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Heart transplantation in children with markedly elevated pulmonary vascular resistance: Impact of right ventricular failure on outcome

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pulmonary hypertension;
pulmonary vascular resistance;
pulmonary vasodilator;
right ventricular failure

BACKGROUND: Pulmonary hypertension causes increased morbidity and mortality in adults after heart transplantation. The effect of markedly elevated pulmonary vascular resistance (PVR) on post-transplant outcomes in children has not been well described.

METHODS: Outcomes were compared in a retrospective study between 58 children with an elevated PVR index (PVRI) $\geq$ 6 U/m^2 and 205 children with a PVRI $<$ 6 U/m^2. Patients who did and did not respond to acute vasodilator testing and patients who underwent transplant before (pre-1995) and after (post-1995) the availability of inhaled nitric oxide (iNO) were compared.

RESULTS: The pre-transplant diagnoses, and cardiopulmonary bypass and donor ischemic times were similar between the high and low PVRI groups. High PVRI patients were older at transplant (12 $\pm$ 6.2 vs 8 $\pm$ 7.1 years, $p = 0.002$). The post-transplant inotrope score was higher in the high PVRI group (12 $\pm$ 12 vs 2 $\pm$ 2, $p = 0.0001$) and 1-year survival was worse (76% vs 81%, $p = 0.03$). The PVRI fell to $<$ 6 U/m^2 with acute vasodilator testing in 21 of 49 (42%) high PVRI patients. RV failure occurred in 4 (19%) of the responders and in 14 (50%) of the non-responders ($p = 0.037$). One responder (5%) and 4 non-responders (14%) died of RV failure. In the period after 1995, the year iNO became clinically available, the select group of high PVRI patients who received iNO preemptively had a lower incidence of post-transplant RV failure than the group that did not receive preemptive iNO (13% vs 54%, $p = 0.04$).

CONCLUSIONS: Pre-transplant vasodilator testing identified patients at higher risk for RV failure. Patients who did not respond to vasodilator testing had an increased incidence of RV failure and death from RV failure. Preemptive use of iNO was associated with a decreased incidence of RV failure.

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Right ventricular (RV) failure secondary to elevated pulmonary vascular resistance (PVR) has been reported since the early days of heart transplantation and continues to be a well-known cause of significant morbidity and death in transplant recipients.[1–4] In fact, data from the International Society of Heart and Lung Transplantation (ISHLT) annual report in 1993 indicated that RV dysfunction accounted for 50% of all post-transplant cardiac complications and 19% of all early deaths.[5] Since the early days, high PVR in most centers has been considered an exclusion criterion for heart transplantation,[6,7] whereas in others, such patients are only considered for the higher-risk

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heart-lung transplantation.[6,8] Although orthotopic heart transplantation has been successful in adults and children with elevated PVR, controversy remains about what level of elevation of PVR should be considered an absolute contraindication to heart transplant.

The PVR index (PVRI) indexes PVR to body surface area and allows better comparison of the hemodynamics between widely disparately sized patients in the adult and pediatric population. Our center and others have shown in small series that using PVRI and the response to acute vasodilator testing can help in the selection of patients who will have a better peri-operative outcome.[9,10] However, no large series have reported outcome after orthotopic heart transplantation in patients with markedly elevated PVRI. We have adopted a protocol of preemptive treatment of these patients with pulmonary vasodilators in the peri-transplant period to decrease the incidence of RV failure and mortality from RV failure in this difficult sub-group of patients. In this study, we review our 21-year experience of transplantation in children with markedly elevated PVRI of 6 IU or greater and the effect of RV failure on outcome.

Methods

This was a retrospective record review of all patients who had heart transplantation at the Program for Pediatric Cardiomyopathy, Heart Failure and Transplantation of the Morgan Stanley Children's Hospital of New York Presbyterian, Columbia University Medical Center, between June 1984 and January 2005. The study was approved by the Columbia University Institutional Review Board.

Pre-transplant data obtained included diagnoses, gender, age at transplantation, hemodynamic variables, and the amount of inotropic/vasodilator support necessary immediately before transplantation. A modification of an inotrope score previously described by Wernovsky et al[11] was used to quantify the severity of a patient's condition and level of medical support necessary. The modified inotrope score was calculated as [dosages of dopamine + dobutamine + (epinephrine $\times$ 100) + (milrinone $\times$ 10)]. All doses were calculated in μg/kg/min. The pre-transplant hemodynamic data obtained included systolic and mean pulmonary artery pressures (PAP), pulmonary capillary wedge pressures (PCWP), transpulmonary gradient, and cardiac index (CI). The PVRI was calculated as [(mean PAP – mean PCWP)/CI] and reported as indexed resistance units (IU). Acute vasodilator testing was performed in all patients whose PVRI was $\geq$ 6 IU when hemodynamically feasible to determine reversibility. In patients requiring acute vasodilator testing, cardiac output was maximized with dobutamine and milrinone or amrinone before testing with 100% supplemental oxygen and escalating doses of sodium nitroprusside infusion titrated to effect or to systemic hypotension.

Response to acute vasodilator testing was defined as a decrease in PVRI to $<$ 6 IU. Our cutoff value of PVRI of 6 IU to define a responder was based on institutional experience and on previous work by Addonizio et al,[10] which suggested that risk of RV failure was higher in both adults and children with PVRI $>$ 6 IU at transplantation. Patients with PVRI $>$ 6 IU were maintained on chronic optimized inotropic/vasodilator therapy until heart transplantation was performed. Repeat cardiac catheterization and vasodilator testing were performed as indicated to further optimize pulmonary vasodilation. The same hemodynamic parameters after vasodilator testing at maximal effect were recorded for study comparisons.

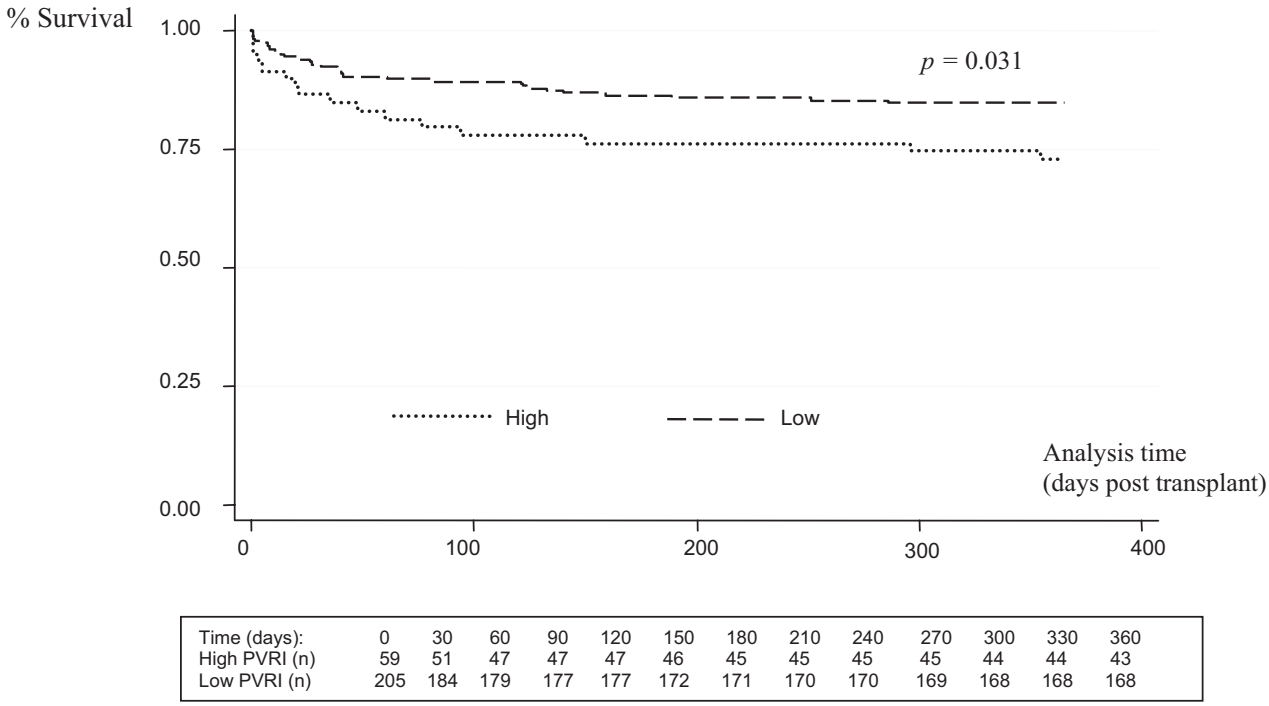
Surgical measures at the time of transplantation, including cardiopulmonary bypass time and donor heart ischemic time, were collected. Post-transplant outcomes included the inotrope score, incidence of post-transplant RV failure, death from RV failure, hospital length of stay, and survival at 3 months and 1 year were collected. RV failure was defined as the presence of one or more of the following: rising central venous pressure, with low cardiac output, RV hypocontractility with a normally functioning, underfilled left ventricle diagnosed by the attending echocardiographer, that required medical or surgical intervention.

The post-operative interventions included increased inotropic/vasodilator support, initiation or increased dose of inhaled nitric oxide or intravenous prostacyclin, prolonged sedation and mechanical ventilation or use of a right ventricular assist device (VAD) or extracorporeal membrane oxygenation (ECMO). After 1995 when inhaled nitric oxide (iNO) became clinically available in our institution, it was aggressively instituted preemptively (initiated in operating room in high risk patients with pre-operative high PVRI or unfavorable hemodynamics after separating from cardiopulmonary bypass) or as therapy for RV failure in the intensive care unit. Inhaled NO was administered at a dose of 20 ppm through the ventilator in intubated patients or by nasal canula in non-intubated patients.

Statistical methods

Post-transplant outcomes, including incidence of RV failure, need for mechanical circulatory support (VAD or ECMO), and death from RV failure were compared between patients who had a high PVRI ($\geq$ 6 IU) and those who had a low PVRI ($<$ 6 IU). Additional analyses in the high PVRI group were performed to assess the influence of elevated pre-transplant PVRI, era of transplantation and post-transplant use of iNO on patient outcomes. Patients with elevated baseline PVRI were divided into 3 sub-groups based on their response to pre-transplant acute vasodilator testing: responders whose PVRI fell to $<$ 6 IU, non-responders whose PVRI remained $>$ 6 IU, and patients who could not be tested secondary to hemodynamic instability. Patients were also stratified by the era of transplantation between 1984 and 1995 vs those who underwent transplant between 1995 and 2005, and by the preemptive use of iNO. The division between eras was chosen as 1995 because iNO, became clinically available in our institution at that time. Preemptive use of iNO was defined as initiation of iNO in the operating room in patients with pre-transplant elevated PVRI.

All data are expressed as mean $\pm$ SD. Categoric data were analyzed using Pearson's chi-squared tests or, where appropriate, a Fisher's exact test. Continuous data were analyzed with analysis of variance or 2-tailed Student's t-test; α was set at 0.05. Kaplan-Meier survival curves were constructed for survival comparisons. All analyses were performed using STATA 9 statistical analysis software (StataCorp College Station, Texas).



Time (days):	0	30	60	90	120	150	180	210	240	270	300	330	360
High PVRI (n)	59	51	47	47	47	46	45	45	45	45	44	44	43
Low PVRI (n)	205	184	179	177	177	172	171	170	170	169	168	168	168

Figure 1 One-year survival after heart transplantation. All-cause mortality at 1 year in patients with indexed pulmonary vascular resistance (PVRI) < 6 IU is 5% less than that in patients with PVRI ≥ 6 IU (survival 81% vs 76%, respectively; $p = 0.031$, Fisher's exact test).

Results

Pre-transplant characteristics

Between 1984 and 2005, 263 children and young adults received heart transplants, of which 58 (22%) had a baseline PVRI ≥ 6 IU. Table 1 compares the pre-transplant characteristics of the high and low PVRI groups. The high PVRI group was significantly older at the time of transplant and they had higher pre-transplant inotrope scores. The pre-transplant diagnoses of the high PVRI patients were congenital heart disease in 19 (33%), dilated cardiomyopathy in 26 (45%), hypertrophic cardiomyopathy in 5 (8%), and restrictive cardiomyopathy in 8 (14%). This was not significantly different between the two groups.

Intra-operative and post-operative course

A comparison of the high PVRI and low PVRI groups according to their intra-operative and post-operative characteristics (Table 2) found no difference in cardiopulmonary bypass time or donor heart ischemic time. Patients in the high PVRI group required significantly more inotropic support in the post-operative period, with a mean inotrope score of 12 ± 12 vs 2 ± 2 ($p = 0.0001$).

Survival

Overall survival in the high PVRI group was significantly lower than that in the low PVRI group (Figure 1). The 3-month survival was 81% in the high PVRI group and

Table 1 Patient Population: 1984–2005 ($N = 263$)

Variable[a]	High PVRI ($n = 58$)	Low PVRI ($n = 205$)	p-value[b]
PVRI baseline	10.8 ± 5.2 (6–29.6)	2.9 ± 0.4 (1–5.6)	
TPG baseline	21.5 ± 10.8 (6–47)	12 ± 2 (7–23)	
Age	12 ± 6.2 (0.4–22.1)	8.8 ± 7.1 (0.1–25.4)	0.002
Male gender	32 (55)	109 (53)	0.88
Diagnosis of CHD	19 (33)	82 (40)	0.36
Pre-Tx inotrope score	10 ± 8 (5–30)	2 ± 2 (0–10)	0.001

CHD, congenital heart disease; PVRI, indexed pulmonary vascular resistance; TPG, transpulmonary gradient; Tx, transplant.

[a]Continuous data are presented as mean $\pm$ standard deviation and (range); categoric data as number (%).

[b]All comparisons tested with Student's t-test.

Table 2 Intra- and Post-Operative Characteristics

Variable[a]	High PVRI (n = 58)	Low PVRI (n = 205)	p-value[b]
CPB time, min	158 ± 70	165 ± 33	0.28
Ischemic time, min	202 ± 82	214 ± 76	0.29
Post-Tx inotrope score	12 ± 12 (3–60)	2 ± 2 (0–10)	0.0001
Hospital LOS, days	34 ± 39 (9–296)	34 ± 51 (8–280)	>0.99

CPB, cardiopulmonary bypass; LOS, length of stay; PVRI, indexed pulmonary vascular resistance; Tx, transplant.

[a]Data are presented as mean ± standard deviation (range).

[b]All comparisons tested with Student's t-test.

87% in the low PVRI group (p = 0.03), and the 1-year survival was 76% and 81% respectively (p = 0.03). Hospital length of stay was not different in the 2 groups.

Sub-group analyses of high PVRI group

Vasodilator testing

Of the 58 high PVRI patients identified at cardiac catheterization, 9 (16%) were too unstable to undergo acute vasodilator testing (Figure 2), but 21 (36%) responded to vasodilator testing, with their PVRI decreasing to 4.2 ± 1.0 IU (range, 2.2–5.9 IU). In the 28 non-responders (48%), the PVRI only decreased to 8.5 ± 3.2 IU (range, 6.0–17.5 IU). All patients received maximal vasodilators until transplant.

RV failure

RV failure developed in 20 of the 58 patients (34.5%) with high PVRI. The occurrence of RV failure was significantly higher in the non-responders. RV failure developed in 14 non-responders (50%) but in only 4 (19%) of the responders and 2 (22%) of the non-tested patients (p = 0.037), figure 3. Four patients required ECMO/VAD for RV failure, of which 3 survived. Overall mortality from RV failure was 6 (10.3%). Death from RV failure occurred in 4 (14%) of the non-responders, 1 (5%) of the responders, and 1 (11%) of the non-tested patients (p = NS). The incidence of RV failure and death from RV failure were further assessed by era before and after 1995. There were 29 patients in each era. The incidence of RV failure in the pre-1995 era was 38% compared with 33% in the post-1995 era. Death from RV failure was 50% less in the post-1995 era than in the pre-1995 era (figure 4). Although these comparisons did not reach statistical significance, the trend is impressive and may represent the effect of iNO on outcome among these high-risk patients. The overall 1-year survival was not different in the high PVRI group by era.

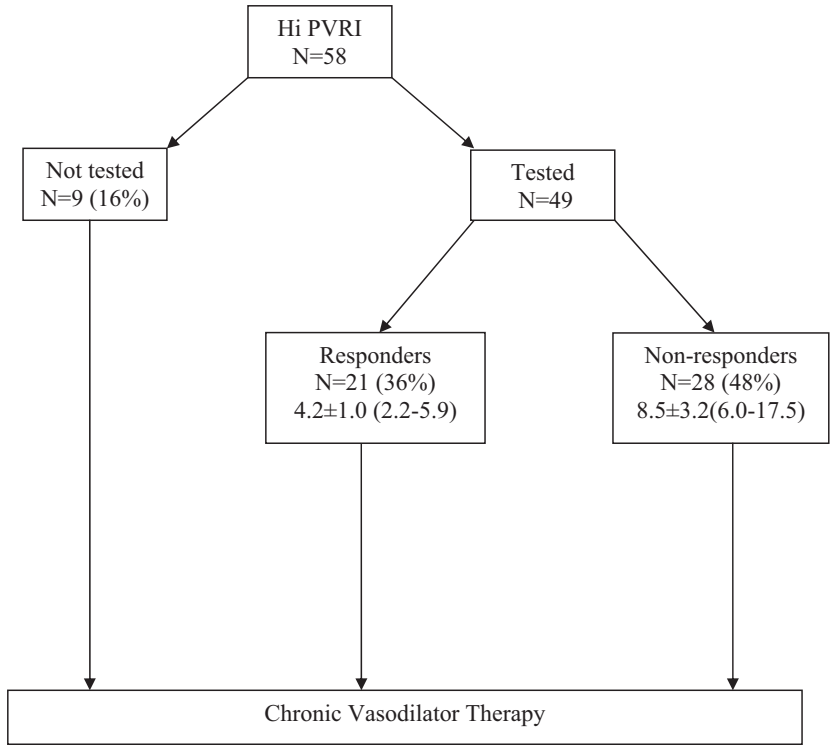


Figure 2 Response to vasodilator testing in the high peripheral vascular resistance index (PVRI) group.

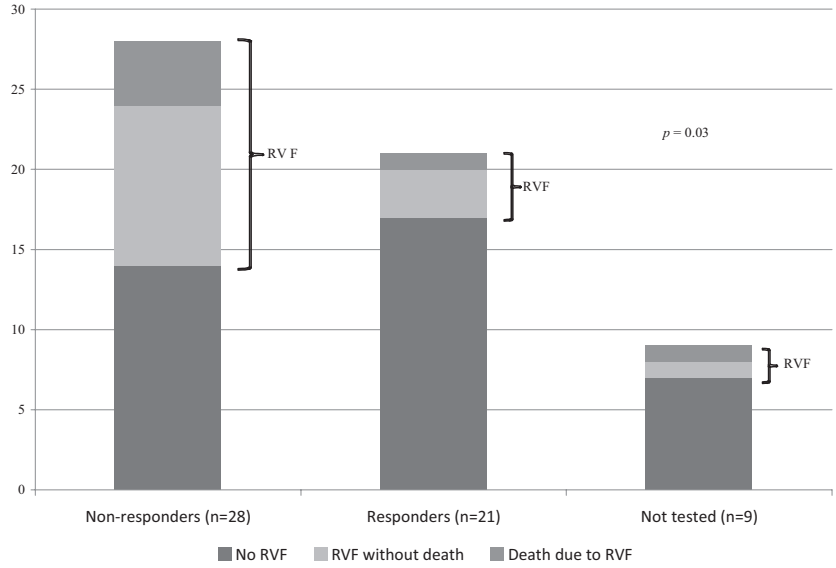


Figure 3 Vasodilator response and incidence of right ventricular failure (RVF) and death due to RVF among the 3 groups: non-responders, responders, and non-tested. The incidence of RVF was significantly higher among non-responders to vasodilator testing ($p = 0.03$, Fisher's exact test).

Inhaled NO

Inhaled NO became readily available for clinical use in our institution in 1995. During this period, 29 patients had high PVRI. To ascertain the effect of iNO on outcome in the high PVRI group, the patients were stratified into 2 groups: 10 patients who received preemptive iNO and 13 patients who did not. The incidence of RV failure was 54% in the patients who did not receive preemptive iNO vs 13% in those who did ($p = 0.04$). This was significantly higher and represents a relative risk reduction of 77% with iNO (Figure 5). The probability of RV failure in patients who received preemptive iNO (positive predictive value) was 12.5%, and the probability of RV failure in patients who did not receive preemptive iNO (negative predictive value) was 46%. Also, 2 deaths occurred in the group that did not receive preemptive iNO, but no patients died in the iNO group ($p = 0.19$). The mean duration of intubation, intensive care unit length of stay, and overall hospital length of stay were similar in these 2 groups (Table 3).

Discussion

In this study we report an aggressive approach to the diagnosis and treatment of pulmonary hypertension in patients

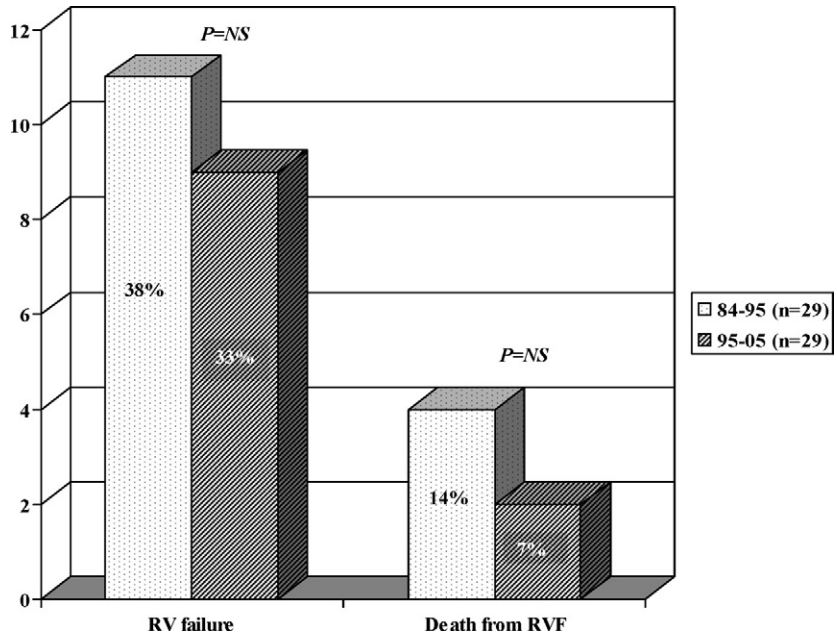


Figure 4 Right ventricle failure (RVF) and death from RVF by era. Among patients with elevated peripheral vascular resistance index (PVRI), there was no significant difference in the incidence of RVF or death from RVF between the two eras (1984–1995 vs 1995-2005), by Fisher's exact test.

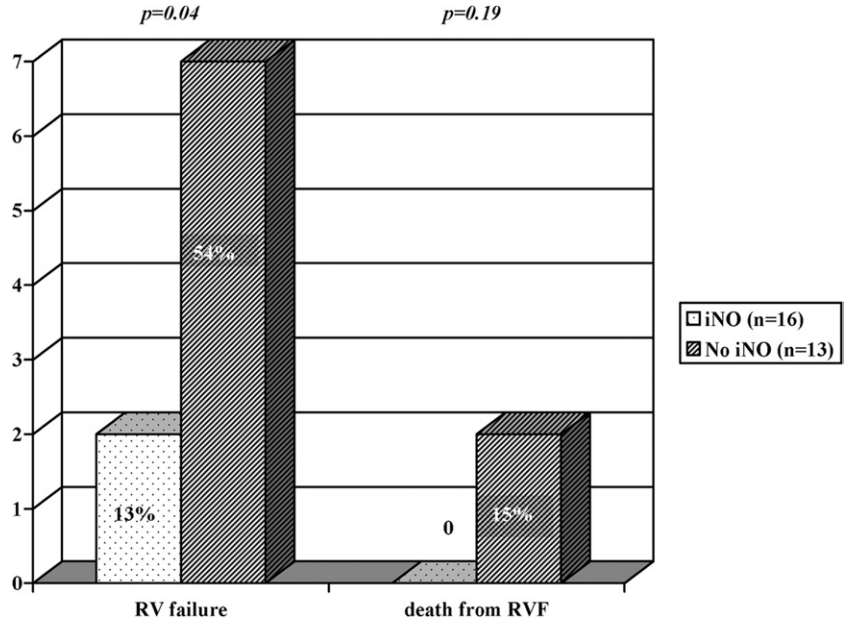


Figure 5 Effect of preemptive use of inhaled nitric oxide (iNO) on outcome. The incidence of right ventricle failure (RVF) was significantly reduced in patients who were treated preemptively with iNO ($p = 0.014$, Fisher's exact test). No significant difference in mortality from RVF was demonstrated ($p = 0.19$, Fisher's exact test).

undergoing heart transplantation. A high proportion of patients (22%) who underwent transplant during the study period had baseline pulmonary hypertension. Survival was 71%, somewhat lower than would be expected but comparable to survival after transplant in patients with congenital heart disease.[12] Significant controversy exists regarding heart transplantation in patients with severely elevated PVR. There is also no consensus on what level PVRI is an absolute contraindication to heart transplantation. Although our institutional cutoff PVRI of 6 IU has been used for several years, this criterion has limitations because it is based on a study comprising both adults and children. Several management strategies have been suggested: (1) use of an oversized heart in conjunction with pharmacologic support to decrease PVRI after transplantation,[13] (2) use of a "pre-conditioned" domino heart from a patient undergoing heart-lung transplantation for pulmonary hypertension,[14,15] (3) heterotopic heart transplantation,[16,17] or (4) heart-lung transplantation.[18]

Table 3 Comparison of Use of Preemptive Inhaled Nitric Oxide on Outcome

Variable[a]	INO ($n = 16$)	No iNO ($n = 13$)	p-value
Length of intubation, days	5.9 ± 6.0	4.5 ± 6.7	0.577[b]
Length of stay, days			
ICU	13.1 ± 9.0	14.2 ± 14.6	0.673[b]
Hospital	23.3 ± 5.1	25.6 ± 14.7	0.816[b]
RVF	2 (13)	7 (54)	0.040[c]
Death due to RVF	0	2 (15)	0.192[c]

ICU, intensive care unit; RVF, right ventricle failure.

[a]Continuous data are presented as the mean ± standard deviation; categoric data are presented as number (%).

[b]Comparisons tested with Student's t-test.

[c]Comparisons tested with Fisher's exact test.

One study showed that iNO with aggressive vasodilator and inotropic support improved hemodynamic status; however, the sub-group of patients with a non-reactive pulmonary vascular bed remained high-risk heart transplant candidates.[19] In this study we demonstrate that heart transplantation can be performed successfully with excellent outcomes in patients with markedly elevated PVRI of 6 IU or higher. The pre-transplant inotrope score was higher in the high PVRI group, likely reflecting the use of high-dose inotropic and vasodilator therapy to improve PVR. Despite the higher inotrope score, the overall post-transplant hospital length of stay was similar to the group with low PVRI. In concurrence with other studies,[9,20,21] the risk of post-transplant RV failure was high in this patient population, and RV failure accounted for most of the early post-transplant deaths. Even though the incidence of RV failure remained high in the elevated PVRI group (34%), death from RV failure was low (10.3%). These morbidity and mortality data represent an improvement compared with earlier results reported from the ISHLT database.[5] Careful risk stratification, aggressive management of pulmonary hypertension, and the preemptive use of iNO may have contributed to the improved outcome of this very high-risk patient population. In a series reported by Klotz et al[22] of 49 adults with reversible pulmonary hypertension and a baseline mean PVR of 4.5 ± 3.1 WU, the incidence of acute RV failure was 64% and death from RV failure was 70% in their early experience. Their mortality decreased to 0% in the new era. Our data show similar improvement even though the baseline PVRI was much higher.

Acute vasodilator testing is an important tool in the risk stratification of patients. This study defined response to acute vasodilator testing as PVRI falling to < 6 IU, regardless of the initial PVRI. Although this definition is very rigorous, we believe it is the best means of stratifying patients according to their postoperative risk of morbidity and mortality. As shown in the results, RV failure developed in 14 of the 28 non-responders (50%), 3 (11%) required mechanical circulatory support, and 4 (14%) died of RV failure, while among the 21 responders, RV failure developed in only 4 (19%), none required mechanical circulatory support, and only 1 (5%) died of RV failure. Our inference from these data is that acute vasodilator testing identifies patients at the highest risk of morbidity and mortality related to RV failure and allows early institution of measures that may prevent these complications. In our cohort, aggressive pre-transplant vasodilator and inotropic therapy were instituted in all patients with elevated PVRI, and when indicated, the patients received repeat cardiac catheterization before transplantation to assess the efficacy of treatment and further adjustment of therapy.

With analysis of the data by era (pre-1995 and post-1995), there was no difference in the incidence of RV failure or death from RV failure. The lack of statistical difference between the 2 eras may reflect inadequate numbers, but we speculate that despite improved myocardial preservation, post-operative care, and the availability of iNO, RV failure remains an important complication of heart transplantation of patients with pulmonary hypertension and elevated PVR. However, when the data were specifically analyzed for the effect of preemptive use of post-operative iNO on RV failure, a relative risk reduction of 77% (decrease from 54% to 13%, $p = 0.04$) was found. RV failure resulted in 2 deaths in the patients who were not treated preemptively with iNO; whereas no deaths occurred in the group that received preemptive iNO. Although these findings were not controlled for other vasodilator agents, inotropic agents, and other aspects of intensive care management, such as mechanical ventilation, we believe that aggressive treatment of high PVR and the early institution of postoperative iNO may have decreased the risk of overt RV failure with a concomitant decrease in the risk of death from RV failure.

The overall 3-month survival after heart transplantation was 81% in the group with markedly elevated PVRI and 87% in the low PVRI group during our 21-year experience. Although this difference is significant, the outcomes are most certainly better than what could be attained long-term had these children been listed for heart-lung transplantation. Our improved outcomes with early preemptive use of iNO will most probably narrow this difference in the future, as will the advent of newer pulmonary vasodilators, such as sildenafil.[23]

This retrospective study reflects the evolution in the clinical care of patients with high PVRI during the study period, including the availability of NO. Thus, it is not possible to compare the efficacy of specific treatment protocols described in the study. Patients who received preemptive iNO treatment were not randomized to the therapy and therefore prone to selection bias. In some of our analyses, the patient numbers were too small to power for statistical significance.

In conclusion, we demonstrate in this single-center study that early recognition, appropriate risk stratification, and aggressive management of pulmonary hypertension in the pre-transplant and post-transplant period results in acceptable early and medium-term outcomes in high PVRI patients. It also allows successful transplantation of patients who heretofore have not been offered orthotopic heart transplantation. The effect on long-term outcomes of our institution-specific guidelines for the standardized care of these high-risk patients is yet to be determined.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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