reenter the transplantation list.

Key words: cardiac transplantation, pulmonary hypertension, pulmonary vascular resistance, right ventricular failure.

Advanced heart failure patients considered for heart transplantation frequently have Pulmonary hypertension (PH). Patients with restrictive and dilated cardiomyopathy (CMP), who have chronic heart failure with elevated

filling pressures are especially under risk. Severe PH is considered a contraindication for heart transplantation as PH leads to right ventricular dysfunction. Right ventricular failure is an important cause of mortality and morbidity after orthotopic heart transplantation (OHT).¹⁻³

The right ventricle of the donor may fail to accommodate the high PVR of the recipient.

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Preoperative pulmonary artery pressure and PVR were found to affect mortality after heart transplantation.²⁻⁷ Pulmonary hypertension due to chronic heart failure with PVRi > 4 Wood units.m², transpulmonary gradient > 15 mmHg adversely affect the outcome of OHT. Thus patients are evaluated with cardiac catheterization before consideration for cardiac transplantation. Several drugs are used before and/or during cardiac catheterization to decrease pulmonary arterial pressure and pulmonary vascular resistance (PVR) and to test the reversibility of high PVR.^{3-5,8-11}

We aimed to evaluate management strategies in our pediatric cardiac transplantation candidates with PH and high PVR prior to OHT.

Material and Methods

Twenty-six cardiac transplantation candidates (age: 10.2 ± 4.6, range 1-17 years) underwent cardiac catheterization for determination of PVR and pulmonary arterial pressure. They were admitted to the hospital and received 1-3 days of IV vasodilator therapy; 0.5-3 µg/kg/min nitroglycerin and/or 0.5-3 µg/kg/min nitroprusside, 5-15 µg/kg/min dobutamin and/or dopamin to keep systolic blood pressure above 80 mmHg, in addition to their usual drugs such as furocemide, spironolactone, angiotensin converting enzyme inhibitors and beta blockers. All patients who had PH and high PVRi underwent a pulmonary vasoreactivity test with IV iloprost. Patients with PH and PVRi greater than 4 Wood units.m² after vasoreactivity test received additional therapy including IV vasodilator and inotropic treatment for longer than three days. Additionally, five patients received specific anti-PH therapy. This study was approved by the ethics committee of our university (28/05/2019-KA19/199).

Results

Thirteen patients had dilated CMP, 11 had restrictive CMP, one had hypertrophic CMP and one had severe left ventricular failure

years after a Rastelli operation for transposition of great arteries, ventricular septal defect and pulmonary stenosis. Nineteen of the 26 patients underwent OHT. Mean pulmonary arterial pressure of the patients ranged between 11 and 82 mmHg (30.4 ± 16 mmHg), PVRi between 0.41-21.4 Wood units.m² (5.3 ± 5.7). Nine patients had PVRi above 4 Wood units.m². Six of these patients were reevaluated after receiving IV treatment for longer than three days. Additionally, five patients received specific anti-PH drugs before reevaluation. Patient 1 received sildenafil for 7 days besides intravenous inotropic and vasodilator treatment of 10 days. Patient 4 received bosentan for one month. Patient 7 received bosentan for one week which was stopped due to elevation of liver enzyme levels. She received inhaled iloprost for four months and was admitted to the hospital 7 days before cardiac catheterization and was put on dobutamin and nitroglycerin. IV iloprost was started 24 hours before catheterization. Patient 8 received inhaled iloprost for six months and bosentan for five months, and was admitted to the hospital three days before cardiac catheterization and was put on dobutamin and nitroglycerin. Patient 9 was put on bosentan for two months, and was admitted to the hospital 10 days before cardiac catheterization and was put on dobutamin, nitroglycerin, and nitroprusside. He also received IV iloprost for 24 hours before catheterization.

Eventually all underwent pulmonary vasoreactivity test with IV iloprost. Six patients had PVRi <4 Wood units.m². Five of these underwent OHT. The four-year-old patient (Patient 3) with restrictive CMP had a PVRi of 8.8 Wood units.m². After OHT PVRi was 5.27 Wood units.m². Despite bosentan and inhaled iloprost treatment he died due to right heart failure three months after transplantation. The course of the other five patients was uneventful. The hemodynamic variables and clinical course of these 9 patients are summarized in Table I.

Informed consent was obtained from all individual participants included in the study.

Table I. Hemodynamic variables and clinical course of 9 patients with high PVRI.

Patient	Age year	Cardiac diagnosis	MPAPp mmHg	PVRIp Wood U.m ²	MPAPv mmHg	PVRIV Wood U.m ²	Management for PH	MPAPa mmHg	PVRla Wood U.m ²	Result
1	14.5	DCMP	59.0	21.4			0.5-3 µg/kg/min NG and 0.5-3 µg/kg/min nitroprusside 10 days, 10 µg/kg/min dobutamin 9 days, 25 mg sildenafil four times/day for 7 days	52	12.08	
2	5.5	DCMP	37.0	4.9	24.0	1.1	Vasoreactivity test with iloprost	44.0	3.94	STX
3	4.0	RCMP	36.0	14.6			0.5-3 µg/kg/min NG and 0.5-3 µg/kg/min nitroprusside 8 days, 10 µg/kg/min dobutamin 8 days	37.0	8.8	Died 3 months after TX with RV failure
4	11.0	RCMP	35.0	13.9	35.0	12.5	Bosentan 62.5 mg twice daily for 1 month, 24.0 0.5-3 µg/kg/min NG, 10 µg/kg/min dobutamin for 7 days before the second cardiac catheterization	24.0	3.39	STX
5	13.5	RCMP	25.0	6.1	25.0	4.30				STX
6	11.0	DCMP	40.0	6.2	35.0	1.16				STX
7	3.0	RCMP	42.0	7.8			Inhaled iloprost 4 months, Bosentan was stopped due to side effects, 7 days dobutamin and NG, 1 day IV iloprost	25	0.8	STX
8	3.5	RCMP	47	8.3		4.3	Inhaled iloprost six months. Bosentan five months, 3 days dobutamin, NG	49	10.1	
9	15	RCMP	82	18.6			Vasoreactivity test with iloprost		4.2	In TX list
							Bosentan for 2 months, 10 days dobutamin, NG, 1 day IV iloprost	96	9.3	
							Vasoreactivity test with iloprost	64	2.8	Not in TX list

DCMP: dilated cardiomyopathy, MPAPa: mean pulmonary artery pressure after antiPH treatment, MPAPv: mean pulmonary artery pressure before vasoreactivity test, MPAPp: mean pulmonary artery pressure after vasoreactivity test, NG: nitroglycerin, PH: pulmonary hypertension, PVRla: pulmonary vascular resistance after antiPH treatment, PVRIp: pulmonary vascular resistance before vasoreactivity test, PVRIV: pulmonary vascular resistance after vasoreactivity test, RCMP: restrictive cardiomyopathy, RV: right ventricle, STX: successful transplantation, TX: transplantation.

Discussion

Pulmonary hypertension and right ventricular failure is an important cause of mortality and morbidity after OHT.¹⁻⁷ Elevated PVRi is generally considered to be a contraindication for heart transplantation in most centers.^{2,3,11} In some studies, it has been reported that high PVRi should not be a contraindication and this is not related to mortality for OHT.^{12,13} Chiu et al.¹² reported that survival was similar in both unmatched and propensity-matched analyses of groups of patients using either a threshold of PVRi ≥ 6 or PVRi ≥ 9 WUx m². The evolving management of right ventricular dysfunction following OHT, use of mechanical circulatory support and targeted therapy for pulmonary hypertension may allow survival of transplanted patients with high PVRi. In spite of favorable results, concerns about adverse outcome of pre-transplantation pulmonary hypertension continues. Costard-Jackle et al.⁴ reported a 3.3% mortality rate due to PH or right ventricular failure in 301 patients which was responsible for 26% of deaths within 90 days after OHT. A pediatric study reported by Addonizio et al.¹⁴ correlated outcomes of pediatric patients with various levels of PVRi. Pulmonary vascular resistance index above 6 Wood units.m² was related with poor survival due to right ventricular failure. Gajarski et al.¹⁵ compared their results in pediatric heart transplant recipients with a mean PVRi of 11.5 ± 3.5 Wood units.m² with those having mean PVRi of 2.3 ± 0.4 Wood units.m². After prostaglandin E₁ infusion as a vasodilator, PVRi decreased to 3.9 ± 0.9 Wood units.m² in those with high PVRi. They concluded that the reactivity of the pulmonary vascular bed rather than the absolute measure of the PVR correlated with outcome as the mortality was similar in two groups.

Patients with chronic heart failure may have PH resulting from several reasons. Increased left ventricular end-diastolic pressure causing increased left atrial and increased pulmonary capillary pressures eventually leads to high pulmonary arterial pressure. Pulmonary

hypertension due to heart failure was classically thought to develop as a passive consequence of high filling pressures of the left ventricle.¹⁶⁻¹⁹ However pulmonary pressures and PVR may remain high after heart transplantation for a varying time and may decrease gradually.^{7,11} This suggests the occurrence of structural changes in pulmonary vessels. Delgado et al.²⁰ demonstrated an increase in the medial thickness of the muscular pulmonary arteries of patients dying early after OHT. In patients with congestive heart failure persistent elevation of left ventricular end-diastolic pressure leads to passive pulmonary venous congestion and reactive pulmonary vasoconstriction.^{16,17,21} Persistent elevation of pulmonary capillary pressure due to increased left ventricular filling pressure may result in histological changes in the pulmonary vasculature.^{16-19,22} At the beginning PVR is reversible with pulmonary vasodilators until prolonged pulmonary venous congestion causes remodelling of the pulmonary arterial wall with abnormalities of the elastic fibers, intimal fibrosis and medial hypertrophy. At this time PH may be defined as fixed as it is resistant to pulmonary vasodilators. Ortiz et al.²³ have investigated the evolution of right heart pressures in an adult series in the first year after heart transplantation with respect to background cardiac disease. The right heart pressures showed an important decrease in the first days after heart transplantation with stabilization by the third month but without returning to normal. However, the PVRi in this series was less than 4 Wood units.m². We applied intravenous drugs for deloading and for decreasing afterload to optimize the hemodynamics before evaluating the PVR. This conditioning is important as pulmonary edema and systemic vasoconstriction may adversely affect pulmonary pressure and cardiac index. Several reports in pediatric and adult patients have stated that intensive treatment with inotropes, vasodilators and in some cases left ventricular assist device can lower PVR and allow for transplantation.^{3,11,24,25} Mahajan et al.⁹ reported a series of 21 adult patients with dilated CMP with persistent moderate to severe PH despite intravenous medical therapy. All

patients received 1 to 3 days of IV cardiac drug therapy including vasodilators, inotropes and diuretics with the goal of optimizing hemodynamics with maximally tolerated doses of IV vasodilators. Twenty-one patients who had persistent moderate to severe PH underwent testing with 100% oxygen and inhaled nitric oxide. Nitric oxide caused a more significant decrease in pulmonary arterial pressure and PVRi than oxygen. Nine of the patients had PVR decreased below 4 Wood units and were included in the transplantation list.

Several drugs have been used for testing the reversibility of high PVR. Sablotzki et al.²⁶ investigated hemodynamic effects of inhaled aerosolized iloprost and inhaled nitric oxide in heart transplant candidates with elevated PVR. They showed that inhaled iloprost induced pulmonary vasodilation greater than the effects of 10 and 30 ppm nitric oxide and they recommended iloprost as a routine screening drug for vascular reactivity in heart transplantation candidates. We used intravenous iloprost for this purpose. Adenosine was also successfully used by Haywood et al.⁸ for the reversal of pulmonary vasoconstriction in biventricular failure and was found to be superior to nitroprusside. In another study however adenosine was less effective with more side effects than inhaled nitric oxide in a group of patients with pulmonary arterial hypertension.²⁷

Despite cautious treatment with vasodilators, inotropes and diuretics to optimize hemodynamics and to decrease pulmonary edema before evaluation of pulmonary arterial pressure and PVR some patients still have high PVR not allowing transplantation. Specific treatment for PH can further help to relist patients with high PVR.^{3,5,11,28,29} Kao et al.²⁸ reported a 14 year-old patient with dilated CMP who was previously operated for aortic coarctation and ventricular septal defect in infancy. The patient had a PVRi of 27 Wood units.m². After two months of continuous prostacyclin infusion of up to 14 ng/kg/min repeat cardiac catheterization revealed

PVRi of 3.7 Wood units.m². She underwent heart transplantation one month later with extracorporeal membrane oxygenation support for the first four days. Perez-Villa et al.²⁹ reported one of the initial experiences with bosentan, an oral endothelin-receptor antagonist to overcome high pulmonary artery pressure and PVR in 7 patients who were considered ineligible for heart transplantation. After six weeks of bosentan therapy five of them had a PVR <2.5 Wood units and underwent successful heart transplantation.

The use of a left ventricular assist device (LVAD) has been proposed as an effective treatment for reducing PVRi in potential heart transplant candidate's refractory to medical vasodilator therapies.^{30,31} In current studies after LVAD implantation, the patients experienced a profound decrease in PVRi on follow-up cardiac catheterization. The resulting dramatic improvement in PVRi in a relatively short period of time allowed for successful OHT.^{25,32} In addition, the use of ventricular support devices help to avoid sudden loss of OHT candidates waiting for transplant. In our study, we showed that the patients with high pulmonary artery pressure and PVRi could be included in the waiting list after treatment with vasodilators, inotropes and diuretics. It was also possible to detect reversible PVR after vasodilator, inotropic and diuretic treatment. These therapies have been shown to reduce the incidence of right heart failure and potentially reduce the morbidity and mortality of post-transplantation right heart failure in single institution reports.^{3,33,34}

Several studies showed that the current treatments after OHT decrease the contribution of PVRI elevation on right ventricular failure and early mortality.^{13,35} Improved management of PH and right ventricular dysfunction may have changed the relationship between PVR and post-transplant mortality.

In this study, the lack of comparative analysis due to the small number of patients was a limitation. Non-standardization of specific anti-PH treatment was considered as a disadvantage.

In conclusion cardiac transplantation candidates with PH and high PVR should be evaluated after conditioning with vasodilator and inotropic treatment. Specific treatment for PH and vasoreactivity testing may help selected patients reenter the transplantation list.

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