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Splanchnic Near-Infrared Spectroscopy and Risk of Necrotizing Enterocolitis After Neonatal Heart Surgery

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Abstract

Infants with critical congenital heart disease, especially patients with a single-ventricle (SV) physiology, are at increased risk for the development of necrotizing enterocolitis (NEC). Decreased splanchnic oxygen delivery may contribute to the development of NEC and may be detected by regional oximetry (rSO₂) via splanchnic near-infrared spectroscopy (NIRS). This prospective study enrolled 64 neonates undergoing biventricular (BV) repair or SV palliation for CHD and monitored postoperative splanchnic rSO₂ before and during initiation of enteral feedings to determine whether changes in rSO₂ are associated with risk of NEC. Suspected or proven NEC was observed in 32 % (11/34) of the SV subjects and 0 % (0/30) of the BV subjects ($p = 0.001$). Compared with the BV subjects, the SV palliated subjects had significantly lower splanchnic rSO₂ before and during initiation of enteral feedings, but the groups showed no difference after correction for lower pulse oximetry (SpO₂) in the SV group. The clinical parameters were similar among the SV subjects with and without NEC except for cardiopulmonary bypass times, which were longer for the patients who experienced NEC (126 vs 85 min; $p = 0.03$). No difference was

observed in splanchnic rSO_2 or in the SpO_2 – rSO_2 difference between the SV subjects with and without NEC. Compared with the patients who had suspected or no NEC, the subjects with proven NEC had a lower average splanchnic rSO_2 (32.6 vs 47.0 %; $p = 0.05$), more time with rSO_2 less than 30 % (48.8 vs 6.7 %; $p = 0.04$) at one-fourth-volume feeds, and more time with SpO_2 – rSO_2 exceeding 50 % (33.3 vs 0 %; $p = 0.03$) before feeds were initiated. These data suggest that splanchnic NIRS may be a useful tool for assessing risk of NEC, especially in patients with an SV physiology.

Keywords

Necrotizing enterocolitis; Congenital heart; Regional oximetry; NIRS; Splanchnic ischemia; Mesenteric ischemia

Introduction

With improvements in diagnosis, surgical techniques, and perioperative care, mortality associated with neonatal congenital heart surgery (CHS) has steadily declined during the past few decades. Therefore, attention has shifted toward minimizing the morbidities commonly associated with critical congenital heart disease (CCHD), CHS, and cardiopulmonary bypass (CPB).

Necrotizing enterocolitis (NEC), a neonatal disease in which the mucosal barrier of the gut is inflamed and breached by pathogenic enteric bacteria, resulting in intestinal injury, is one such morbidity associated with CCHD and CHS [17, 18]. In particular, single-ventricle (SV) heart disease and systemic-to-pulmonary artery shunting are associated with the development of NEC [17, 18].

One proposed etiology for an increased incidence of NEC among these neonates is impaired splanchnic blood flow and oxygen delivery leading to splanchnic ischemia. Abnormalities in Doppler-measured splanchnic blood flow have been demonstrated both before and after CHS [8] and are associated with NEC [2] in this population.

Near-infrared spectroscopy (NIRS), a noninvasive technology that continuously detects regional oximetry (rSO_2) [16], has been used to assess splanchnic ischemia. Subjects with [21] and without [6] CHD diagnosed with NEC have been shown to have lower splanchnic rSO_2 values than control subjects. In a prospective study of premature neonates, those who would go on to experience NEC also had lower splanchnic rSO_2 levels than those who never experienced NEC [3]. This study aimed primarily to evaluate whether low splanchnic rSO_2 levels can predict the development of NEC in neonates with CCHD after CHS with CPB.

Materials and Methods

This study enrolled subjects at the University of Michigan Congenital Heart Center at C.S. Mott Children's Hospital during a 4-year period, from May 2008 through May 2012. All neonates (ages 0–28 days) with a SV lesion undergoing surgical palliation that included a systemic-to-pulmonary artery shunt were eligible for participation. A comparison group

consisted of neonates with ductal-dependent systemic or pulmonary blood flow undergoing biventricular (BV) repair with CPB who did not have hemodynamically significant residual postoperative cardiac lesions.

The exclusion criteria for both the SV and BV groups ruled out prematurity (postconceptional age < 35 weeks), intracerebral hemorrhage or significant congenital cerebral disorder (detected by cranial ultrasound or head computed tomography [CT] scan if clinically indicated), history of enteral feeding, known genetic or chromosomal disorders, and significant gastrointestinal pathology (including but not limited to congenital diaphragmatic hernia, gastroschisis, and abdominal situs abnormalities). Parents or legal guardians of eligible neonates were approached after CHS and before initiation of feedings, and written informed consent was obtained.

Demographic information including gender, gestational age, age at surgery, weight at surgery, cardiac diagnosis, type of CHS performed, risk adjustment in congenital heart surgery (RACHS-1) category [9], type and size of systemic-to-pulmonary artery connection, CPB and aortic cross-clamp times, and circulatory arrest (CA) times (if necessary) were recorded. Additional clinical information was collected including 48-h lactate level, 48-h modified vasoactive-inotropic score (VIS) [7], and need for extra-corporeal membrane oxygenation (ECMO) support. Infant feeding logs were created, and the feeding type and route, caloric density, and volume of feedings were recorded on an hourly basis.

Coincident with initiation of feeds, a pediatric-sized rSO₂ sensor was placed on the abdomen. The sensor was oriented transversely in the midline no more than 1 cm below the umbilicus. An INVOS 5100B oximeter (Somanetics Corp., Troy, MI, USA) was used to monitor splanchnic oximetry continuously. Splanchnic rSO₂ values were collected at 5- to 30-s intervals until feeding goals were met or until monitoring was discontinued. To minimize the impact of fluctuations in individual rSO₂ measurements, 20-min moving averages were calculated for the analysis. Recorded splanchnic rSO₂ values lower than 15 % were eliminated because this was the lower limit of the oximeter's detection and therefore determined to be potentially unreliable.

Splanchnic oximetry values of SV and BV were compared at four time points: (1) before initiation of feeds (NPO), (2) at 25 % goal volume of continuous feeds (one fourth), (3) at 100 % goal volume of continuous feeds (full), and (4) at 100 % goal volume of every-3-h bolus feeds (bolus). If the sensor was placed incorrectly or not recording properly at the desired time point, then rSO₂ was not reported.

Pulse oximetry (SpO₂) was recorded hourly during the study period. The general practice was to record SpO₂ in the foot, but no difference was observed between hand and foot oxygen saturations in any enrolled subject. The difference in pulse oximetry and splanchnic oximetry (SpO₂-rSO₂) was calculated and compared between groups at each of the four time points described earlier.

The primary outcome was the development of NEC, defined according to the modified Bell staging criteria [17]. Demographic and clinical data were presented as frequency (%) for categorical variables, and as median (interquartile range) or mean $\pm$ standard deviation, as

appropriate, for continuous variables. Group comparisons (BV vs SV and +NEC vs -NEC) of demographic and clinical data including splanchnic rSO_2 and SpO_2-rSO_2 measurements were made using the chi-square test or Fisher's exact test for categorical variables and the Wilcoxon rank sum test or t test for continuous variables. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA), with statistical significance set at a p value lower than 0.05 using two-sided tests.

Results

The study enrolled 64 neonates: 30 (46.9 %) undergoing BV repair and 34 (53.1 %) undergoing SV palliation. The demographic and clinical characteristics of the neonates are shown in Table 1. No differences were observed in CPB or CA times, maximum 48-h VIS, or peak lactate values between SV palliation and BV repair. A majority of the BV subjects (80 %, 24/30) and SV subjects (67.6 %, 23/34) had a RACHS-1 score of four or greater. Overall, 17.2 % (11/64) of the neonates experienced NEC, with 8 experiencing suspected NEC (Bell stage 1a or 1b) and 3 experiencing proven NEC (Bell stage 2a or greater). The median time of NEC diagnosis was on postoperative day 11.5. The NEC diagnosis was determined for the majority of the subjects (63.6 %, 7/11) after they had reached goal bolus feeds, for fewer subjects (27.3 %, 3/11) after they had reached full continuous-volume feeds, and for only one subject (9.1 %) who had not yet reached full-volume feeds. All 11 subjects who experienced NEC were in the SV group (32.4 vs 0 % in BV group; $p = 0.001$).

Table 2 shows the average splanchnic rSO_2 , proportion of time below rSO_2 thresholds of 30 and 40 %, average SpO_2-rSO_2 , and proportion of time above SpO_2-rSO_2 thresholds of 40, 50, and 60 % in the SV and BV subjects during the four feeding conditions. In all four feeding conditions, the SV subjects had lower splanchnic rSO_2 than the BV subjects (all $p < 0.001$). Furthermore, a greater proportion of the SV subjects had rSO_2 values below the 30 and 40 % thresholds than BV subjects after initiation of feeds. However, after adjustment for the expected lower systemic arterial oxygen level (and hence SpO_2) in the SV group, no difference was observed in SpO_2-rSO_2 between the BV and SV subjects in any feeding conditions.

Because no BV subject experienced NEC, any association between demographic and clinical characteristics and the development of NEC could be determined only for the SV subjects (Table 3). Only longer CPB time was associated with the development of NEC in the SV subjects (NEC: 126 min vs no NEC: 85 min; $p = 0.03$).

Table 4 shows the average splanchnic rSO_2 , proportion of time below rSO_2 thresholds of 30 and 40 %, average SpO_2-rSO_2 , and proportion of time above SpO_2-rSO_2 thresholds of 40, 50, and 60 % in the SV subjects with and without NEC before and during initiation of feeds. No significant difference was detected between the groups in any of the four feeding conditions. Figure 1 depicts splanchnic rSO_2 and average SpO_2-rSO_2 among the BV subjects, all the SV subjects, and the SV subjects with and without NEC.

Table 5 shows the average splanchnic rSO_2 , proportion of time below rSO_2 thresholds of 30 and 40 %, average SpO_2-rSO_2 , and proportion of time above SpO_2-rSO_2 thresholds of 40,

50, and 60 % for the subjects with proven NEC (Bell stage 2a or higher) compared with the subjects who had suspected (Bell stage 1a or 1b) or no NEC. No demographic or clinical characteristics differed between these two groups (data not shown). The proven NEC group had a lower average splanchnic rSO_2 (32.6 vs 47.0 %; $p = 0.05$), a greater proportion of time with rSO_2 less than 30 % at one-fourth feeds (48.8 vs 6.7 %; $p = 0.04$), and a greater proportion of time with SpO_2-rSO_2 greater than 50 % (33.3 vs 0 %; $p = 0.03$), whereas NPO compared with that of the suspected or no NEC group. Figure 2 depicts the splanchnic rSO_2 and the average SpO_2-rSO_2 among the SV subjects with proven NEC, suspected NEC, or no NEC.

Discussion

To our knowledge, this is the first study to evaluate splanchnic oximetry prospectively in neonates with CCHD and its relationship to the risk for NEC development. A previous case report describing a 4-week-old infant with CHD and NEC showed low splanchnic rSO_2 (which improved) together with his clinical course after bowel rest and antibiotics [21]. Several other studies evaluated splanchnic regional oxygenation and its relationship with markers of low cardiac output (both positive [10, 12] and negative [1] correlations) and early postoperative outcomes [11], but the association with NEC was not evaluated.

In this study, all NEC events were observed in the SV group, consistent with the findings of previous studies [17, 18]. However, splanchnic rSO_2 showed no corresponding difference between the SV patients with and without NEC before or after initiation of feedings. This finding was somewhat surprising given the presumed pathophysiology of splanchnic ischemia that predisposes to NEC in the neonatal CCHD population [17, 20]. However, in the design of this study, the group of patients with “suspected NEC” (Bell state 1a or 1b) may not have truly experienced bowel ischemia as the etiology for blood in their stools. For instance, all these patients were receiving aspirin for prophylaxis against systemic-to-pulmonary artery shunt thrombosis, and impaired platelet function may have pre-disposed them to mild gastrointestinal bleeding, placing them in the “suspected NEC” or Bell 1a or 1b category.

Therefore, a secondary analysis was performed to compare those subjects with proven NEC (Bell stage 2a or higher, characterized as having at least intestinal pneumatosis on abdominal radiograph) and all the other SV subjects (without NEC and Bell stage 1a or 1b). The results showed a clear trend toward impaired regional oxygenation in the proven NEC group compared with the suspected or no NEC group, although the small number of proven NEC cases ($n = 3$) makes statistical interpretation difficult. With NEC reported for only about 1 % of neonates with CHD after CHS, a larger study with appropriate power is necessary for a true delineation of this association [17].

In the study by McElhinney et al. [17], NEC was not associated with increased mortality in the CHD population, but the hospital stay was an average of 17 days longer. At our institution, the diagnosis of NEC (suspected or proven) is typically treated with a period of NPO, total parenteral nutrition, and antibiotics followed by a period of slow reinstitution of enteral feeds until goal volume and calories are achieved. Because the few patients with

proven NEC showed a trend for lower splanchnic rSO_2 , these data may suggest a role for splanchnic NIRS of distinguishing between proven and suspected NEC. However, any potential association between impaired oxygenation and NEC disease severity does not imply causality.

A large SpO_2 - rSO_2 difference may be one factor that contributes to a more advanced presentation of NEC. A diagnosis of suspected NEC will remain clinically important until further investigation clarifies this relationship. Splanchnic NIRS also may be helpful for monitoring individual response to treatment and timing of reinstitution of feeds. Again, a larger and potentially multi-institutional study is necessary to investigate this possible use of splanchnic rSO_2 monitoring.

This study was limited by its small sample, particularly the small number of proven NEC cases (Bell stage 2a or higher). An additional limitation was the wide variability during splanchnic rSO_2 monitoring. Whereas the brain and kidney are relatively fixed respectively within the skull and retroperitoneum, much of the gut is mobile within the abdominal cavity, with varying degrees of gas- or stool-filled bowel loops. Therefore, splanchnic oximetry as measured by a probe affixed to the abdominal skin is potentially prone to greater variability than its cerebral or renal counterparts. Regional NIRS monitoring of the liver, which is less mobile than the bowel, has been shown to correlate with systemic venous saturation [19]. This may be an alternative site for splanchnic rSO_2 monitoring in the future, although the liver is supplied by the celiac artery, and the majority of CHD patients experience NEC in locations primarily supplied by the superior mesenteric artery [4].

Another limitation of this study was that many of the target feeding time points were missed. As seen in Tables 2, 4, and 5, a greater proportion of subjects had rSO_2 captured at one fourth and full feeds than in NPO and bolus conditions. This was primarily due to late initiation and early discontinuation of splanchnic rSO_2 measurement for NPO and bolus conditions, respectively. Furthermore, at any of the feeding condition time points, the probe may have become dislodged or the machine may have been malfunctioning. Although the subjects with missing data showed no clear pattern, there may be a confounding factor leading to this discrepancy and biasing these results.

Interestingly, this study demonstrated an association between CPB time and the development of NEC (suspected and proven). Whereas CPB time may be a surrogate marker for disease or surgical complexity, inflammation and ischemia-reperfusion injury associated with CPB may be a risk factor for the development of NEC [15, 20]. Other investigators have shown that before CHS, CHD patients have deranged gut permeability compared with normal control subjects [13]. However, these investigators also showed that CPB causes increased derangements compared with heart surgery without CPB. In a separate study of patients after the Norwood procedure, these same investigators found extreme permeability derangements in one patient who subsequently experienced NEC and died [14].

In contrast, other investigators found a higher incidence of NEC among patients with hypoplastic left heart syndrome after hybrid stage one palliation, a surgery- and catheter-based intervention that does not require CPB, compared with patients who underwent the

Norwood procedure [5]. Although the former group had baseline characteristics making them sicker (e.g., greater proportion requiring mechanical ventilation preoperatively), CPB time clearly is not the only risk factor in this population. Further understanding of this interaction of CPB with intestinal injury and the development of intestine-protective strategies are certainly areas for future investigation.

In summary, regional oximetry of the splanchnic vascular bed can be measured by NIRS. This study showed no demonstrable difference in splanchnic rSO_2 between BV repair and SV palliation after correction for higher SpO_2 in the SV subjects. All cases of NEC involved the SV subjects, and the risk of NEC was associated with longer CPB times. No difference in regional oximetry was demonstrated between those who experienced NEC (suspected or proven) and those who did not before or during any feeding regimen. However, a trend toward impaired regional oxygenation was observed among those with proven NEC, although this must be interpreted with caution given the small sample. We believe a larger study is warranted to describe fully the potential association of low splanchnic rSO_2 and the development of NEC in neonates with CCHD undergoing cardiac surgery.

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Fig. 1.

Mean splanchnic regional oximetry (rSO₂) (a) and mean difference between pulse oximetry (SpO₂) and splanchnic rSO₂ (b) are shown in four feeding conditions. The *biventricle* control subjects show a higher splanchnic rSO₂ than the *single-ventricle* subjects in all feeding conditions (all $p < 0.001$), but the difference is not significant when the SpO₂– rSO₂ difference is compared between the groups. The single-ventricle patients with and those without necrotizing enterocolitis showed no significant difference in rSO₂ or SpO₂– rSO₂ in any of the four feeding conditions. The one fourth continuous hourly rate was 25 % of the goal, and the full, continuous hourly rate was at 100 % of the goal. The bolus goal volume was administered every 3 h. *NEC* necrotizing enterocolitis, *SV* single-ventricle palliation, *BV* biventricle repair, *NPO* no enteral feeding

Fig. 2.

Single-ventricle patients with proven necrotizing enterocolitis (NEC) (Bell stage 2a or higher) are compared with single-ventricle patients with no NEC and suspected NEC (Bell stage 1 a or b). The mean splanchnic regional oximetry (rSO₂) (a) and the mean difference between pulse oximetry (SpO₂) and splanchnic regional oximetry (rSO₂) (b) are shown in four feeding conditions. At one-fourth volume feeds, rSO₂ was lower and SpO₂-rSO₂ was higher in the proven NEC subjects than in the suspected and no NEC group ($p = 0.05$ and 0.07 , respectively). The one-fourth continuous hourly rate was 25 % of the goal, and the full, continuous hourly rate was at 100 % of the goal. The bolus goal volume was administered every 3 h. SV single-ventricle palliation, NPO no enteral feeding

Table 1
Patient and clinical characteristics of subjects with single-ventricle palliation or two ventricle repair (*n* = 64)

Characteristics	All (<i>n</i> = 64)	Type of ventricle		<i>p</i> value ^a
		SV (<i>n</i> = 34)	BV (<i>n</i> = 30)	
Developing NEC	11 (17.2)	11 (32.4)	0 (0.0)	0.001
NEC stage (<i>n</i> = 11)				
1a: Suspected NEC	2 (18.2)	2 (18.2)		
1b: Suspected NEC	6 (54.5)	6 (54.5)	NA	
2a: Proven NEC, mildly ill	3 (27.3)	3 (27.3)		
Postoperative days to NEC diagnosis (<i>n</i> = 10)	11.5 (10–22)	11.5 (10–22)	NA	
Cardiac diagnosis				
HLHS or variant	22 (34.4)	22 (64.7)	NA	
Other single ventricle	12 (18.8)	12 (35.3)		
Hypoplastic/interrupted aortic arch	15 (23.4)		15 (50.0)	NA
Transposition with or without other disease	14 (21.9)	NA	14 (46.7)	
Other BV repair	1 (1.6)		1 (3.3)	
Weight at surgery (kg)	3.3 ± 0.5	3.3 ± 0.4	3.3 ± 0.5	0.84
CPB time (min) (<i>n</i> = 63)	106 (78–149)	95 (75–138)	126 (84–157)	0.08
CA time (min) (<i>n</i> = 44)	33.5 (25–42)	37 (30–43)	30 (24–38)	0.22
Maximum VIS for the first 48 h	18.4 ± 9.4	19.0 ± 7.3	17.7 ± 11.4	0.61
Peak lactate for the first 48 h	5.1 (4.0–7.6)	6.4 (4–7.8)	4.7 (3.9–6.5)	0.21
ECMO	5 (7.8)	4 (11.8)	1 (3.3)	0.36
Type of feeding				
Breast milk	51 (79.7)	26 (76.5)	25 (83.3)	0.50
Formula	13 (20.3)	8 (23.5)	5 (16.7)	
Time from feeding initiation to full bolus (h) (<i>n</i> = 61)	88 (61–129)	88 (69.5–130)	83 (53–103)	0.28

Data are presented as *n* (%) for categorical variables and median (interquartile range) or mean ± standard deviation, as appropriate, for continuous variables

SV single ventricle palliation BV biventricle repair NEC necrotizing enterocolitis NA not applicable, HLHS hypoplastic left heart syndrome, CPB cardiopulmonary bypass, CA circulatory arrest, VIS vasoactive-inotropic score, ECMO extracorporeal membrane oxygenation

^a *p* value from chi-square test or Fisher's exact test, as appropriate, for categorical variables and Wilcoxon rank sum test or *t* test, as appropriate, for continuous variables for comparison of each characteristic between the SV and BV patients

Table 2
Splanchnic regional oximetry and pulse oximetry–regional oximetry difference in single-ventricle palliation and two-ventricle repair subjects in four feeding conditions ($n = 64$)

Feeding condition	All (<i>n</i> = 64)	Type of ventricle		<i>p</i> value ^a
		SV (<i>n</i> = 34)	BV (<i>n</i> = 30)	
Average rSO ₂ (%)				
NPO (<i>n</i> = 31) ^b	58.2 ± 16.5	51.6 ± 14.8	70.3 ± 12.0	0.001
One fourth (<i>n</i> = 47)	51.6 ± 15.3	45.6 ± 12.4	62.3 ± 14.3	0.0001
Full (<i>n</i> = 49)	48.6 ± 12.3	43.8 ± 9.0	56.2 ± 13.1	0.0003
Bolus (<i>n</i> = 40)	49.2 ± 10.0	44.1 ± 7.9	55.5 ± 8.8	0.0001
Proportion of time with absolute rSO ₂ <30 % (%)				
NPO (<i>n</i> = 31)	0 (0–5.5)	0.6 (0–11.4)	0 (0–0.3)	0.11
One fourth (<i>n</i> = 47)	1.4 (0–25.5)	12.4 (0.2–31.5)	0 (0–2.2)	0.02
Full (<i>n</i> = 49)	3.3 (0.04–13.9)	4.8 (1.9–21.5)	0.1 (0–6.4)	0.02
Bolus (<i>n</i> = 40)	2.6 (0.4–17.1)	12.1 (2.4–21.0)	0.7 (0–2.3)	0.003
Proportion of time with absolute rSO ₂ <40 % (%)				
NPO (<i>n</i> = 31)	0.6 (0–24.4)	2.7 (0–49.3)	0 (0–1.3)	0.07
One fourth (<i>n</i> = 47)	8.9 (0.3–51.5)	39.8 (1.9–54.4)	0.4 (0–11.8)	0.005
Full (<i>n</i> = 49)	18.1 (2.2–39.4)	28.4 (13.4–47.3)	3.7 (0–18.1)	0.004
Bolus (<i>n</i> = 40)	17.8 (2.9–38.2)	32.0 (12.9–41.1)	4.1 (1.3–17.6)	0.003
Average SpO ₂ –rSO ₂ difference (%)				
NPO (<i>n</i> = 31)	28.6 ± 14.2	29.3 ± 15.4	27.4 ± 12.3	0.72
One fourth (<i>n</i> = 47)	35.1 ± 14.1	35.4 ± 13.3	34.7 ± 15.7	0.88
Full (<i>n</i> = 49)	38.0 ± 11.6	36.2 ± 9.9	40.9 ± 13.8	0.17
Bolus (<i>n</i> = 40)	39.4 ± 9.5	37.0 ± 9.7	42.4 ± 8.7	0.07
Proportion of time with SpO ₂ –rSO ₂ difference >40 % (%)				
NPO (<i>n</i> = 31)	2.4 (0–33.2)	5.2 (0–39.5)	0 (0–18.6)	0.44
One fourth (<i>n</i> = 47)	20.4 (0–75.8)	34.1 (0–85.8)	14.1 (0–50.1)	0.44
Full (<i>n</i> = 49)	29.9 (4.6–74.2)	26.5 (4.6–68.1)	68.5 (0–99.6)	0.20
Bolus (<i>n</i> = 40)	45.2 (15.8–72.4)	33.5 (9.1–55.0)	52.4 (29.5–88.1)	0.09
Proportion of time with SpO ₂ –rSO ₂ difference >50 % (%)				
NPO (<i>n</i> = 31)	0 (0–0.6)	0 (0–0.3)	0 (0–3.7)	0.96
One fourth (<i>n</i> = 47)	0.5 (0–35.9)	2.6 (0–43.9)	0 (0–33.1)	0.43
Full (<i>n</i> = 49)	4.8 (0–33.1)	1.9 (0–18)	23 (0–38.2)	0.21
Bolus (<i>n</i> = 40)	9.7 (0–29.9)	8.1 (0–26.8)	9.7 (3.2–35.3)	0.41
Proportion of time with SpO ₂ –rSO ₂ difference >60 % (%)				
NPO (<i>n</i> = 31)	0 (0–0)	0 (0–0)	0 (0–0)	0.58
One fourth (<i>n</i> = 47)	0 (0–5.3)	0 (0–1.8)	0 (0–8.1)	0.89
Full (<i>n</i> = 49)	0 (0–4.8)	0 (0–0)	0 (0–10.3)	0.31
Bolus (<i>n</i> = 40)	0 (0–5.8)	0 (0–2.9)	0.7 (0–7.0)	0.39

Data are presented as median (interquartile range) or mean ± standard deviation, as appropriate, for continuous variables

rSO2 regional oximetry, *NPO* no enteral feeding, *SpO2* pulse oximetry, *SV* single ventricle palliation, *BV* biventricle repair

^a *p* value from Wilcoxon rank sum test or *t* test, as appropriate, for continuous variables for comparison of each characteristic between the patients after SV palliation and after BV repair

^b For all feeding conditions, $n < 64$, indicating that some subjects did not have regional oximetry measured in that feeding condition

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Table 3
Patient and clinical characteristics of single-ventricle palliated subjects with and without necrotizing enterocolitis (NEC) (*n* = 34)

Characteristics	Developing NEC		<i>p</i> value ^a
	Yes (<i>n</i> = 11)	No (<i>n</i> = 23)	
Cardiac diagnosis			
HLHS or variant	7 (63.6)	15 (65.2)	1.00
Other single ventricle	4 (36.4)	8 (34.8)	
Shunt or conduit			
Shunt	9 (81.8)	20 (87.0)	1.00
Conduit	1 (9.1)	3 (13.0)	
NA	1 (9.1)	0 (0.0)	
Weight at surgery (kg)	3.3 ± 0.4	3.3 ± 0.5	0.98
CPB time (min) (<i>n</i> = 33)	126 (98–141)	85 (69–111)	0.03
CA time (min) (<i>n</i> = 25)	37 (25–47)	36.5 (32–41)	0.74
Maximum VIS for the first 48 h	21.9 ± 9.0	17.6 ± 6.1	0.12
Peak lactate for the first 48 h	6 (4–7.5)	6.5 (3.8–7.9)	0.86
ECMO	1 (9.1)	3 (13.0)	1.00
Type of feeding			
Breast milk	7 (63.6)	19 (82.6)	0.39
Formula	4 (36.4)	4 (17.4)	
Time to full/bolus feeds (h) (<i>n</i> = 32)	124 (107–131)	87 (61–128)	0.20

Data are presented as *n* (%) for categorical variables and median (interquartile range) or mean ± standard deviation, as appropriate, for continuous variables

HLHS hypoplastic left heart syndrome, NA not applicable, CPB cardiopulmonary bypass, CA circulatory arrest, VIS vasoactive-inotropic score, ECMO extracorporeal membrane oxygenation

^a *p* value from Fisher's exact test for categorical variables and Wilcoxon rank sum test or *t* test, as appropriate, for continuous variables for comparison of each characteristic between the patients with and without development of NEC

Table 4
Splanchnic regional oximetry and pulse oximetry–regional oximetry difference in single-ventricle palliation subjects with and without necrotizing enterocolitis (NEC) in four feeding conditions ($n = 34$)

Feeding condition	Developing NEC		<i>p</i> value ^a
	Yes (<i>n</i> = 11)	No (<i>n</i> = 23)	
Average rSO ₂ (%)			
NPO (<i>n</i> = 20) ^b	46.9 ± 16.3	54.1 ± 14.0	0.32
One fourth (<i>n</i> = 30)	42.8 ± 12.2	47.0 ± 12.5	0.39
Full (<i>n</i> = 30)	40.6 ± 8.7	45.4 ± 8.9	0.17
Bolus (<i>n</i> = 22)	44.0 ± 8.0	44.1 ± 8.1	0.99
Proportion of time with absolute rSO ₂ <30 % (%)			
NPO (<i>n</i> = 20)	5.5 (0–32.8)	0 (0–4.2)	0.28
One fourth (<i>n</i> = 30)	16.0 (0.2–38.8)	7.4 (0.1–30.1)	0.50
Full (<i>n</i> = 30)	8.0 (3.5–28.5)	3.5 (0.8–21.4)	0.32
Bolus (<i>n</i> = 22)	14.7 (5.4–20.6)	10.2 (1.6–22.4)	0.79
Proportion of time with absolute rSO ₂ <40 % (%)			
NPO (<i>n</i> = 20)	14.8 (0–87.7)	0.7 (0–24.4)	0.50
One fourth (<i>n</i> = 30)	43.7 (1.9–65.6)	25.0 (1.9–53.4)	0.54
Full (<i>n</i> = 30)	37.2 (30.1–69.0)	24.0 (9.4–44.2)	0.20
Bolus (<i>n</i> = 22)	35.3 (21.3–40.4)	27.9 (12.9–46.6)	0.69
Average SpO ₂ –rSO ₂ difference (%)			
NPO (<i>n</i> = 20)	32.8 ± 17.8	26.4 ± 13.7	0.25
One fourth (<i>n</i> = 30)	40.0 ± 15.4	33.0 ± 12.0	0.18
Full (<i>n</i> = 30)	39.0 ± 9.4	34.8 ± 10.0	0.27
Bolus (<i>n</i> = 22)	37.6 ± 8.5	36.7 ± 10.5	0.83
Proportion of time with SpO ₂ –rSO ₂ difference >40 % (%)			
NPO (<i>n</i> = 20)	14.8 (0–100)	3.8 (0–33.2)	0.54
One fourth (<i>n</i> = 30)	56.1 (0–85.8)	15.1 (0.2–68.1)	0.37
Full (<i>n</i> = 30)	28.3 (16.0–74.2)	24.9 (0.1–48.8)	0.42
Bolus (<i>n</i> = 22)	39.9 (13.3–50.5)	30.3 (7.4–60.5)	0.95
Proportion of time with SpO ₂ –rSO ₂ difference >50 % (%)			
NPO (<i>n</i> = 20)	0 (0–65.0)	0 (0–0)	0.18
One fourth (<i>n</i> = 30)	30.2 (0–45.9)	0.9 (0–15.4)	0.15
Full (<i>n</i> = 30)	0 (0–18.1)	5.7 (0–15.4)	0.44
Bolus (<i>n</i> = 22)	11.4 (1.2–26.8)	8.1 (0–26.8)	0.89
Proportion of time with SpO ₂ –rSO ₂ difference >60 % (%)			
NPO (<i>n</i> = 20)	0 (0–15.0)	0 (0–0)	0.06
One fourth (<i>n</i> = 30)	0.1 (0–8.5)	0 (0–0.6)	0.16
Full (<i>n</i> = 30)	0 (0–4.8)	0 (0–0)	0.64
Bolus (<i>n</i> = 22)	0 (0–2.1)	0 (0–5.3)	0.76

Data are presented as median (interquartile range) or mean $\pm$ standard deviation, as appropriate, for continuous variables

rSO2 regional oximetry, *NPO* no enteral feeding, *SpO2* pulse oximetry

^a *p* value from Wilcoxon rank sum test or *t* test, as appropriate, for continuous variables for comparison of each characteristic between the patients with and without NEC

^b For all feeding conditions, $n < 34$, indicating that some subjects did not have regional oximetry measured in that feeding condition

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Table 5
Splanchnic regional oximetry and pulse oximetry–regional oximetry difference in single-ventricle palliation subjects with proven necrotizing enterocolitis (NEC) versus suspected or no evidence of NEC in four feeding conditions ($n = 34$)

Characteristics	NEC stage		<i>p</i> value ^a
	Proven NEC (<i>n</i> = 3)	Suspected or no NEC (<i>n</i> = 31)	
Average rSO ₂ (%)			
NPO (<i>n</i> = 20) ^b	42.7 ± 15.0	52.5 ± 14.9	0.39
One fourth (<i>n</i> = 30)	32.6 ± 8.8	47.0 ± 12.0	0.05
Full (<i>n</i> = 30)	42.4 ± 0.6	43.9 ± 9.3	0.82
Bolus (<i>n</i> = 22)	50.0 ± 12.1	43.5 ± 7.5	0.27
Proportion of absolute rSO ₂ <30 % (%)			
NPO (<i>n</i> = 20)	19.1 (5.5–32.8)	0.05 (0–11.1)	0.20
One fourth (<i>n</i> = 30)	48.8 (26.6–74.3)	6.7 (0.1–28.7)	0.04
Full (<i>n</i> = 30)	8.9 (4.7–13.1)	4.4 (1.5–22.8)	0.80
Bolus (<i>n</i> = 22)	11.7 (2.4–21.0)	12.1 (2.2–21.3)	1.00
Proportion of absolute rSO ₂ <40 % (%)			
NPO (<i>n</i> = 20)	51.2 (14.8–87.7)	0.7 (0–43.1)	0.26
One fourth (<i>n</i> = 30)	77.6 (42.7–98.2)	26.9 (1.5–53.7)	0.08
Full (<i>n</i> = 30)	33.6 (31.4–35.8)	26.4 (12.9–55.6)	0.74
Bolus (<i>n</i> = 22)	24.5 (10.7–38.4)	32.0 (15.4–43.8)	0.65
Average SpO ₂ –rSO ₂ difference (%)			
NPO (<i>n</i> = 20)	39.1 ± 19.6	28.2 ± 15.1	0.36
One fourth (<i>n</i> = 30)	48.6 ± 12.5	33.9 ± 12.8	0.07
Full (<i>n</i> = 30)	38.5 ± 5.4	36.0 ± 10.1	0.74
Bolus (<i>n</i> = 22)	31.7 ± 12.1	37.5 ± 9.6	0.43
Proportion of SpO ₂ –rSO ₂ difference >40 % (%)			
NPO (<i>n</i> = 20)	57.4 (14.8–100)	1.9 (0–33.2)	0.15
One fourth (<i>n</i> = 30)	59.7 (51.5–100)	20.4 (0–85.8)	0.16
Full (<i>n</i> = 30)	43.4 (18.7–68.1)	26.5 (2.4–61.9)	0.68
Bolus (<i>n</i> = 22)	30.9 (17.4–44.4)	33.5 (8.3–57.8)	0.82
Proportion of SpO ₂ –rSO ₂ difference >50 % (%)			
NPO (<i>n</i> = 20)	33.3 (1.6–65.0)	0 (0–0)	0.03
One fourth (<i>n</i> = 30)	35.9 (15.9–99.8)	1.9 (0–43.9)	0.09
Full (<i>n</i> = 30)	9.0 (0–18.1)	1.9 (0–15.4)	1.00
Bolus (<i>n</i> = 22)	15.9 (2.7–29.2)	8.1 (0–26.5)	0.57
Proportion of SpO ₂ –rSO ₂ difference >60 % (%)			
NPO (<i>n</i> = 20)	7.5 (0–15.0)	0 (0–0)	0.09
One fourth (<i>n</i> = 30)	5.3 (0–64.5)	0 (0–1.3)	0.15
Full (<i>n</i> = 30)	2.4 (0–4.8)	0 (0–0)	0.51
Bolus (<i>n</i> = 22)	1.4 (0–2.9)	0 (0–4.0)	0.90

Data are presented as median (interquartile range) or mean $\pm$ standard deviation, as appropriate, for continuous variables.

rSO₂ regional oximetry, *NPO* no enteral feeding, *SpO₂* pulse oximetry

^a *p* value from Wilcoxon rank sum test or *t* test, as appropriate, for continuous variables for comparison of each characteristic between the single-ventricle palliation subjects with NEC stage of 2a and those with 1a, 1b, or no NEC

^b For all feeding conditions, *n* < 34, indicating that some subjects did not have regional oximetry measured in that feeding condition