

# Vasoactive–inotropic score after pediatric heart transplant: A marker of adverse outcome

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**Abstract:** VIS, a quantitative index of pressor support, has been shown to be a predictor of morbidity and mortality in infants younger than six months who underwent CPB. Data on its prognostic utility following pediatric OHT are lacking. This study compared clinical outcomes in children with differential VIS after pediatric OHT. A retrospective cohort study of 51 consecutive heart transplants from 2004 to 2011 was performed at a pediatric tertiary care facility. Peak VIS was computed within initial 24 and 48 h after OHT and was weighted for peak dose and administration of any or all of six pressors. Patients with peak VIS  $\geq 15$  constituted high VIS group. Children who persistently required a higher magnitude of pressor support for the first 48 h after OHT, as reflected by high peak VIS, had significantly longer ICU stay (30.2 vs. 15.9 days,  $p = 0.01$ ), pressor (11.4 vs. 6.8 days,  $p = 0.02$ ) and ventilatory durations (12.4 vs. 5.9 days,  $p = 0.05$ ), and higher rates of short-term morbidities. Patients with longer CPB (213 vs. 153 min,  $p = 0.005$ ) time have higher peak VIS. High peak VIS at 48 h is an effective, yet simple clinical marker for adverse outcomes in pediatric OHT recipients.

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Pediatric orthotopic heart transplantation is the therapeutic option of choice for children with end-stage congenital or acquired heart disease (1). Advancements in medical therapy, refinements in surgical techniques, and availability of mechanical circulatory support systems have resulted in higher post-transplant survival rates in recent decades (2–4). Despite this, early postoperative morbidity and mortality continue to be significant following pediatric OHT (5–7).

Currently, there is only limited use of early postoperative markers that reflect the clinical status of the individual patient as well as predict outcomes after pediatric cardiac surgery. Inotropic score is one such objective clinical tool. It was initially described by Wernovsky et al. to quantify the extent of circulatory support that neonates received after arterial switch operation (8). Since then, several studies have used inotropic score as a

measure of disease severity (9–11). More recently, a modification of this scoring system called the vasoactive–inotropic score (VIS) was validated as a predictor of outcome after pediatric cardiac surgery (12, 13). VIS is a quantitative index of pressor support and takes into consideration use of milrinone, norepinephrine, and vasopressin in addition to dopamine, dobutamine, and epinephrine. Gaies et al. showed that VIS was a predictor of morbidity and mortality in infants younger than six months who underwent CPB (12).

There are no data on the prognostic utility of VIS following pediatric OHT. The aim of our study was to compare clinical outcomes in groups of children with differential VIS after pediatric OHT. Our hypothesis was that a persistently high VIS in the initial 48 h post-OHT would be associated with higher morbidity and mortality, relative to a low VIS.

## Methodology

This was a retrospective study conducted at a single center, Children's Hospital of Michigan. Approval for the study and for waiver of parental

Abbreviations: CHD, congenital heart disease; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; OHT, orthotopic heart transplant; VIS, vasoactive–inotropic score.

consent and subject assent was obtained from the Institutional Review Board at Wayne State University and research authorization from Children's Hospital of Michigan. The charts of all patients, 18 yr or younger, who underwent OHT between 2004 and 2010 at our institution were reviewed. Demographic, clinical, and immediate postoperative outcome data were collected. Demographic data included age, gender, diagnosis, and list status at the time of OHT. Preoperative clinical data pertaining to requirement of inotropic support, mechanical ventilation, or mechanical circulatory support in the immediate pretransplant period were also collected. Intraoperative characteristics including surgical technique of OHT, CPB time, and graft ischemia time were abstracted. Implantation of the donor heart was performed orthotopically using the bicaval or the bicaval technique. Before being weaned off CPB, patients were started on vasoactive medications by the attending anesthesiologist/surgeon. The graft ischemic time was defined in the study as the time interval between the application of aortic cross-clamp in the donor and the removal of aortic cross-clamp in the recipient. In our center, rewarming is started only after the aortic cross-clamp is removed. Hence, the ischemic time in this study only includes the cold ischemic phase with temperatures maintained below 30 °C. In the postoperative period, patients received close hemodynamic monitoring in the pediatric ICU with pulse oximetry, central venous pressure, left atrial pressure, and arterial pressure.

Vasoactive infusions were titrated, changed, or discontinued at the discretion of the cardiothoracic surgeons and pediatric intensivists based on individual clinical scenarios. Initial choices for vasoactive medication were milrinone, dobutamine, and dopamine. Epinephrine, norepinephrine, and vasopressin were used as second-line vasoactive agents. The doses of all the vasoactive infusions were obtained from the flow sheets at three hourly intervals for up to 48 h post-transplant. VIS was calculated using the formula proposed by Gaies et al. (12).

$$\text{VIS} = \text{dopamine (mcg/kg/min)} + \text{dobutamine (mcg/kg/min)} + 100 \times \text{epinephrine (mcg/kg/min)} + 100 \text{ norepinephrine (mcg/kg/min)} + 10 \times \text{milrinone (mcg/kg/min)} + 10\,000 \times \text{vasopressin (mUnits/kg/min)}$$

The VISs that were attained at three hourly intervals during the first 24 h and between 24–48 h post-transplant were computed. A VIS of 15 or above on two or more of eight readings was taken as high inotropic requirement (high VIS 24 h). VIS of <15 at all time points of observation was considered to be low inotropic

requirement (low VIS 24 h). The cutoff of peak VIS of 15 was predetermined based on the five-group classification system proposed by Gaies and colleagues (12). According to the authors, a moderate cardiovascular support on admission to the ICU after congenital heart surgery typically includes vasoactive infusions at dosages that result in a VIS of approximately 15. We required this cutoff to be exceeded on two or more occasions (representing 3-h period each) over 24 h. Further analysis was performed comparing patients with persistent high VIS (48 h), defined as peak VIS > 15 on two or more readings in each of the two 24-h periods (0–23 h, 24–48 h after OHT), and all others, low VIS (48 h).

A standard protocol was followed for immunosuppression post-OHT. All patients received induction therapy with intravenous thymoglobulin for five days. High-dose methyl prednisolone was initiated intraoperatively and continued for a total of six doses. Maintenance immunosuppressive regimen included tacrolimus, mycophenolate mofetil, and tapering dose of oral steroids. Decisions regarding the immunosuppressive therapy were made by the attending transplant cardiologist.

The primary outcome variable for our study was the total length of ICU stay after OHT. Secondary outcome variables included post-transplant requirement of mechanical circulatory support, duration of mechanical ventilation, number of days on vasoactive infusions, acute renal failure necessitating renal replacement therapy, and death prior to initial discharge after OHT.

#### Statistics

All data were reported as mean and standard deviation (s.d.) for continuous variables and frequency (percent) for categorical variables. The two groups (high and low VIS 24 h and persistent high and low VIS 48 h) were compared using independent sample t-test, Fisher's exact test, or chi-square test depending on the distribution of the data. Regression analysis was performed to examine the association between ICU stay and high VISs, after adjusting for potential confounders found to be significant on univariate analysis. Statistical analyses were performed using SPSS version 17 (SPSS Inc., Chicago, IL, USA).

#### Results

A total of 55 patients underwent OHT at our institution from January 2004 to December 2010. Of these, four patients were older than 18 yr at

the time of OHT and were excluded from the study. The median age at the time of OHT of our study cohort (N = 51) was 1.3 yr (range: 1 wk–17.9 yr). Of these, 25 (49%) were males. Based on the listed ethnicity, 21 (42%) were Caucasian, 26 (51%) African American, one (2%) Hispanic, and two (4%) were Asian. The indication for OHT was CHD in 20 (39%), cardiomyopathy in 29 (57%), and tumor in two (4%) patients. The list status was 1A in 46 (90%) patients at the time of OHT. Prior to OHT, mechanical circulatory support was required in 13 (26%) patients, of which nine were on left ventricular assist device and four on ECMO. In the pretransplant period, 14 (28%) patients were mechanically ventilated and 30 (60%) required inotropic support. The computed VIS ranged from 3 to 48, with a median of 14 in the 0- to 24-h period and 12 in the 24- to 48-h period after OHT.

Initial 24 h post-OHT

In the first 24 h after OHT, 28 (55%) patients had peak VIS of 15 or more on two or more occasions and were categorized as high VIS (24 h) group. The 23 (45%) patients, who had VIS of <15, comprised the low VIS (24 h) group. On comparing the groups, the low VIS (24 h) group tended to have a predominance of cardiomyopathy rather than CHD. Demographic data including age, gender, ethnicity, and list status at the time of OHT were similar among the groups (Table 1). Preoperative requirements of mechanical ventilation, inotropic support, or mechanical circulatory support were also not different between the groups.

Table 2 compares operative characteristics and outcome among the two groups. A biatrial approach was used for OHT in 22 patients each (79% vs. 96%, p = 0.08) in the high and low VIS (24 h) groups, respectively. Children in the high VIS (24 h) group had significantly longer CPB time (188 min) than those in the low VIS (24 h) group (148 min) (p = 0.03). The graft ischemia time was similar between the groups. The outcome variables including length of ICU stay, duration of mechanical ventilation, and duration of vasoactive therapy were not significantly different between the groups. Acute renal failure necessitating renal replacement therapy was diagnosed in six patients in the high VIS (24 h) group, compared with one patient in the low VIS (24 h) group, a difference that did not reach statistical significance (p = 0.11). Post-OHT ICU length of stay, death, and post-OHT ECMO all tended to be higher in the high VIS (24 h) group.

Table 1. Demographic and preoperative data of high and low vasoactive–inotropic score groups at 24 h after orthotopic heart transplant

N (%)*	High VIS (24 h) (N = 28)	Low VIS (24 h) (N = 23)	p-value
Age (yr) median (range)	1.1 (0.02–17.5)	1.2 (0.05–17.9)	0.61
Male	15 (54%)	10 (44%)	0.33
Ethnicity			
Caucasian	10 (36%)	11 (48%)	0.39
African American	15 (53%)	11 (48%)	
Hispanic	1 (4%)	0 (0%)	
Asian	2 (8%)	1 (4%)	
Status 1A	28 (100%)	21 (92%)	0.47
Diagnosis			
CHD	14 (50%)	6 (27%)	0.09
Cardiomyopathy	14 (50%)	15 (65%)	
Tumor	0 (0%)	2 (8%)	
Preop mechanical ventilation	7 (25%)	7 (30%)	0.46
Preop inotropic therapy	17 (60%)	13 (56%)	0.49
Preop LVAD/ECMO	9 (32%)	4 (18%)	0.46

\*Value expressed as number (percentage).

CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenator; LVAD, left ventricular assist device; OHT, orthotopic heart transplant; Preop, preoperative; VIS, vasoactive–inotropic score.

Table 2. Comparison of intra-operative and outcome variables - 24 h after orthotopic heart transplant

Mean (±s.d.) or n (%)	High VIS (24 h) (N = 28)	Low VIS (24 h) (N = 23)	p-value
Graft ischemia time (min)	191 (±56)	195 (±43)	0.76
CPB time (min)	188 (±79)	148 (±52)	0.03
Biatrial technique	22 (78%)	22 (95%)	0.08
Intensive care unit stay (days)	24 (±22.5)	15.4 (±10.8)	0.09
Mechanical ventilation (days)	9.6 (±12.7)	5.6 (±6.9)	0.17
Vasoactive infusion (days)	8.8 (±8)	7.5 (±4.2)	0.5
Post-op ECMO	3 (11%)	1 (5%)	0.61
Acute renal failure	6 (21%)	1 (5%)	0.11
Death	3 (11%)	1 (5%)	0.61

CPB, cardiopulmonary bypass; OHT, Post-op, postoperative; ECMO, extracorporeal membrane oxygenator; VIS, vasoactive–inotropic score.

48 h post-OHT

Between 24–48 h after OHT, 15 patients continued to require high dose of vasoactive infusions. These patients with a VIS of 15 or higher on two or more occasions in the 24- to 48-h postoperative period were categorized as persistent high VIS (48 h) group. The remaining 36 patients (71%) who had peak VIS <15 between 24 and 48 h after OHT constituted the low VIS (48 h) group. All the patients with a low VIS in the first 24 h post-OHT continued to require low inotropic support in the subsequent 24 h.

On comparing the persistent high VIS (48 h) group with low VIS (48 h) group (Table 3), the only significant difference was that in the

persistent high VIS (48 h) group, 67% of patients underwent OHT for CHD compared with 27% of the patients in the low VIS (48 h) group ( $p = 0.01$ ). Preoperative requirement of mechanical ventilation, inotropic support, or mechanical circulatory support was not different between the groups.

Comparison of the operative and outcome data is detailed in Table 4. Biatial technique was used for OHT in the majority of patients in both groups. Patients in the persistent high VIS (48 h) group had significantly longer CPB time (213 [ $\pm 83$ ] vs. 153 [ $\pm 57$ ],  $p = 0.005$ ). The persistent high VIS (48 h) group patients required longer duration of vasoactive infusion therapy ( $p = 0.02$ ), post-OHT ICU stay ( $p = 0.01$ ), and higher rate of renal failure ( $p < 0.001$ ), compared with low VIS (48 h) group. Three patients in the persistent high VIS (48 h) group and one patient in the low VIS (48 h) group required ECMO support after OHT. This difference was not statistically significant.

The overall mortality rate in the immediate post-transplant period was 7.8%. Three (20%) subjects in the persistent high VIS (48 h) group died compared with one (4%) in the low VIS (48 h) group ( $p = 0.08$ ). Cause of death was sepsis in two patients and multiorgan dysfunction in the third patient in the persistent high VIS (48 h) group and postoperative bleeding in the patient in the persistent low VIS (48 h) group.

On regression analysis, with diagnosis (CHD vs. cardiomyopathy), CPB time, persistent high

Table 4. Comparison of intra-operative and outcome variables—persistent high and low vasoactive–inotropic score groups at 48 h after orthotopic heart transplant

Mean (s.d.) or n (%)	High VIS (48 h) (N = 15)	Low VIS (48 h) (N = 36)	p-value
Graft ischemia time (min)	200 ( $\pm 56$ )	189 ( $\pm 48$ )	0.48
CPB time (min)	213 ( $\pm 83$ )	153 ( $\pm 57$ )	0.005
Biatial technique	12 (80%)	32 (97%)	0.4
Intensive care unit stay (days)	30.2 ( $\pm 27.4$ )	15.9 ( $\pm 11.3$ )	0.01
Mechanical ventilation (days)	12.4 ( $\pm 15.7$ )	5.9 ( $\pm 10.2$ )	0.05
Vasoactive infusion (days)	11.4 ( $\pm 9.8$ )	6.8 ( $\pm 3.8$ )	0.02
Post-op ECMO	3 (20%)	1 (4%)	0.07
Renal failure	6 (40%)	1 (3%)	<0.001
Death	3 (20%)	1 (4%)	0.07

CPB, cardiopulmonary bypass; Post-op, postoperative; ECMO, extracorporeal membrane oxygenator; VIS, vasoactive–inotropic score.

VIS at 48-h group, and mechanical circulatory support prior to OHT as covariates, ICU stay was significantly associated with persistent high VIS at 48-h group ( $p = 0.04$ ). There was no significant association between ICU stay and any other variables. High VIS at 24 h was not significantly associated with length of ICU stay.

## Discussion

In this study, we evaluated the association between VIS following OHT in children and short-term outcomes. Our study shows that persistently high VIS in the first 48 h after pediatric OHT is associated with short-term morbidities such as renal failure, increased post-OHT length of stay, and duration of pressor therapy. Although not statistically significant, death tended to be higher in those with persistent high VIS until 48 h. High VIS as defined (more than 15 on  $\geq 2$  times three h apart in 24 h) was common (55%) in the initial 24 h after OHT and does not appear to be associated with adverse outcomes. A third of subjects continued to require high dose of vasoactive agents in the subsequent 24 h, high VIS (48 h) group. CHD was the predominant underlying indication for pediatric OHT in the persistent high VIS (48 h) group.

Vasoactive inotropic score was initially proposed by Gaies et al. (12). They evaluated 174 infants (age 0–6 months) undergoing cardiovascular surgery with CPB and concluded that the maximum VIS over the first 48 h after cardiac surgery was a good predictor of poor clinical outcome such as death, cardiac arrest, mechanical circulatory support, renal replacement, and/or neurological injury. High VIS was strongly associated with poor outcomes and length of stay and duration of mechanical ventilation.

Table 3. Demographic and preoperative data: persistent high and low vasoactive–inotropic score groups at 48 h after orthotopic heart transplant

N (%)*	High VIS (48 h) (N = 15)	Low VIS (48 h) (N = 36)	p-value
Age (yr) median (range)	1.1 (0.02–17.9)	1.3 (0.04–17.9)	0.39
Male	7 (47%)	18 (50%)	0.53
Ethnicity			
Caucasian	5 (33%)	16 (47%)	0.37
African American	8 (53%)	18 (50%)	
Hispanic	1 (7%)	0 (0%)	
Asian	1 (7%)	1 (3%)	
Status 1A	14 (93%)	30 (83%)	0.76
Diagnosis			
CHD	10 (67%)	10 (28%)	0.01
Cardiomyopathy	5 (33%)	24 (67%)	
Tumor	0 (0%)	2 (5%)	
Preop mechanical ventilation	5 (33%)	9 (25%)	0.54
Preop inotropic therapy	11 (73%)	19 (53%)	0.17
Preop LVAD/ECMO	4 (26%)	9 (25%)	0.07

\*Value expressed as number (percentage).

CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenator; LVAD, left ventricular assist device; OHT, orthotopic heart transplant; Preop, preoperative; VIS, vasoactive–inotropic score.

Davidson et al., in a study on 70 infants ( $\leq 90$  days of age) undergoing cardiothoracic surgery found that a higher VIS at 48 h after cardiothoracic surgery was strongly associated with increased length of ventilation and prolonged ICU and total hospital stay (13). Their results also showed that high VIS at 48 h was better than VIS maximum in predicting short-term morbidity, suggesting that the duration, rather than the intensity of pressor support, may be a marker of adverse outcomes. Butts et al. studied low cardiac output syndrome and maximum VIS in neonates ( $n = 76$ ) undergoing cardiac surgery requiring CPB (14). They reported a moderate association of increasing VIS with longer duration of mechanical ventilation as well as ICU stay. Again maximum VIS did not correlate with the total hospital length of stay.

All these previous studies on VIS have been on neonates and infants up to 6 months of age. Our study cohort included all patients  $< 18$  yr of age at the time of transplant and had a median age of 1.4 yr. This is the first study to evaluate the prognostic utility of VIS following pediatric OHT.

We evaluated both the intensity of vasoactive therapy and the duration for which high-intensity therapy was required. Our study showed that high VIS in the initial 24 h was quite common after OHT, specifically in those with longer CPB time, but was not significantly associated with adverse short-term outcomes. We speculate that high requirement of vasoactive agents in the initial 24 h after OHT was probably due to the transient circulatory changes secondary to prolonged CPB. In contrast, a persistent high VIS for 48 h may be a marker of worse underlying physiology. These findings are similar to those reported recently by other investigators. (12–14).

Children undergoing OHT for CHD tended to have high VIS (48 h) in this study. This goes along with the findings from previous studies as well (15–17). It has been shown that perioperative morbidity in patients with CHD undergoing OHT is higher when compared with patients with cardiomyopathy undergoing OHT. Reoperation, need for reconstructive procedures, high technical complexity of the surgical procedure, increased pulmonary vascular resistance, and allograft sensitization may all contribute to the higher postoperative severity of illness in these patients. Patients with CHD also have a significantly longer CPB time; however, neither diagnosis nor CPB time were independently associated with postoperative length of stay following OHT in our study.

Renal failure in the perioperative period has been shown to be associated with increased mortality and morbidity after OHT (18–20). Our data suggest that there is a higher occurrence of acute renal failure in patients persistently needing high vasoactive support in the initial 48 h after OHT. The association between high VIS and postoperative renal failure may have physiological plausibility—renal failure in this scenario is often prerenal related to hypoperfusion of the kidney. Further, renal failure may be a key factor in the pathway to adverse outcomes such as prolonged length of stay and death.

Persistent requirement of vasoactive agents as shown by high VIS (48 h) may likely be a surrogate marker of disease severity, rather than the cause of increased morbidity. However, there have been a few studies which show that use of vasopressin and dopamine in the immediate postoperative period is associated with poor short-term outcomes (21, 22).

The VIS is an objective measure of the level of inotropic support and therefore severity of illness. This tool may have potential utility in the comparison of VIS-adjusted outcomes across transplant centers for research and clinical improvement purposes. In addition, as a persistent high VIS at 48 h is associated with longer ICU stay and short-term adverse outcomes following OHT, it may be useful in counseling families at an early time point. It is possible that a high VIS, if validated in larger multicenter studies, may aid in risk stratification for future trials of therapeutic interventions in this population.

#### **Study limitations**

Our study is a retrospective review from a single institution. Even though the sample size was small, the pediatric OHT population is relatively rare but homogenous. Due to the retrospective nature, data collection depended on the extent of documentation in the medical records. The clinical management of patients was not protocol-driven and may have varied based on the judgment and practice of individual clinicians. Our retrospective study was not intended to investigate the causality between use of various vasoactive agents and short-term morbidity following OHT in children.

#### **Conclusion**

To our knowledge, this is the first study comparing outcomes of pediatric heart transplantation based on the post-transplant VIS. This study validates the use of VIS in pediatric OHT recipients. Persistent requirement of high doses of

vasopressor and inotropes at 48 h post-OHT (high VIS 48 h) is independently associated with increased short-term morbidity after pediatric OHT. Further prospective studies with stringent protocols for inotrope management are required to assess the role of VIS in predicting long-term outcome and to evaluate a causal relationship, if any, between high inotrope use and adverse outcomes including mortality.

#### Authors' contributions

Yamuna Sanil involved in data collection, analysis, and drafting of the article; Sanjeev Aggarwal contributed to concept/design, statistics, interpretation, and critical revision of the manuscript.

#### Financial disclosures

None.

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