Exploring the Role of Polycythemia in Patients With Cyanosis After Palliative Congenital Heart Surgery

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Objectives: To understand the relationship between polycythemia and clinical outcome in patients with hypoplastic left heart syndrome following the Norwood operation.

Design: A retrospective, single-center cohort study.

Setting: Pediatric cardiovascular ICU, university-affiliated children's hospital.

Patients: Infants with hypoplastic left heart syndrome admitted to our medical center from September 2009 to December 2012 undergoing stage 1/Norwood operation.

Interventions: None.

Measurements and Main Results: Baseline demographic and clinical information including first recorded postoperative hematocrit and subsequent mean, median, and nadir hematocrits during the first 72 hours postoperatively were recorded. The primary outcomes were in-hospital mortality and length of hospitalization. Thirty-two patients were included in the analysis. Patients did not differ by operative factors (cardiopulmonary bypass time and cross-clamp time) or traditional markers of severity of illness (vasoactive inotrope score, lactate, saturation, and Pao_2/Fio_2 ratio). Early polycythemia (hematocrit value > 49%) was associated with longer cardiovascular ICU stay (51.0 [± 38.6] vs 21.4 [± 16.2] d; $p < 0.01$) and total hospital length of stay (65.0 [± 46.5] vs 36.1 [± 20.0] d; $p = 0.03$). In a multivariable analysis, polycythemia remained independently associated with the length of hospitalization after controlling for the amount of RBC transfusion (weight, 4.36 [95% CI, 1.35–7.37]; $p < 0.01$). No difference in in-hospital mortality rates was detected between the two groups (17.6% vs 20%).

Conclusions: Early polycythemia following the Norwood operation is associated with longer length of hospitalization even after controlling for blood cell transfusion practices. We hypothesize that polycythemia may be caused by hemoconcentration and used as an early marker of capillary leak syndrome. (*Pediatr Crit Care Med* 2016; XX:00–00)

Key Words: congenital heart disease; hypoplastic left heart syndrome; Norwood operation; outcomes; postoperative care

There is a lack of understanding regarding the significance of hematocrit levels in the early postoperative period in cyanotic patients undergoing congenital heart surgery. Oxygen delivery relies on cardiac output, hemoglobin concentration, and arterial oxygen saturation. In the first few days following cardiopulmonary bypass (CPB), cardiac output is diminished, which implies that oxygen delivery may be improved with higher hematocrit levels (1). However, the practice of raising hemoglobin and hematocrit levels following palliative cardiac surgery is controversial for patients with cyanotic heart disease with recent reports that link poor outcomes to liberal RBC transfusion strategies (2–6).

Despite the goal-directed therapeutic implications, hematocrit levels are often by-products of various physiologic events, such as hemorrhage, phlebotomy, and RBC transfusions, in the early postoperative period. In addition, inflammation, acute renal injury, and systemic capillary leak syndrome with subsequent shifting plasma volumes importantly influence hemoglobin and hematocrit levels (7–9). Recent reports demonstrate that hematocrit levels can be used as a biomarker of various physiologic states and, more specifically, that hemoconcentration resulting from low intravascular plasma volume has been used as a marker of illness severity for a variety of diseases (10–12).

The purpose of this study is to understand the relationship of polycythemia with clinical outcome for patients with hypoplastic left heart syndrome (HLHS) following the Norwood operation. We hypothesize that high hematocrit levels in the early postoperative period may be reflective of capillary leak syndrome with

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low intravascular plasma volume and consequently linked to poor outcomes.

MATERIAL AND METHODS

This was a retrospective, single-center study performed at Lucile Packard Children's Hospital (LPCH) at Stanford University Medical Center. We identified and included all infants with HLHS or its variants who underwent stage 1 surgical palliation consisting of a modified Norwood procedure with right ventricle to pulmonary artery conduit between September 2009 and December 2012. Demographic features (age, gender, and weight), comorbidities (prematurity and chromosomal abnormalities), additional high-risk cardiac abnormalities (restrictive or intact atrial septum, total anomalous pulmonary venous return, scimitar syndrome, and left ventricle sinusoids), and intraoperative factors (CPB time (13) and cross-clamp time) were collected. Postoperative characteristics of illness severity that were recorded included peak vasoactive inotrope score as previously defined (14), delayed sternal closure, utilization of extracorporeal oxygenation (ECMO), average lactate levels (15, 16), Pa_{O_2}/Fi_{O_2} (P/F) ratio, systemic saturation measurement by pulse oximetry, heart rate, and systolic/diastolic blood pressures within the first 72 hours following the operation. Total fluid intake and output, including urine output and chest tube output, were also collected. Other postoperative variables collected included the duration of mechanical ventilation, average albumin and total protein levels, peak blood urea nitrogen, and creatinine levels following the operation. The Institutional Review Board at Stanford University Medical Center approved the study protocol.

Definitions

Several variants of hematocrit were analyzed. We identified the first recorded hematocrit at postoperative admission to the cardiovascular ICU (CVICU). Subsequently, mean, median, and nadir hematocrits were determined by processing all hematocrit measurements during the first 72 hours following the operation and recorded as continuous variables and as categorical variables based on the parametric distribution of all measured hematocrits. We defined early polycythemia as an average hematocrit value greater than 49% (equivalent to a hemoglobin level of ≈ 16 g/L) in the first 72 hours following surgery based on the distribution of all hematocrit values collected during the study period (**Fig. 1**). Because cohort assignment was calculated by the average hematocrit in the first 72 hours, patients who died within the first 72 hours following their operation were excluded from the analysis. The volume of blood transfusions was also collected and indexed to the patient's weight. The blood transfused at our center is stored in AS-3 preservative.

Clinical Management

All patients requiring intensive care following congenital heart surgery are admitted to the CVICU at LPCH. Patients requiring CPB empirically receive methylprednisolone sodium succinate

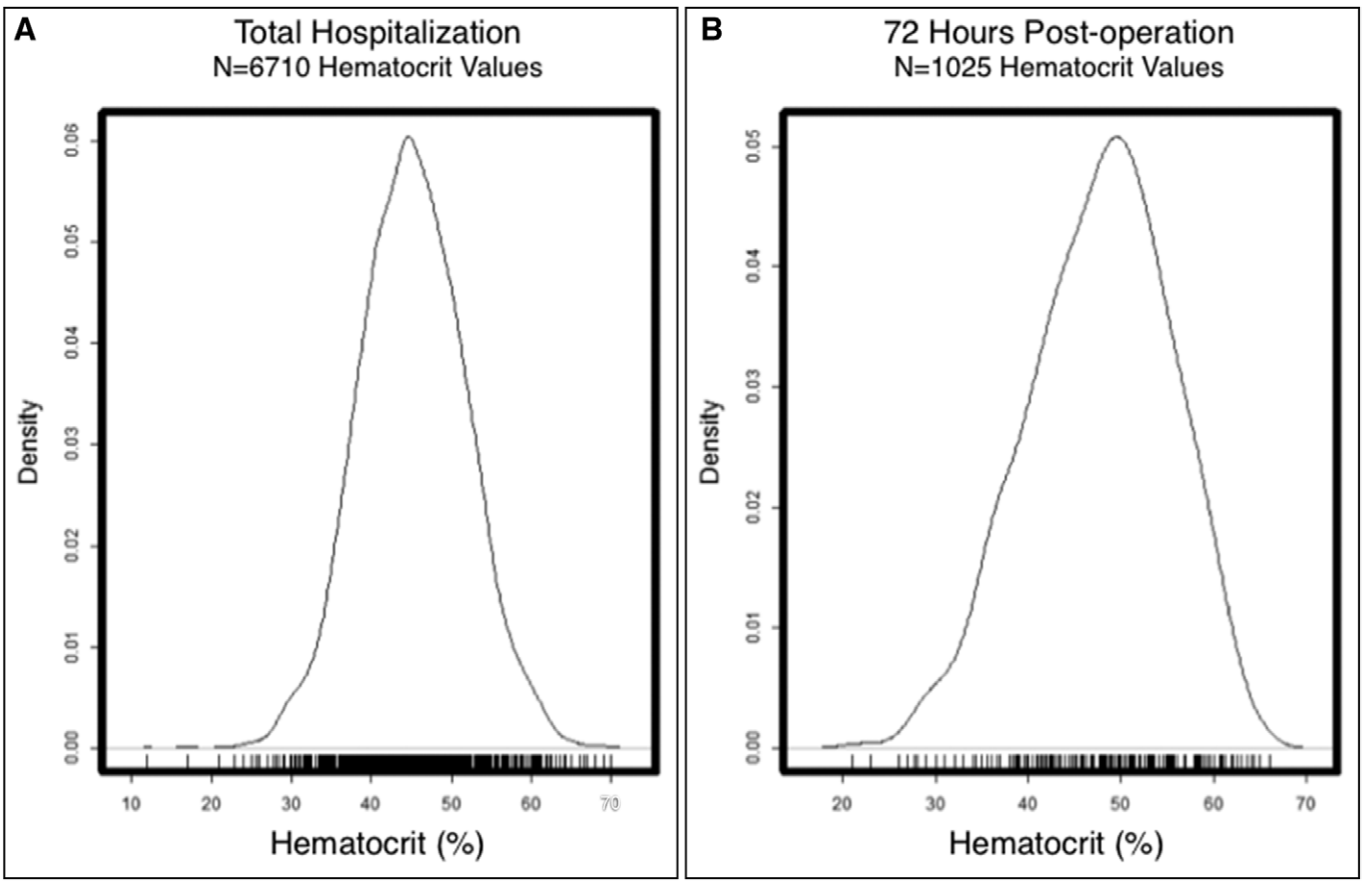

Figure 1. Distribution of hematocrit values within the total hospitalization (**A**) and within the first 72 hr following the Norwood operation (**B**).

(30 mg/kg [maximum 1 g]) at the initiation of the CPB. Other intraoperative support strategies, including deep hypothermic circulatory arrest and modified ultrafiltration, are not customarily used. Our center does not have a protocol for blood transfusions, which remains at the discretion of the clinicians based on their interpretation of oxygenation and patient stability. Arterial blood gases were measured every 2 hours until lactate levels were below 2 mg/dL and every 4 hours or as needed in the subsequent postoperative days. The general consensus is that Pa_{O_2} levels between 40 and 45 mm Hg are desirable during the immediate postoperative course for cyanotic patients following the Norwood procedure.

Outcome

The primary outcomes were 1) mortality and 2) length of hospitalization. Mortality was defined as death occurring during the hospitalization following cardiac surgery and does not include interstage mortality. The length of hospitalization was stratified into days in the CVICU and total hospitalization.

Statistical Analysis

We used descriptive statistics to compare patients with and without early polycythemia with variables expressed as mean (with SD) or median (with interquartile range) according to their parametric distribution. Unless otherwise specified, chi-square test, the Wilcoxon rank test, and *t* tests were used to assess the association between variables and polycythemia. Linear regression analysis was used for multivariable analysis to explore the relationship between the hospital length of stay and average hematocrit value (%), the amount of blood cell transfusion (mL/kg), P/F ratio, and vasoactive inotrope score. Factors associated with duration of hospital stay on multivariable analysis were identified using a combination of variable weight, 95% CI, and *p* values in the linear regression. Calculations were performed using R stats package, version (2.15.2, R Foundation, University of Auckland, New Zealand).

RESULTS

Between September 2009 and December 2012, 34 patients with HLHS or HLHS variant underwent the Norwood procedure. Two patients died within the first 72 hours and were excluded from analyses, leaving 32 patients for analysis. Among this patient cohort, a total of 6,710 hematocrit values were collected during the hospitalization; of which, 1,025 values were observed within the first 72 hours (early) following cardiac surgery. When patients were divided into groups with normal hematocrit and early polycythemia, 17 (53%) had a normal hematocrit profile in the first 72 hours and 15 (47%) had early polycythemia. In both groups, age, gender, weight at the time of cardiac surgery, and preoperative and initial hematocrit level following cardiac surgery were comparable. The groups did not differ in terms of additional cardiac or noncardiac comorbidities. Patients with early polycy-

TABLE 1. Characteristics of Patients Undergoing Stage 1/Norwood Operation in the Two Hematocrit Cohorts

Characteristics	72-Hr Mean Hematocrit		
	Nonpolycythemia	Polycythemia[a]	*p*
Demographic			
Age (d)	4.9 ± 2.6	4.4 ± 2.9	0.34
Gender, female, *n* (%)	10 (58.8)	8 (53.3)	0.9
Weight (kg)	3.05 ± 0.53	2.95 ± 0.64	0.65
Prematurity,[b] *n* (%)	2 (11.8)	3 (20)	0.65
Chromosomal abnormality, *n* (%)	4 (23.5)	2 (13.3)	0.66
Restrictive/intact atrial septum, *n* (%)	2 (11.8)	2 (13.3)	0.9
Additional cardiac comorbidity,[c] *n* (%)	3 (17.6)	2 (13.3)	0.9
Preoperative hematocrit (%)	43.3 ± 6.2	45.2 ± 6.7	0.43
Preoperative hemoglobin (mg/dL)	14.8 ± 2	14.9 ± 2.3	0.88
Immediate postoperative hematocrit (%)	38.9 ± 5.2	42.7 ± 6.3	0.07
Immediate postoperative hemoglobin (mg/dL)	16.2 ± 1.8	17.6 ± 2.2	0.06
72-hr hematocrit (%), median (IQR)	45 (43–46.3)	53.2 (50.8–54.5)	< 0.01
72-hr hemoglobin (mg/dL)	16.4 ± 1.4	18.4 ± 0.9	< 0.01
72-hr nadir hematocrit (%)	32.7 ± 4.8	38.5 ± 4.1	< 0.01
72-hr nadir hemoglobin (mg/dL)	14.8 ± 1.8	16.4 ± 1.2	< 0.01

(*Continued*)

TABLE 1. (*Continued*). Characteristics of Patients Undergoing Stage 1/Norwood Operation in the Two Hematocrit Cohorts

Characteristics	72-Hr Mean Hematocrit		
	Nonpolycythemia	Polycythemia[a]	*p*
Operative			
Cardiopulmonary bypass time (min)	183.1 ± 75.1	181.8 ± 50.4	0.37
Cross-clamp time (min)	87.8 ± 30.3	88.7 ± 29.4	0.87
Postoperative			
Delayed sternal closure, *n* (%)	14 (82.4)	13 (86.7)	0.9
Extracorporeal oxygenation, *n* (%)	4 (23.5)	0 (0)	0.1
Ventilator time (d)	8.3 ± 3.8	15 ± 17.9	0.2
Vasoactive inotrope score at 72 hr	11.5 ± 2.8	14 ± 4.4	0.06
Lactate (mg/dL)	3.1 ± 1.4	2.9 ± 1.3	0.44
Spo_2 (%)	87.4 ± 6.9	84.2 ± 2.4	0.52
Pao_2/Fio_2 ratio	178 ± 81	135 ± 45	0.08
Heart rate, beats/min	157 ± 11.9	153.5 ± 7.8	0.34
Systolic blood pressure, mm Hg	69.6 ± 7.8	68.4 ± 4.9	0.67
Diastolic blood pressure, mm Hg	48.3 ± 4.1	44 ± 4	0.02
Frequency of RBCT	1.2 ± 0.7	1.3 ± 0.5	0.74
Amount of RBCT (mL/kg), median (IQR)	15 (0–25.2)	10 (0–13.8)	0.27
Peak blood urea nitrogen (mg/dL)	33.2 ± 11.5	39.2 ± 13.8	0.19
Peak creatinine (mg/dL)	1.0 ± 0.3	1.1 ± 0.4	0.48
Albumin (mg/dL)	2.5 ± 0.4	2.6 ± 0.3	0.78
Total protein (mg/dL)	4.7 ± 0.6	4.6 ± 0.4	0.77
Fluids			
72-hr total input (L), median (IQR)	1.1 (0.9–1.5)	1.1 (0.99–1.4)	0.73
72-hr total output (L), median (IQR)	1.4 (1.1–1.6)	1.0 (0.7–1.2)	0.04
Urine output (L), median (IQR)	2.9 (2.6–3.3)	2.1 (1.8–2.3)	0.02
Chest tube output (L), median (IQR)	2.8 (2.6–3.4)	2.1 (1.9–2.3)	0.02
72-hr fluid balance (mL), mean (SD)	−80 (324.5)	192.7 (336.9)	0.03

IQR = interquartile range, RBCT = RBC transfusion.
[a]> 49%.
[b]< 38-wk gestation.
[c]Includes total anomalous pulmonary venous return, left ventricle sinusoids, and scimitar syndrome.
± values are mean ± SD.

themia also had higher median and nadir hematocrits in the first 72 hours following cardiac surgery (**Table 1**).

Early Polycythemia and Severity Parameters

The two groups were analyzed based on various clinical severity parameters. Patients who developed early polycythemia had lower diastolic blood pressures compared with those without polycythemia (44.0 ± 4.0 vs 48.3 ± 4.1; $p = 0.015$). However, the groups did not differ in operative characteristics (CPB and cross-clamp time) and postoperative clinical characteristics, such as delayed sternal closure, utilization of ECMO, average lactate levels, Spo_2, heart rate, systolic blood pressure, peak blood urea nitrogen and creatinine, or average albumin and total protein levels. Indicators of clinical severity, such as ventilator time and vasoactive inotrope score, were not significantly different between the two groups. An analysis of RBC transfusion showed that the groups did not differ in terms of frequency or the amount of RBCs transfused (Table 1).

TABLE 2. Length of Stay Differences Between the Polycythemic and Nonpolycythemic Cohorts

Outcome	72-Hr Mean Hematocrit		
	Nonpolycythemia	Polycythemia[a]	*p*
Cardiovascular ICU LOS (d)			
Mean (SD)[b]	21.4 (16.2)	51 (38.6)	< 0.01
Median (IQR)[b]	14 (11–29)	30 (25–66)	< 0.01
Total hospital LOS (d)			
Mean (SD)[c]	36.1 (20)	65 (46.5)	0.03
Median (IQR)[b]	30 (21–58)	45 (35–79)	0.03
In-hospital mortality (%), mean (SD)[c]	3 (17.6)	3 (20)	1

LOS = length of stay, IQR = interquartile range.
[a]Polycythemia defined as hematocrit > 49%.
[b]Rank-sum test.
[c]Fisher exact test.

Early Polycythemia and Outcome

There was a significant association between early polycythemia and length of stay. Patients with early polycythemia stayed in the hospital more than twice as long as patients without early polycythemia (36.1 ± 20 vs 65 ± 46.5 d; $p = 0.034$); of which, nearly 80% of the time was spent in the ICU, compared with 59% in patients without early polycythemia (**Table 2**). Early polycythemia remained associated with CVICU length of stay after excluding early deaths (**Fig. 2**). In the multivariable analysis (**Table 3**; and **Supplemental Tables 1–3**, Supplemental Digital Content 1, http://links.lww.com/PCC/A221), the average hematocrit value was identified to be a significant predictor of hospital length of stay (weight, 4.36 [1.35–7.37]; $p < 0.01$), indicating that early polycythemia continued to be associated with longer hospital length of stay after controlling for the volume of blood cells transfused and other markers of clinical severity (P/F ratio and vasoactive inotrope score). No difference in in-hospital mortality rates was detected between the two groups (17.6% vs 20%).

DISCUSSION

The principal finding of this study was that early polycythemia in patients with HLHS was associated with longer length of hospital stay, without an observed increase in mortality. This association remained robust after controlling for RBC transfusions.

The concept of an "optimal hematocrit" balancing oxygen delivery and hyperviscosity for cyanotic heart disease has led to differences in management and conflicting RBC transfusion strategies (17–21). Yet there are multiple elements that determine hematocrit levels in patients following cardiac surgery and CPB. Specifically, important shifts in plasma volume from systemic and pulmonary capillary leak, insensible fluid losses, and decongestion therapies are physiologic changes that have been described following CPB for pediatric cardiac surgery (9, 13, 22). The results from this study suggest that the discrepancy in hematocrit and hemoglobin levels between our two cohorts, in the absence of differential blood cell transfusion or fluid resuscitation strategies, can be biologically and plausibly explained by hemoconcentration. Hemoconcentration as a marker of either worsening or improving disease activity has been well studied in other disease processes. Early hemoconcentration was reported to be an early risk factor of mortality among patients with acute pancreatitis (10) and a distinguishing characteristic for necrotizing pancreatitis (11). In the other direction, hemoconcentration in adult patients treated for acute heart failure is a biomarker for effective decongestion therapy and correlated with favorable clinical outcome (12).

We found that early polycythemia following the Norwood operation was associated with longer duration of ICU length of stay when compared with patients without early polycythemia. These results are consistent with a report that suggested a link between higher nadir hemoglobin during a similar postoperative period and early mortality in a comparable population

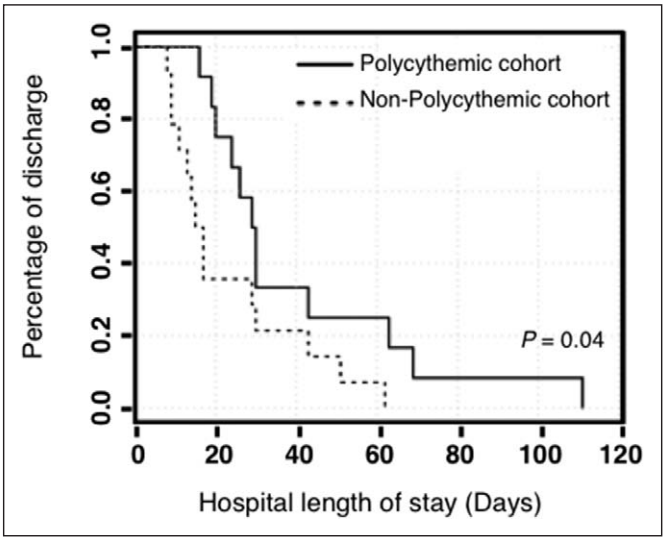

Figure 2. Time-to-event analysis revealing a pattern of later discharge from the hospital in patients with early polycythemia among survivors of the Norwood operation.

TABLE 3. Factors Associated With Hospital Length of Stay on Linear Regression Analysis

Characteristics	Weight (95% CI)	p^a
Average hematocrit value (%)	4.36 (1.35 to 7.37)	< 0.01
Amount of blood cell transfusion (mL/kg)	−0.03 (−0.17 to 1.12)	0.73
Pao_2/Fio_2 ratio	0.21 (−0.01 to 0.42)	0.08
Vasoactive inotrope score	−1.58 (−5.2 to 2.04)	0.40

[a]*p* values were determined by *t* test.

(26). However, that report also described patients exposed to varying RBC transfusion practices. The relationship between polycythemia and RBC transfusion was carefully examined in our analysis. In contrast to other reports, our populations did not differ in the frequency or the amount of RBC transfusions, permitting us to analyze outcome differences independent of this controversial practice. Although the statistical measures of association are strong, analyses of small sample size are susceptible to outlier subjects. These findings should be confirmed in a larger, multi-institutional cohort.

We speculate that hemoconcentration in cyanotic neonates following the Norwood operation is a result of capillary leak syndrome: a conjecture supported by our observation of relative fluid overload in the absence of discrepant fluid resuscitation practices. Neonates undergoing CPB are at similar risk of important fluid shifts; of which, capillary leak syndrome poses the greatest risk of mortality and morbidity (7, 8). Evidence of inflammation driving capillary leak syndrome following CPB can often be detected before the clinical manifestations are evident (23). Yet tissue measurements of inflammation are not commonly available or used and serum markers are varied, indiscriminant, and nonspecific (24).

In the absence of readily available biomarkers to predict illness severity following this complex and high-risk operation (25), we venture that hemoconcentration could be used as an early marker of capillary leak syndrome in the early postoperative period.

We did not find that our two cohorts, albeit relatively small in sample, did not differ in terms of various other indicators of severity of illness within the first 72 hours nor did they differ in duration of CPB or cross-clamp time. Differences in hospital duration were not explained by disparities in important cardiac and noncardiac comorbidities, vasoactive inotrope scores, and average lactate, albumin, or total protein levels. Given that nearly half of the patients experienced early polycythemia, hemoconcentration may be a useful biomarker for clinicians and investigators to determine which patients are at risk of inferior outcome following the Norwood operation. Larger prospective studies are needed to determine the prospective utility of hemoconcentration as a biomarker for severity of illness in patients following CPB.

There are a number of important limitations to our study that deserve discussion. First, this is an experience from a single institution and may not be generalizable to other hospitals. Institutions that adopt a more liberal approach to transfusion practices may find different relevance of polycythemia in the immediate postoperative period. However, with increasing awareness of the association between liberal transfusion strategies and adverse outcomes, institutions may be shifting toward a more conservative strategy. Polycythemia under those conditions may reflect hemoconcentration as described in this report. Second, this is a retrospective study, which cannot prove causality. Polycythemia or hemoconcentration may be associated with, but not cause, prolongation of hospital length of stay. Third, it is challenging to account for all the variables that summarize clinical severity or practice variability. Thus, it is possible that there are other important characteristic(s) that may account for the observed differences in outcome between the two cohorts. In addition, the small sample size may not have been powered enough to demonstrate between-group differences in other variables, such as vasoactive inotrope score and P/F ratio, which may have prognostic capabilities in this patient population. Despite the small sample size, differences in length of stay between our two cohorts were significant and meaningful, suggesting that hemoconcentration shares an important association with clinical outcome. Finally, we excluded patients who died early, which may influence the relationship of hemoconcentration with mortality. These patients were excluded as they could not be assigned to a cohort based on our calculation of polycythemia.

CONCLUSIONS

Early polycythemia following Norwood operation was common and was associated with longer length of hospitalization even after controlling for RBC transfusions. We hypothesize that polycythemia may be a result of hemoconcentration and may be used as an early marker of capillary leak syndrome in the early postoperative period.

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