Vasoactive–inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass*

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LEARNING OBJECTIVES

After participating in this educational activity, the participant should be better able to:

1. Recognize the common vasoactive agents used in infants after cardiopulmonary bypass.
2. Recognize the components of the vasoactive-inotropic score.
3. Identify how the vasoactive-inotropic score can be used in aiding outcome prediction in infants after cardiopulmonary bypass.

Unless otherwise noted below, each faculty or staff's spouse/life partner (if any) has nothing to disclose.

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Objective: **Inotrope score has been proposed as a marker of illness severity after pediatric cardiac surgery despite a lack of data to support its use as such. The goal of this study was to determine the association between inotropic/vasoactive support and clinical outcome in infants after cardiac surgery.**

Design: **Retrospective chart review.**

Setting: **Dedicated pediatric cardiothoracic intensive care unit at an academic, tertiary care medical center.**

Patients: **One hundred seventy-four patients 0 to 6 months of age admitted to the cardiothoracic intensive care unit after cardiac surgery with cardiopulmonary bypass between August 2007 and June 2008. Forty-three percent were neonates, and 39% had functional single ventricle physiology.**

Interventions: **None.**

Measurements and Main Results: **Hourly doses of all vasoactive medications were recorded for the first 48 hrs after admission to the cardiothoracic intensive care unit and a vasoactive–inotropic score was calculated. The maximum vasoactive–inotropic score level over the first 48 hrs was a good predictor of poor clinical outcome (death, cardiac arrest, mechanical circulatory support, renal replacement therapy, and/or neurologic injury). After controlling for diagnosis, high maximum vasoactive–inotropic score was strongly associated with a poor outcome with an adjusted odds ratio of 8.1 (95% confidence interval, 3.4–19.2; $p < .001$) compared with patients with a low maximum vasoactive–inotropic score. High vasoactive–inotropic score was also associated with prolonged cardiothoracic intensive care unit stay, duration of mechanical ventilation, and time to negative fluid balance.**

Conclusions: **The amount of cardiovascular support in the first 48 hrs after congenital heart surgery with cardiopulmonary bypass predicts eventual morbidity and mortality in young infants. The degree of support is best characterized by a maximum vasoactive–inotropic score obtained during this period. The usefulness of vasoactive–inotropic score as an independent predictor of clinical outcome in infants after cardiac surgery may have important implications for future cardiothoracic intensive care unit research. (Pediatr Crit Care Med 2010; 11:234–238)**

KEY WORDS: congenital; cardiac surgery; intensive care; cardiology; outcomes

***See also p. 307.**

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Infants who undergo congenital heart surgery (CHS) with cardiopulmonary bypass (CPB) are at high risk for significant postoperative morbidity and mortality (1–6). Although these potential adverse outcomes have been well described, there remains a critical need to identify and quantify clinical factors from the early postoperative period that are indicative of illness severity and short-term outcome. Identification of these variables could improve both clinical care and clinical research in the postoperative setting after CHS.

The inotrope score was initially described in a study by Wernovsky and colleagues (7). The purpose of this score was to quantify the amount of cardiovascular support received by neonates after the arterial switch operation to adjust the interpretation of measured thermodilution cardiac output based on the degree of support. This inotrope score and various adaptations have subsequently been used in clinical research as a measure of illness severity in patients undergoing CHS (8–11) despite the fact that the score has yet to be established as a predictor of outcome. In fact, there are only limited data to support the use of any clinical marker as an outcome predictor in the early postoperative period, thus hampering clinical management and high-quality research in the pediatric cardiac intensive care setting.

To address this knowledge gap, we undertook this study with the purpose of evaluating inotropic score as a predictor of morbidity and mortality in the early postoperative period among infants who underwent CHS with CPB. We hypothesized that patients who had higher levels of cardiovascular support in the first 48 hrs after CPB would be more likely to experience morbidity and/or mortality compared with those who required less.

MATERIALS AND METHODS

We conducted a medical record review of a consecutive cohort of all infants 0 to 6 mos of age who underwent CHS with CPB at our institution between August 2007 and June 2008. One hundred seventy-four infants admitted to the cardiothoracic intensive care unit (CICU) after CHS were identified from the Michigan Congenital Heart Center database. Approval for the study was obtained from the University of Michigan human subject Institutional Review Board before data collection began. Demographic and clinical data were abstracted from electronic records and paper charts. These data included patient age at the time of surgery, anatomic diagnosis, primary procedure performed, preoperative use of inotropic and vasoactive medications, and CPB, aortic crossclamp, and circulatory arrest times. In addition, patients were categorized by the Risk Adjustment in Cardiac Surgery (RACHS-1) method as described by Jenkins (12, 13).

Vasoactive medications are typically started in the operating room at the discretion of the attending cardiac surgeon and anesthesiologist based on individual patient characteristics, including age, residual lesions, transesophageal echocardiographic findings, and physiological status. On arrival to the CICU, medications are adjusted by the bedside nurse under the direction of the CICU medical team. Patients with hypotension typically receive dopamine and epinephrine initially, but vasopressin is commonly used when patients have tachyarrhythmias or sinus rates that prohibitively limit the length of diastole. There are no protocols for the initiation or titration of particular medications in either location.

Inotrope Score and Vasoactive–Inotrope Scoring. The hourly doses of the following inotropic and vasoactive medications were recorded for the first 48 hrs after postoperative admission to the CICU: dopamine, dobutamine, epinephrine, norepinephrine, milrinone, and vasopressin. In our analysis, the inotrope score (IS) was calculated as described by Wernovsky (7) (Box 1). We expanded this formula to include other vasoactive agents commonly used in current practice to define a vasoactive–inotropic score (VIS) (Box 1). We chose to use coefficients for milrinone, vasopressin, and norepinephrine that would convert them to an integer value and to give each medication equal weight in the calculation as originally done by Wernovsky and colleagues (7).

Box 1

Wernovsky IS = dopamine dose (μg/kg/min)
+ dobutamine dose (μg/kg/min)
+ 100 × epinephrine dose (μg/kg/min)

VIS = IS + 10 × milrinone dose (μg/kg/min)
+ 10,000 × vasopressin dose (U/kg/min)
+ 100 × norepinephrine dose (μg/kg/min)

The maximum IS and VIS for both the first 24 hrs and subsequent 24 hrs were calculated. Also, the mean IS and VIS were obtained by averaging the hourly scores during the first and second 24-hr periods. Subjects were classified into one of five mutually exclusive groups, determined *a priori* based on clinical experience, representing increasing inotrope support (Table 1). In our institution, a patient who requires moderate cardiovascular support on return to the intensive care unit is typically receiving vasoactive infusions at dosages that would result in a VIS of approximately 15. Thus, we set scores in this range as the midpoint in the classification scheme for the first 24 hrs and reasoned that most patients would be on lower doses during the second 24 hrs. Patients were assigned to the highest classification group achieved during either the first or subsequent 24-hr periods (i.e., a patient with a group 4 score at 24 hrs and a group 3 score at 48 hrs was classified as group 4 support).

Table 1. Classification system based on inotropic score

Group[a]	IS or VIS in First 24 hrs	IS or VIS 24–48 hrs
1	<10	<5
2	10–14	5–9
3	15–19	10–14
4	20–24	15–19
5	≥25	≥20

IS, inotrope score; VIS, vasoactive–inotropic score.

[a]Group assignment based on highest support level in either time period. (Example: Patient with maximum IS 22 in first 24 hrs and 14 in the subsequent 24 hrs would be classified as group 4).

Outcome Variables. The primary outcome of analysis, developed *a priori*, was a dichotomous composite morbidity and mortality variable, termed "poor outcome." A poor outcome occurred if a patient experienced at least one of the following: death (in-hospital at any point or within 30 days if out of the hospital), cardiac arrest, need for mechanical circulatory support, need for renal replacement therapy, or central nervous system injury (stroke with associated clinical findings or seizure). Morbidity events were identified from the medical record. For mortality, the vital status of each patient was confirmed either from the medical record or by contacting their primary cardiologist.

Secondary outcomes included CICU length of stay, time to first extubation, and time to first negative fluid balance. To reduce the influence of systems factors, we used our institution's computer order entry system to determine time periods for these variables. Cardiothoracic intensive care unit length of stay was considered to end when an order was written to transfer the patient regardless of how long a patient remained in the unit thereafter to control for the influence of floor bed availability. Similarly, time to first extubation was determined from the time of CICU admission to the time of the extubation order. The time to first negative fluid balance was defined as the time from admission to the end of the first 8-hr shift in which total output (urine + chest tube) exceeded total input. Patients were classified into the upper 25% (i.e., prolonged)

Table 2. Patient characteristics

Characteristic	N = 173
Age at surgery	
0–1 mos, n (%)	75 (43%)
1–6 mos	98 (57%)
Female, %	45%
Functional single ventricle, n (%)	68 (39%)
RACHS-1 category, n (%)	
1–3	109 (63%)
4–6	64 (37%)
Median CPB time, mins (range)	85 (32–556)
Median aortic crossclamp time, mins (range)	36 (0–218)
Postoperative use of vasoactive agents, n (%)	
Dopamine	151 (87%)
Epinephrine	95 (55%)
Vasopressin	56 (32%)
Milrinone	107 (62%)
Median maximum VIS (range)	
24 hrs	13 (0–50)
48 hrs	10 (0–50)
Median maximum IS	
24 hrs	10 (0–33)
48 hrs	7 (0–50)

RACHS-1, Risk Adjustment in Congenital Surgery; CPB, cardiopulmonary bypass; VIS, vasoactive–inotropic score; IS, inotrope score.

Table 3. Frequency of primary and secondary outcomes

Outcome	
Combined morbidity–mortality (poor outcome), n (%)	35 (20%)
Death	20 (12%)
Mechanical circulatory support	14 (8%)
Renal replacement therapy	2 (1%)
Cardiac arrest	15 (9%)
Central nervous system injury	10 (6%)
Time to first extubation, hrs, median (75th percentile cutoff)	94.9 (172)
CICU length of stay, days, median (75th percentile)	5.5 (10.9)
Time to first negative fluid balance, hrs, median (75% ile)	37.0 (44.5)

CICU, cardiothoracic intensive care unit.

versus the lower 75% of time to event for each of these secondary outcome variables.

Statistical Analysis. We calculated and plotted the true-positive rate (sensitivity) against the false-negative rate (1-specificity) for each group category (per Table 1) in relation to poor outcome status for each of the four scoring methods (maximum VIS and IS, mean VIS and IS). We then used receiver operating characteristics to compare the areas under the curve for each scoring method. For the scoring method and cutoff point subsequently chosen as most accurate (maximum VIS), we used unconditional logistic regression to calculate odds ratios and 95% confidence intervals to estimate the strength and precision of the statistical associations between VIS and each dichotomous outcome measure. Potential confounding of these associations was assessed for a variety of covariates, but only RACHS-1 score, dichotomized as 0 to 3 vs. 4 to 6, was found to appreciably change the risk estimates (>10%), so RACHS-1 was included in each of the final multivariate models.

Table 4. Performance characteristics of IS and VIS

Scoring Method	ROC Area	SE	Lower 95% CI	Upper 95% CI
Maximum VIS	0.83	0.035	0.76	0.90
Mean VIS	0.82	0.039	0.75	0.90
Maximum IS	0.78	0.042	0.70	0.86
Mean IS	0.77	0.046	0.68	0.86

VIS, vasoactive–inotropic score; IS, inotrope score; ROC, receiver operating characteristic; CI, confidence interval.

RESULTS

One hundred seventy-four infants had hourly inotrope doses recorded for the first 48 hrs after surgery; patients who were discharged or died within the first 48 hrs had hourly doses recorded until that point. One patient was discharged from the CICU to another institution's intensive care unit and was thus excluded from the final analysis of 173 patients. Patient demographic data are displayed in Table 2. Deep hypothermic circulatory arrest was used in 61 patients (35%). Twenty-eight (16%) patients required vasoactive support before their operation; dopamine was used in 14 cases (8%), epinephrine in two (1%), vasopressin in one, and milrinone in 17 (10%). No patient received either norepinephrine or dobutamine.

The frequencies of primary and secondary outcomes are displayed in Table 3. Thirty-five patients experienced a poor outcome (20%), including 20 deaths (12%). Of these, 20 (57%) outcome events occurred in patients with single ventricle physiology, and 12 (34%) occurred after stage 1 palliation for patients with a hypoplastic left ventricle.

Comparing Different Measures of IS in Relation to Outcome. The performance characteristics of the four inotrope score measures are shown in Table 4. The areas under the receiver operating characteristic curves for the four measures were not statistically different from one another; all functioned well as predictors of a poor outcome. The receiver operating characteristic area under the curve was highest for the maximum VIS at 0.83, and the SE was the smallest (0.035) of the four methods. Thus, we chose to further analyze maximum VIS given its ease of measurement and its inclusion of additional medications now commonly used in practice (vasopressin and milrinone).

Table 5. Sensitivity and specificity proportions for predicting poor outcome according to maximum VIS cut points

Maximum VIS Group	1	2	3	4	5
Sensitivity	1.0	0.97	0.91	0.71	0.40
Specificity	0	0.39	0.61	0.80	0.92

VIS, vasoactive–inotropic score.

Determining the Optimal Cutoff for 'High VIS.' We next sought to dichotomize maximum VIS into a "high" and "low" variable based on the sensitivity and specificity of this measurement as a predictor of poor outcome at various cutoff points. The sensitivity and specificity of maximum VIS at the five different *a priori* cut points is shown in Table 5. We selected cutoff point 4 (maximum VIS 20–24 in first 24 hrs, 15–19 in subsequent 24 hrs) as the optimal cutpoint with a sensitivity of 0.71 and a specificity of 0.80 for predicting a poor outcome. In subsequent analyses, the outcomes of patients with a maximum VIS in groups 4 and 5 (high VIS) were combined and compared with those of patients with a maximum VIS ≤3 (low VIS).

Estimating the Strength of Association Between Maximum VIS and Outcome. Results from the logistic regression modeling, representing the relative odds for a given outcome in patients with high VIS versus low VIS after controlling for RACHS-1 category, are shown in Table 6.

High maximum VIS was strongly associated with poor outcome with an adjusted odds ratio of 8.1 (95% confidence interval, 3.4–19.2; $p < .001$). On average, patients in the high VIS category were also more likely than those in the low VIS category to experience prolonged time to first extubation (odds ratio, 5.5; 95% confidence interval, 2.5–12; $p < .001$), prolonged CICU length of stay (odds ratio, 2.4; 95% confidence interval, 1.1–5.2;

Table 6. Association of maximum VIS with outcome

Outcome	N	Percent	OR[a]	95% CI	*p* Value
Poor outcome	35	20%	8.1	3.4–19.2	<.001
Prolonged time to extubation	42	25%	5.5	2.5–12.0	<.001
Prolonged CICU length of stay	43	25%	2.4	1.1–5.2	.02
Prolonged time to negative fluid balance	43	25%	3.0	1.4–6.7	.006

VIS, vasoactive–inotropic score; OR, odds ratio; CI, confidence interval; CICU, cardiothoracic intensive care unit; RACHS-1, Risk Adjustment in Congenital Surgery.

[a]OR represents odds of a poor outcome in high VIS group relative to low VIS group after controlling for RACHS-1 category.

$p = .02$), and prolonged time to negative fluid balance (odds ratio, 3.0; 95% confidence interval, 1.4–6.7; $p = .006$). Further data analysis demonstrated no effect modification by patient age or single-ventricle anatomy on the association between VIS and poor outcome.

DISCUSSION

The results of this study provide evidence that infants requiring high levels of vasoactive support during the early postoperative period after CHS with CPB have an increased likelihood of morbidity and mortality. The data suggest that the degree of support is best defined by calculating a maximum VIS using the doses of dopamine, epinephrine, vasopressin, and milrinone administered in the first 48 hrs after admission to the cardiac intensive care unit.

Whether this scoring measure will consistently predict adverse outcomes in similar patient populations remains to be determined through other clinical research efforts designed to validate our findings. It is important to note that our data do not justify the modification of an individual patient's treatment to avoid having a high VIS; we are not suggesting that inotrope and vasoactive support cause adverse outcomes. We would argue that a high VIS is a surrogate marker of illness severity after cardiac surgery in infants, and our objective in this study was simply to determine whether a measure of vasoactive support could serve as an intermediate predictor of eventual clinical outcome.

This objective is important because clinicians who manage pediatric cardiac surgical patients after CPB in the CICU currently lack good evidence to estimate the likelihood of eventual morbidity and mortality. Despite the large volume of clinical and physiological data obtained at the time of admission and on subsequent days in the intensive care unit, previous studies either do not address or have failed to show an association between these data and eventual clinical outcomes. This explains, in part, why no validated severity of illness index exists for this patient population.

A robust severity of illness scoring system would be a tremendous advance in evidenced-based practice in the CICU. Such a measure would be particularly useful to practitioners trying to decide between various diagnostic and therapeutic options for patients recovering from CHS, some of which are highly invasive with potentially high risks. Furthermore, the ability of clinicians to counsel families on their child's likelihood of recovery from surgery is limited by the lack of these data. Finally, quality of care metrics, including accurate measures of mortality and morbidity outcomes, are needed for comparison purposes within and across CICUs (14). We would not claim that the VIS can fulfill these needs by itself, but we do hypothesize based on our data that this measure may be a useful component of a severity of illness index. It will be important to investigate other clinical data from the early postoperative period to identify additional intermediate predictors of outcome in pediatric cardiac surgical patients and to develop a multivariable illness severity score that could lead to improved clinical care and guide therapeutic decision-making.

Our findings related to VIS and its ability to predict outcome may also have important implications for clinical research in the CICU. The lack of verified intermediate predictors of outcome complicates the design of clinical trials that are meant to show a benefit in the perioperative period. It is difficult for investigators to choose primary outcomes that accurately assess the efficacy of interventions designed to improve myocardial and multiorgan recovery after CPB. Mortality alone is an inadequate end point because fatality rates are now so low outside of patients undergoing single ventricle palliation; thus, required study sample sizes based on mortality are prohibitively large to conduct in single-institution CHS populations. However, other clinical indicators of early postoperative recovery, like time to first extubation, time to negative fluid balance, measures of acute kidney injury, and CICU length of stay, may be difficult to interpret as research outcomes because of significant variations in practice patterns and systems-based influences. As such, there is disagreement among clinical investigators on the optimal design of clinical intervention trials. The Pediatric Logistic Organ Dysfunction score was developed to deal with this problem in the general pediatric critical care community (15) and serves as a model for what might be achieved in pediatric CICUs with further study of clinical variables like the VIS.

We chose to study the amount, rather than the specific types, of vasoactive and inotropic support as it relates to outcome. However, universal agreement is lacking among pediatric cardiac intensivists regarding the optimal use of inotropic and vasoactive drugs in infants undergoing CHS, and evidenced-based literature is limited. Hoffman and colleagues demonstrated in a randomized, placebo-controlled trial that prophylactic administration of milrinone may prevent the onset of low cardiac output syndrome in patients undergoing repair or palliation of biventricular congenital heart disease (16). The use of milrinone is now common in many CICUs. Some authors have suggested that dopamine and vasopressin may be associated with unfavorable elevations in myocardial oxygen consumption, systemic vascular resistance, and perhaps with worse clinical outcomes in select groups of patients (17, 18), whereas others have come to different conclusions (19). However, retrospective studies, including our own, are inadequate to answer these questions about the selective use of specific agents because an individual clinician's choice to use a particular medication (i.e., vasopressin) may be directly related to factors that impact outcome, most notably severity of illness. This confounding by indication cannot generally be controlled for retrospectively. Prospective trials, preferably randomized, will be necessary to better determine the best

strategy for use of specific medications in a given clinical situation.

Beyond those already discussed, this study has some important limitations to consider. First, this is an analysis of data from a single center with a relatively high proportion of single ventricle and other complex anatomic diagnoses in the cohort. Although we adjusted for diagnosis using RACHS-1, our findings may not be generalizable to other patient populations. Similarly, because we included only infants, it is not known whether VIS would predict morbidity and mortality in older children undergoing CHS. The reasons for use of specific medications for individual patients cannot be determined retrospectively, and the choice to use certain medications in our institution may be different from other CICUs. Finally, although we tested both the maximum and mean values of vasoactive support within the first 48 hrs after CPB, it is possible that other methods of defining the degree of cardiovascular support may be superior to these formulas.

CONCLUSIONS

We have provided suggestive evidence that the amount of cardiovascular support in the first 48 hrs after CHS with CPB predicts eventual morbidity and mortality in young infants. We found the degree of support best characterized by a maximum VIS in the first or subsequent 24 hrs after admission. Future research is needed to determine whether these results are reproducible, what other clinical data independently predict clinical outcomes of interest in patients undergoing CHS with bypass, and to develop a CICU-specific index of illness severity. We believe such a tool would improve evidenced-based practice, measurement of quality, and design of clinical trials in the CICU.

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