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Comparison of Maximum Vasoactive Inotropic Score and Low Cardiac Output Syndrome As Markers of Early Postoperative Outcomes After Neonatal Cardiac Surgery

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Abstract

Low cardiac output syndrome (LCOS) and maximum vasoactive inotropic score (VIS) have been used as surrogate markers for early postoperative outcomes in pediatric cardiac surgery. The objective of this study was to determine the associations between LCOS and maximum VIS with clinical outcomes in neonatal cardiac surgery. This was a secondary retrospective analysis of a prospective randomized trial, and the setting was a pediatric cardiac intensive care unit in a tertiary care children's hospital. Neonates ($n = 76$) undergoing corrective or palliative cardiac operations requiring cardiopulmonary bypass were prospectively enrolled. LCOS was defined by a standardized clinical criteria. VIS values were calculated by a standard formula during the first 36 postoperative hours, and the maximum score was recorded. Postoperative outcomes included hospital mortality, duration of mechanical ventilation, intensive care unit (ICU) and hospital lengths of stay (LOS), as well as total hospital charges. At surgery, the median age was 7 days and weight was 3.2 kg. LCOS occurred in 32 of 76 (42%) subjects. Median maximum VIS was 15 (range 5–33). LCOS was not associated with duration of mechanical ventilation, ICU LOS, hospital LOS, and hospital charges. Greater VIS was moderately associated with a longer duration of mechanical ventilation ($p = 0.001$, $r = 0.36$), longer ICU LOS ($p = 0.02$, $r = 0.27$), and greater total hospital costs ($p = 0.05$, $r = 0.22$) but not hospital LOS ($p = 0.52$). LCOS was not associated with early postoperative outcomes. Maximum VIS has only modest correlation with duration of mechanical ventilation, ICU LOS, and total hospital charges.

Keywords

Vasoactive inotropic score; Low cardiac output syndrome; Neonates; Cardiac surgery; Postoperative outcomes; Cardiopulmonary bypass

Introduction

Neonates undergoing cardiac surgery requiring cardiopulmonary bypass (CPB) are at increased risk for morbidity and mortality compared with other age groups [14]. However, with refinements in operative techniques and improvement in perioperative management, mortality rates have significantly decreased [14]. This has allowed the focus of outcomes research to shift from preventing mortality to decreasing morbidities. There has been an extensive amount of research into the preoperative factors associated with poor outcomes. These include patient demographics (anatomy, prematurity, weight, genetic syndrome), biological markers, and the creation of complexity scores [4–6, 13, 16, 23]. However, the absence of validated early postoperative markers that are prognostic of important longitudinal outcomes impedes research in the field. An ideal early outcome measure would be easily measured, reproducible, and, most importantly, independently correlated with other measures of short- and long-term outcomes. A commonly used marker of postoperative outcome is the development of low cardiac output syndrome (LCOS). A clinical definition of LCOS was the primary end point for the PRIMACORP study, a large multi-institutional randomized trial evaluating the efficacy of milrinone in preventing LCOS in infants and children after corrective cardiac surgery [10]. In this study, LCOS was defined as clinical signs and symptoms of LCO (oliguria, tachycardia, poor perfusion, or cardiac arrest) that required inotropic support 100% above baseline, administration of a new inotropic agent, or the use of mechanical circulatory support or other maneuvers used to improve cardiac output (i.e., cardiac pacing). Although they are not previously validated outcome measures, patients with LCOS in this study had longer durations of mechanical ventilation and hospital length of stay (LOS) than patients without LCOS [10].

Another frequently used marker of postoperative outcomes is inotropic score. Inotropic score was first described in the Boston Circulatory Arrest Study to quantify the amount of pharmacologic cardiovascular support required during the postoperative period [25]. Inotropic score has been used in other clinical studies as a measurement of illness severity [2, 3, 11, 15]. However, until recently, inotropic score has not been validated as a surrogate marker of morbidity and mortality. Gaies et al. [7] proposed expanding the inotropic score to include other commonly used vasoactive medications, such as milrinone, vasopressin, and norepinephrine, and called it a vasoactive-inotrope score (VIS). In that study, VIS was associated with post-operative morbidity and mortality in infants <6 months old undergoing cardiac surgery requiring CPB.

Despite being used frequently as an outcome measure in clinical trials, neither LCOS nor VIS has been validated in an exclusively neonatal population undergoing cardiac surgery requiring CPB. The objective of this study was to compare the surrogate markers of LCOS

and VIS with respect to the strength of associations to clinical outcomes after neonatal cardiac surgery.

Methods and Materials

The study was a secondary analysis of a prospective randomized controlled trial comparing preoperative glucocorticoid therapy in 76 neonates ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00934843) Identifier NCT00934843) [8]. The study was approved by the Medical University of South Carolina's Institutional Review Board. Informed written consent was obtained from the parent or legal guardian of all participants.

Study Population

Patient selection, enrollment, and randomization have been previously described [8]. In summary, all inpatient neonates (< 30 days old) scheduled to undergo cardiac surgery involving CPB from the time period of July 2007 through July 2009 were eligible for this study. Exclusion criteria included prematurity (defined as < 36 weeks gestational age at the time of surgery), previous treatment with or contraindication to steroid therapy, or the preoperative use of mechanical circulatory support or active resuscitation at the time of proposed randomization. Patients were randomly assigned to either preoperative placebo and intraoperative methylprednisolone (one dose) or preoperative and intraoperative methylprednisolone (two doses total).

Cardiac Surgical Procedure and Postoperative Protocol

All patients were taken care of after surgery in a dedicated pediatric cardiac intensive care unit (PCICU). Typically, milrinone at 0.5 mcg/kg/min and dopamine at 5 mcg/kg/min were initiated before separation from CPB and titrated as needed. Titration, addition, and discontinuation of vasoactive medications in this study were at the discretion of the cardiac intensivists and surgeons caring for the patients based on each patient's physiological state and were not driven by strict protocol. Considerations involved in the choice of medications included ventricular function, echo-cardiographic findings, and physiological parameters. Typically patients received milrinone and dopamine as first-line inotropic agents. The second-line therapies were often epinephrine for hypotension with ventricular dysfunction or vasopressin when hypotension was present with adequate ventricular function or in patients with tachyarrhythmias.

Study Design

The presence of LCOS within the first 36 h from admission to the PCICU was prospectively determined using the same definition employed in the PRIMACORP study: clinical signs and symptoms of LCO (e.g., tachycardia, oliguria, cold extremities, cardiac arrest, etc.) that required one or more of the following interventions: mechanical circulatory support, escalation of existing pharmacological circulatory support to >100% over baseline, or initiation of new pharmacological circulatory support (excluding therapy for hypertension) [10]. The determination of LCOS was made by 2 independent reviewers (E. M. G., A. M. A.) and then agreed on by both reviewers. For each patient, VIS was calculated hourly during the first 36 h after admission to the PCICU, and the maximum VIS was recorded.

VIS was calculated by the formula listed in Table 1 [7]. Outcomes were postoperative duration of mechanical ventilation, ICU and hospital LOS, total hospital charges, and hospital death.

Statistical Analysis

Outcomes were not normally distributed, and therefore nonparametric statistical tests were used. Continuous outcomes are presented as median with interquartile range (IQR). Patients were grouped into those who met the criteria for LCOS and those who did not. Outcomes were compared between groups using Wilcoxon rank sum test. Maximum VIS as a continuous variable was correlated with outcomes using Spearman correlation test. Statistical analyses were performed with SAS (version 9.1.3; SAS, Cary, NC), and $p < 0.05$ was considered significant.

Results

Data were complete in all 76 patients enrolled. Patient demographics, cardiac diagnoses, surgical procedures performed, and intraoperative parameters have been previously described [8]. Diagnostic classification based on Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) classification, and the presence of a single ventricle is listed in Table 2. Median gestational age was 39 weeks (IQR 38–39.3). Median weight at surgery was 3.2 kg (IQR 2.9–3.5). Deep hypothermic arrest was used in 31 (41%) of the patients. Extracorporeal membrane oxygenation (ECMO) in the operating room was required in two patients. These patients were excluded from the analysis of VIS secondary to the use of ECMO, which was believed to artificially lower the inotropic requirements and, therefore, that maximum VIS would not accurately depict their clinical state. After surgery, dopamine was used in 74 (97%), milrinone in 73 (96%), epinephrine in 31 (41%), vasopressin in 23 (30%), and dobutamine in 1 patient.

The incidence of LCOS was 42% (32 of 76 patients). Twenty-nine of the 32 patients met the criteria for LCOS based on symptoms of LCOS and either initiation of a new inotropic agent or an increase of an inotropic agent $>100\%$ above baseline. The remaining three patients met LCOS criteria for use of mechanical support. The presence of LCOS was not associated with duration of mechanical ventilation, ICU or hospital LOS, or total hospital charges (Table 3).

For the entire cohort, median maximum VIS was 15 (IQR 12–20). Maximum VIS was moderately correlated with duration of mechanical ventilation ($r = 0.36$, $p = 0.001$), ICU LOS ($r = 0.27$, $p = 0.02$), and hospital charges ($r = 0.22$, $p = 0.05$) (Figs. 1, 2, 3). However, maximum VIS was not correlated with total hospital LOS ($r = 0.08$, $p = 0.52$).

There were two deaths resulting in a 97% hospital survival. One death was secondary to gram-negative sepsis 19 days after central-shunt placement and pulmonary arterioplasty for tetralogy of Fallot with pulmonary atresia. The patient did not have LCOS in the early postoperative period, and maximum VIS was 5. The other death occurred from multiorgan failure 38 days after complete repair for truncus arteriosus in a patient with other congenital anomalies. The patient had LCOS in the immediate postoperative period and maximum VIS of 15.

Discussion

In this study of neonates undergoing cardiac surgery with the use of CPB, the important findings are three-fold. First, despite excellent outcomes (97% hospital survival), the incidence of prospectively determined LCOS was high at 42%. Second, despite its correlation with outcomes in older children, LCOS was not associated with early postoperative outcomes in neonatal cardiac surgery. Third, maximum VIS was moderately correlated with some early postoperative outcomes.

The incidence of LCOS in this study was 42%. The PRIMACORP trial, which included 227 patients undergoing corrective surgery at a median age of 3 months, had a considerably lower incidence of LCOS in the placebo group: 25.9% [10]. In previous studies where cardiac output was directly measured in infants undergoing corrective procedures, the incidence of cardiac index <2.0 L/min/m² was approximately 25% [8, 15]. The greater incidence of LCOS in this study may be explained by several factors. Given that our study population was exclusively neonates and that neonatal myocardium is known to be biologically immature (greater noncontractile component of myocardium, decreased norepinephrine stores, lower sarcoplasmic reticulum content, and high reliance on extracellular calcium regulation) [1, 9, 12, 19, 20], it is not surprising that a greater proportion of subjects in our study met the clinical criteria for LCOS. Second, unlike the previous mentioned studies, this study included a significant proportion of patients with single-ventricle physiology (38% in this study) and patients undergoing complex operations (59% had a RACHS-1 score of 4 to 6). These conditions often require significant resource (medication) support; concomitantly, the definition of LCOS in this study was in part determined by increased pharmacologic support. Furthermore, a prospective determination of LCOS may result in a greater incidence compared with retrospectively defined LCOS. In fact, Schroeder et al. [22] reported a similar incidence of prospectively determined LCOS (40%) in 15 infants undergoing cardiac surgery with CPB.

Despite its correlation with outcomes in older children, LCOS was not associated with early postoperative outcomes in neonatal cardiac surgery. The high incidence of LCOS in this population makes it particularly difficult to find subtle differences in early postoperative outcomes. The specificity of the current definition is too low for it to be predictive of outcomes in neonatal cardiac surgery. The relationship between longer hospital course and worse long-term neurodevelopmental outcomes in neonatal cardiac surgery has been reported [21]. The presence of LCOS and its association with long-term outcomes has yet to be explored. However, given its inability to discriminate early postoperative outcomes, it is likely to be imprecise in differentiating long-term outcomes and thus a poor choice for use as a surrogate outcome in future clinical trials involving this particular population.

In a previous study of 173 patients, with 75 (43%) neonates, greater VIS was associated with increased risk of morbidity and mortality, prolonged time to extubation, and longer postoperative ICU LOS [7]. Overall, the use of vasoactive or inotropic agents in that study was similar to the current study. However, the current study had a greater percentage of patients in RACHS-1 classification of 4–6 (59% vs. 37%). In the current study, increasing maximum VIS was moderately associated with longer postoperative mechanical ventilation,

ICU LOS, and total hospital charges. The greater percentage of RACHS-1 class-4 to -6 patients and weaker associations with early operative outcomes seen in the current study are likely reflective of this study being exclusive to neonates. Maximum VIS did not correlate with total hospital LOS. This may be explained by the complexity of other issues affecting hospital LOS in the neonatal population (i.e., feeding difficulties). Therefore, although superior to LCOS, maximum VIS is a weak surrogate marker for early postoperative outcomes. It is unclear if VIS in the immediate postoperative period will be associated with important long-term outcomes.

These results highlight the difficulties in determining important clinically relevant outcome measures in neonatal cardiac surgery. The simple measure of survival is no longer our goal. We aspire for these children to achieve “normal” lives. Research is being performed to quantify quality of life after congenital cardiac surgery [17, 18]. However, early markers that predict significant long-term outcomes remain elusive. Early brain magnetic resonance imaging may be useful in predicting neurodevelopmental outcomes [24]. However, the cost and difficulties obtaining them in this population remains prohibitive. Research is needed to find markers that are easily measured, reproducible, and, most importantly, independently correlate with other measures of short- and long-term outcomes.

Limitations

This study has some important limitations. This is a single-center study with a large population of patients with RACHS-1 classification 4 to 6, indicating that this patient population was at high risk for morbidity and mortality. LCOS and VIS may be more useful markers in less complex populations. Maximum VIS and LCOS were only compared with four other early outcome measures. Their relationship to other early and late outcomes warrants further investigation.

Conclusion

The results of this study indicate that the presence of LCOS as currently defined is not associated with early outcomes in neonates. Maximum VIS, although superior to LCOS, has only a modest correlation with length of postoperative mechanical ventilation, postoperative ICU LOS, and total hospital charges. These findings are important for future design and determination of validated primary outcomes in clinical trials in neonates undergoing cardiac surgery. They also highlight the need for continued research and development of an early marker of operative outcomes.

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Fig. 1.

Scatter plot of maximum VIS and number of postoperative mechanical ventilation days for each patient. There was a modest correlation between maximum VIS and duration of mechanical ventilation ($r = 0.36$, $p = 0.001$)

Fig. 2.

Scatter plot with correlation line showing a moderate correlation between increasing maximum VIS and longer postoperative intensive care unit LOS ($r = 0.27$, $p = 0.02$)

Fig. 3. Scatter plot with correlation line showing a moderate correlation with maximum VIS and total hospital charges ($r = 0.22$, $p = 0.05$)

Table 1

VIS

$$\text{VIS} = (\text{dopamine } [\mu\text{g/kg/min}]) + (\text{dobutamine } [\mu\text{g/kg/min}]) + (10,000 \times \text{vasopressin } [\text{U/kg/min}]) + (10 \times \text{milrinone } [\mu\text{g/kg/min}]) + (100 \times \text{epinephrine } [\mu\text{g/kg/min}]) + (100 \times \text{norepinephrine } [\mu\text{g/kg/min}])$$

Table 2

Diagnostic classification

Classifications	<i>n</i> = 76
RACHS-1 category (%)	
2	6 (8)
3	25 (33)
4	25 (33)
5	1 (1)
6	19 (25)
Corrective surgery	43 (57)
Single ventricle	29 (38)

Table 3

Associations between LCOS and postoperative outcomes

Outcome	Median (IQR) LCOS (<i>n</i> = 32)	Median (IQR) no LCOS (<i>n</i> = 44)	<i>P</i>
Mechanical ventilation (h)	100 (71–152)	75 (46–117)	0.07
ICU LOS (days)	6.8 (5.6–9.8)	6.0 (4.5–8.6)	0.35
Hospital LOS (days)	17.5 (10.0–33.0)	18 (9.5–23.5)	0.85
Hospital charges	\$209K (\$169–\$263)	\$185K (\$138–\$269)	0.17