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RBC Transfusion Induced ST Segment Variability Following the Norwood Procedure

OBJECTIVES: The transfusion of stored RBCs decreases nitric oxide bioavailability, which may have an adverse effect on vascular function. We assessed the effects of RBC transfusion on coronary vascular function by evaluating the relationship between myocardial oxygen delivery and demand as evidenced by ST segment variability.

DESIGN: Retrospective case-control study.

SETTING: Nine-hundred seventy-three-bed pediatric hospital with a 54-bed cardiovascular ICU.

PATIENTS: Seventy-three neonates with hypoplastic left heart syndrome following the Norwood procedure, 38 with a Blalock-Taussig shunt and 35 with a right ventricle to pulmonary artery shunt.

INTERVENTIONS: RBC transfusion.

MATERIALS AND MAIN RESULTS: High-frequency physiologic data were captured 30 minutes prior to the initiation of (baseline) and during the 120 minutes of the transfusion. A rate pressure product was calculated for each subject and used as an indicator of myocardial oxygen demand. Electrocardiogram leads (aVL, V1, II) were used to construct a 3D ST segment vector to assess ST segment variability and functioned as a surrogate indicator of myocardial ischemia. One-hundred thirty-eight transfusions occurred in the Blalock-Taussig shunt group and 139 in the right ventricle to pulmonary artery shunt group. There was no significant change in the rate pressure product for either group; however, ST segment variability progressively increased for the entire cohort during the transfusion, becoming statistically significant by the end of the transfusion. Upon subgroup analysis, this finding was noted with statistical significance in the Blalock-Taussig shunt group and trending toward significance in the right ventricle to pulmonary artery shunt group.

CONCLUSIONS: We found a significant increase in the ST segment variability and evidence of myocardial ischemia temporally associated with RBC transfusions in neonates following the Norwood procedure, specifically among those in the Blalock-Taussig shunt group, which may impact immediate and long-term outcomes.

KEY WORDS: electrocardiogram; hypoplastic left heart syndrome; neonate; Norwood procedure; nitric oxide; red blood cell transfusion

RBC transfusion is common in critically ill adults and children. Patients with cardiac disease are transfused at higher hemoglobin thresholds than those without cardiac disease, and the management of cyanotic congenital heart disease often prompts practitioners to target even higher hemoglobin levels. RBC transfusions in cardiac patients are associated with adverse outcomes, including

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DOI: 10.1097/CCE.0000000000000417

following the Norwood procedure (NP) for palliation of the hypoplastic left heart syndrome (HLHS) (1–4). There is increasing evidence that transfusion of stored RBCs reduces nitric oxide (NO) bioavailability, which may play a role in influencing the postoperative course and clinical outcomes (5–7).

A series of biochemical and biomechanical changes in the RBC and storage media, commonly referred to as the “storage lesion,” reduces RBC survival and function and ultimately contributes to a decrease in NO bioavailability (5–7). NO modulates the interaction between platelets as well as platelet-endothelial cell and neutrophil-endothelial cell interactions, where a decrease in NO bioactivity leads to a procoagulant and proinflammatory milieu (8). In addition, NO modulates vasomotor tone, where a decrease in bioactivity increases resistance to blood flow (8). Collectively, these processes may compromise coronary vascular function, resulting in myocardial ischemia and injury.

Neonates undergoing the NP for palliation of HLHS may be particularly sensitive to the effects of the storage lesion on myocardial perfusion following surgery. Cardiac surgery and the attendant myocardial ischemia reperfusion injury damage the coronary endothelium, impairing NO production and contributing to a decrease in NO bioavailability (9). Following the NP, the immature neonatal myocardium is particularly vulnerable to cardiac ischemia due to multiple factors including obligate cyanosis; increased cardiac demand due to the inefficiency of the parallel circulation and requirement for an elevated cardiac output; obligate retrograde aortic flow to coronary arteries arising from a diminutive, native ascending aorta; and in those undergoing the Blalock-Taussig shunt (BTS), diastolic hypotension and “coronary steal” resulting from diastolic “run-off” into the pulmonary circulation (3, 11, 16).

We hypothesized that RBC transfusion would compromise coronary vascular function and myocardial oxygen delivery, leading to myocardial ischemia and ST segment changes, which could have a significant impact on the immediate postoperative course as well as long-term outcomes.

METHODS

Study Population and Design

Approval for this study was obtained from the Institutional Review Board of Baylor College of Medicine along with

a waiver of written consent (H-45084, Houston, TX). Electronic medical records were obtained for all patients with the diagnosis of HLHS and who received RBC transfusions following the NP while hospitalized in the cardiac ICU from January 28, 2013, to May 18, 2019, at Texas Children’s Hospital. In general, the institutional indication for RBC transfusions in neonates following the Norwood operation is hematocrit less than 40% and clinical symptoms of low cardiac output.

Patients with a pacemaker, requiring mechanical circulatory support or continuous renal replacement therapy, and those with incomplete physiologic and electrocardiogram (ECG) data were excluded. To minimize confounders, we excluded transfusions that occurred with the administration of cryoprecipitate, fresh frozen plasma and platelets, IV calcium, and colloid. We also excluded transfusions that occurred with changes in vasoactive support, as reflected in an increase in Vasoactive Inotropic Score (10), or with the administration of the NO donors, nitroglycerin, and nitroprusside.

Data Collection

Hemodynamic data and five-lead ECG waveforms were collected using the Sickbay clinical platform (Medical Informatics Corp, Houston, TX). ECG, arterial oxygen saturation (Sao₂), and hemodynamic data were captured at a frequency of 0.5 Hz. Recorded hemodynamic data included heart rate (HR), diastolic blood pressure (dBp), systolic blood pressure (sBP), mean arterial blood pressure (mBP), and common atrial pressure. All data were stored on site, behind a HIPAA compliant firewall maintained by Baylor College of Medicine Information Technology. ST segment values were determined based on the GE monitor output algorithm, performed as the J-point plus 60–80 ms, depending on the age of the patient.

Typically, the RBC transfusions are administered over 120 minutes. For notational convenience, the RBC transfusion starting time was set as the origin (0 min) of the time axis. The time window was broken into the baseline interval which ranged from –30 minutes to 0 minutes. The transfusion time (0–120 min) was divided into four epochs of 30 minutes each to account for the increasing amount of transfused blood that the patient received over the 120-minute span. This approach enabled us to compare the baseline period with the transfusion epochs and to compare the epochs during the transfusions.

Signal Processing and Construction of 3D ST Segment Vector

We used a signal processing method to quantify the ST segment variability following the NP (11, 12). To capture the movement of the ST segment in all three spatial dimensions, an ST segment vector was constructed from the collected raw ST segment outputs. Leads II, V₁, and aVL were chosen for analysis due to their quasiorthogonal orientation. **Figure 1** depicts the full 3D view. A 4-minute moving average filter was applied to the raw signals in order to remove rapid, nonphysiologic artifacts, such as those caused by subject movement. The result captured the low-frequency variations of the ST segment that were of interest. Using the filtered signals and the relative positions of the ECG leads, the *x*, *y*, and *z* coordinates of the instantaneous ST segment vector were given by the following equations:

$$ST_x = ST_{V_1} \cos 30^\circ$$

$$ST_y = ST_{aVL} \cos 30^\circ + ST_{II} \cos 60^\circ - ST_{V_1} \sin 30^\circ$$

$$ST_z = ST_{aVL} \sin 30^\circ - ST_{II} \sin 60^\circ$$

where ST_{V_1} , ST_{II} , and ST_{aVL} were the values of the filtered ST segments of the associated ECG leads. Variability was quantified as the range that the ST segment vector covers in the 3D during a 5-minute window of time updated every minute. This value is mathematically expressed as follows:

$$\begin{aligned} \text{ST variability} = & (\max ST_x - \min ST_x) \\ & + (\max ST_y - \min ST_y) \\ & + (\max ST_z - \min ST_z) \end{aligned}$$

Statistical Analysis of ST Segment Vector Variability

Comparisons of the ST vector variability were performed using the baseline (0 to -30 min) window prior to transfusion and the 120-minute window during the transfusion; this latter window was divided into four 30-minute epochs. ST segment vector variability was compared between each of the consecutive 30-minute epochs and the baseline using the paired *t* test. Differences were considered statistically significant at a *p* value of less than 0.05.

Statistical Analysis of Hemodynamic Data

The hemodynamic data analyzed for this study included HR, dBP, sBP, mBP, and SaO₂. A rate pressure product (RPP) was calculated (RPP = sBP × HR). As with ST segment data, these data were collected from 30 minutes before the start of transfusion to 120 minutes after the start of the transfusion. The hemodynamic data for each subject during the transfusion (0–120 min) were evaluated in relation to their baseline average (-30 to 0 min) using a paired *t* test for analysis of

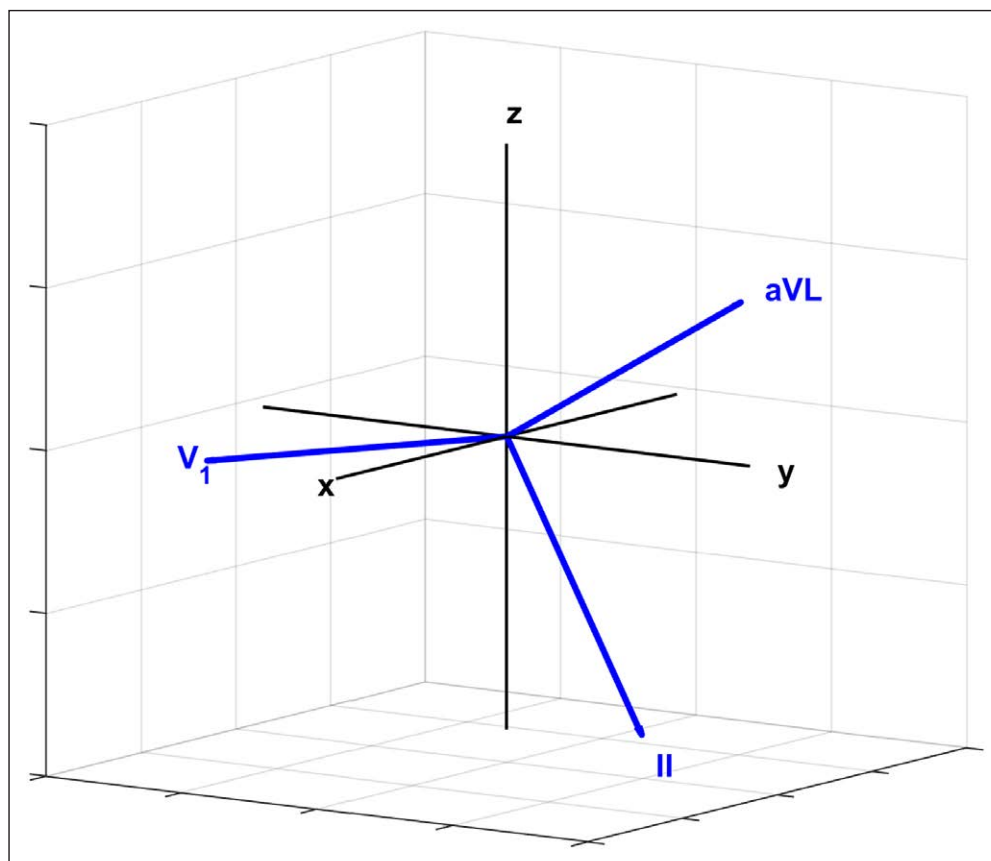


Figure 1. Three-dimensional view of the electrocardiogram leads needed for the ST segment vector calculations. The frontal plane is spanned by the (*y*, *z*) axes. The transverse plane is spanned by the (*x*, *y*) axes. The sagittal plane is spanned by the (*x*, *z*) axes.

the mean differences. Differences were considered statistically significant at a *p* value of less than 0.05.

RESULTS

Using the aforementioned exclusion criteria resulted in 389 RBC transfusions of which 277 had complete physiologic and ECG data for the entire 120-minute study window. Of the 277 RBC transfusions, 138 occurred in patients with a BTS, and 139 in patients with a right ventricle to pulmonary artery shunt (RVPAS). There were 73 unique patients, with 38 patients (52%) receiving the BTS and 35 (48%) a RVPAS. Forty-two patients (57.5%) in the cohort were male. Median birth weight, gestational age, and age at surgery were 3.2 kilograms, 39.1 weeks, and 7 days, respectively. Thirty-eight patients (52.1%) had mitral stenosis, and 31 patients (42.5%) had mitral atresia; 42 patients (57.5%) had aortic atresia, and 30 patients (41.1%) had aortic

stenosis. Survival to discharge for the study cohort was 90.4%. These data are summarized in **Supplemental Table 1** (<http://links.lww.com/CCX/A604>).

Baseline hemodynamic data were gathered for the entire cohort and analyzed according to shunt subtype as presented in **Supplemental Table 2** (<http://links.lww.com/CCX/A605>). No significant differences were noted between the two shunt subtypes with HR, mBP, sBP, RPP, and SaO_2 . However, the dBP in the BTS group was significantly lower than in the RVPAS group at baseline. The changes in hemodynamic data during the transfusion compared with baseline are displayed for the entire cohort and according to shunt type in **Table 1**. During the transfusion, there was a significant decrease in HR and increase in dBP for each shunt type. The sBP increased significantly in the BTS group. There was no change in the RPP in either group.

The change in ST segment vector variability over time is displayed in **Table 2** for the entire cohort and

TABLE 1.
Change in Hemodynamic Data in 30-Minute Epochs Compared With Pretransfusion Baseline for the Entire Study Cohort and According to Shunt Type

| Time Epoch | All | | RVPAS | | BTS | | All | | RVPAS | | BTS | |
|------------|---------------------------------|----------|----------------|----------|----------------|----------|----------------------------------|----------|---------------|----------|---------------|----------|
| | Mean \pm SE | <i>p</i> | Mean \pm SE | <i>p</i> | Mean \pm SE | <i>p</i> | Mean \pm SE | <i>p</i> | Mean \pm SE | <i>p</i> | Mean \pm SE | <i>p</i> |
| | Heart rate (beats/min) | | | | | | Mean blood pressure (mm Hg) | | | | | |
| 0–30 | -0.5 \pm 0.4 | 0.078 | -0.3 \pm 0.6 | 0.306 | -0.8 \pm 0.7 | 0.145 | 0.4 \pm 0.3 | 0.020 | 0.5 \pm 0.4 | 0.037 | 0.3 \pm 0.4 | 0.243 |
| 30–60 | -1.0 \pm 0.7 | 0.016 | -0.5 \pm 0.9 | 0.182 | -1.5 \pm 1.1 | 0.045 | 1.1 \pm 0.4 | <0.001 | 0.8 \pm 0.6 | 0.062 | 1.4 \pm 0.6 | 0.003 |
| 60–90 | -1.6 \pm 0.7 | 0.004 | -1.2 \pm 0.9 | 0.113 | -1.9 \pm 1.1 | 0.015 | 1.7 \pm 0.5 | <0.001 | 1.1 \pm 0.7 | 0.039 | 2.2 \pm 0.5 | <0.001 |
| 90–120 | -2.2 \pm 0.8 | <0.001 | -1.9 \pm 1.0 | 0.015 | -2.4 \pm 1.3 | 0.004 | 2.1 \pm 0.5 | <0.001 | 1.6 \pm 0.7 | 0.007 | 2.6 \pm 0.6 | <0.001 |
| | Systolic blood pressure (mm Hg) | | | | | | Diastolic blood pressure (mm Hg) | | | | | |
| 0–30 | 0.9 \pm 0.4 | 0.012 | 0.7 \pm 0.5 | 0.099 | 1.1 \pm 0.7 | 0.059 | 0.3 \pm 0.3 | 0.090 | 0.3 \pm 0.4 | 0.149 | 0.1 \pm 0.3 | 0.369 |
| 30–60 | 1.9 \pm 0.6 | 0.001 | 1.2 \pm 0.8 | 0.164 | 2.7 \pm 0.8 | 0.001 | 0.7 \pm 0.4 | 0.017 | 0.5 \pm 0.6 | 0.316 | 0.9 \pm 0.4 | 0.007 |
| 60–90 | 2.3 \pm 0.6 | <0.001 | 1.4 \pm 0.8 | 0.104 | 3.2 \pm 0.7 | <0.001 | 1.3 \pm 0.4 | <0.001 | 0.8 \pm 0.6 | 0.165 | 1.7 \pm 0.4 | <0.001 |
| 90–120 | 2.7 \pm 0.6 | <0.001 | 1.8 \pm 0.9 | 0.079 | 3.7 \pm 0.9 | <0.001 | 1.7 \pm 0.4 | <0.001 | 1.4 \pm 0.6 | 0.015 | 1.9 \pm 0.4 | <0.001 |
| | Rate pressure product | | | | | | Arterial O_2 saturation (%) | | | | | |
| 0–30 | 80 \pm 76 | 0.205 | 99 \pm 94 | 0.221 | 64 \pm 121 | 0.540 | 0.5 \pm 0.1 | 0.006 | 0.2 \pm 0.2 | 0.580 | 0.7 \pm 0.2 | <0.001 |
| 30–60 | 175 \pm 110 | 0.153 | 110 \pm 145 | 0.516 | 249 \pm 168 | 0.177 | 1.0 \pm 0.2 | <0.001 | 0.7 \pm 0.2 | 0.009 | 1.3 \pm 0.2 | <0.001 |
| 60–90 | 200 \pm 110 | 0.096 | 89 \pm 159 | 0.613 | 321 \pm 152 | 0.051 | 1.1 \pm 0.2 | <0.001 | 0.6 \pm 0.3 | 0.198 | 1.8 \pm 0.3 | <0.001 |
| 90–120 | 194 \pm 125 | 0.278 | 64 \pm 171 | 0.886 | 337 \pm 182 | 0.158 | 1.0 \pm 0.2 | <0.001 | 0.6 \pm 0.3 | 0.111 | 1.4 \pm 0.3 | <0.001 |

BTS = Blalock-Taussig shunt, RVPAS = right ventricle to pulmonary artery shunt.
p values are computed using the two-sample *t* test.

TABLE 2.

Progressive Change in ST-Segment Variability in 30-Minute Epochs for the Entire Study Cohort and According to Shunt Type

| Time Epoch | All, Mean \pm SE | RVPAS, Mean \pm SE | BTS, Mean \pm SE | RVPAS vs BTS p^a |
|--------------------------------|-----------------------|-------------------------|-----------------------|-----------------------|
| Baseline | 0.436 \pm 0.021 | 0.442 \pm 0.029 | 0.431 \pm 0.032 | 0.79 |
| 0–30 | 0.439 \pm 0.021 | 0.449 \pm 0.024 | 0.429 \pm 0.035 | 0.64 |
| 30–60 | 0.451 \pm 0.021 | 0.470 \pm 0.025 | 0.433 \pm 0.033 | 0.37 |
| 60–90 | 0.455 \pm 0.022 | 0.450 \pm 0.027 | 0.461 \pm 0.034 | 0.80 |
| 90–120 | 0.488 \pm 0.016 | 0.485 \pm 0.023 | 0.490 \pm 0.023 | 0.89 |
| ^b Spearman test p | 0.009 | 0.103 | 0.037 | |

BTS = Blalock-Taussig shunt, RVPAS = right ventricle to pulmonary artery shunt.

^aThe RVPAS vs BTS comparison was assessed using the two-sample t test.

^bSpearman test was used to assess ST segment vector variability over time.

TABLE 3.

Change in ST Segment Vector Variability for Each 30-Minute Epoch Compared With Baseline for the Entire Study Cohort and According to Shunt Type

| Comparison | All | | Right Ventricle to Pulmonary Artery Shunt | | Blalock-Taussig Shunt | |
|------------------|---------------------|------|----------------------------------------------|------|-----------------------|------|
| | Mean \pm SE | p | Mean \pm SE | p | Mean \pm SE | p |
| (0–30) vs base | 0.0027 \pm 0.0186 | 0.44 | 0.0071 \pm 0.0253 | 0.39 | 0.0017 \pm 0.0273 | 0.52 |
| (30–60) vs base | 0.0150 \pm 0.0209 | 0.24 | 0.0278 \pm 0.0287 | 0.17 | 0.0020 \pm 0.0305 | 0.47 |
| (60–90) vs base | 0.0190 \pm 0.0217 | 0.19 | 0.0078 \pm 0.0302 | 0.40 | 0.0303 \pm 0.0313 | 0.17 |
| (90–120) vs base | 0.0514 \pm 0.0217 | 0.01 | 0.0436 \pm 0.0316 | 0.09 | 0.0594 \pm 0.0298 | 0.02 |

p values are computed using the two-sample t test.

according to shunt type. There was a significant increase in variability during the 120-minute infusion for the entire cohort, with a statistically significant increase in variability noted in the BTS group and trending toward significance in the RVPAS group. **Table 3** displays the change in ST segment vector variability, comparing each 30-minute epoch with baseline for the entire cohort and according to shunt type. There is a progressive increase in variability for the entire cohort, which becomes significant by the end of the infusion. Similar findings are appreciated for the BTS group, with a progressive increase in variability appreciated with each 30-minute epoch, which becomes significant by the end of the infusion. **Figure 2** illustrates a significant increase in ST segment variability over time for the entire cohort.

DISCUSSION

We found a significant increase in ST segment variability associated with RBC transfusions in neonates following the NP. The ST segment variability was noted to increase throughout the duration of the infusion for the entire cohort, becoming statistically significant by the end of the transfusion. When evaluated according to shunt type, the BTS group experienced a progressive increase in variability over time, becoming statistically significant by the end of the transfusion; a trend toward significance was observed in the RVPAS group.

These findings support our hypothesis that the transfusion of stored RBCs led to compromised coronary vascular function and myocardial oxygen delivery,

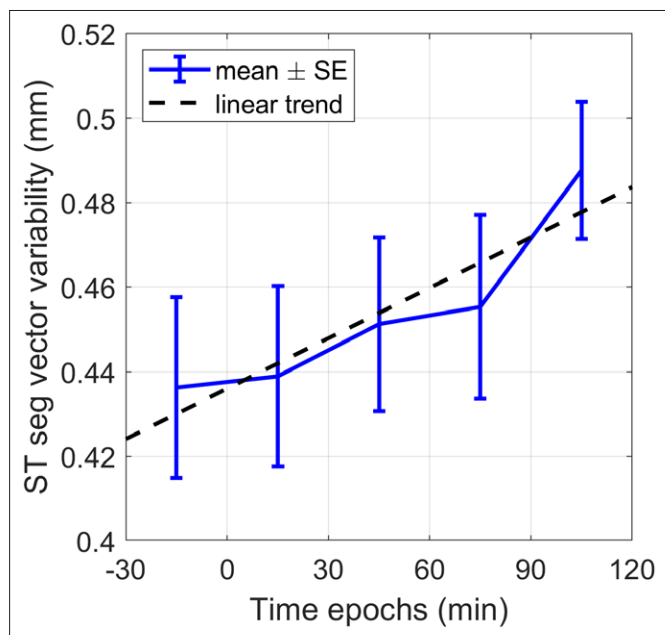


Figure 2. ST segment vector variability (mean \pm SE) over time. The linear trend with positive slope indicates increasing variability over time ($p = 0.047$).

leading to myocardial ischemia, as evidenced by a significant increase in ST segment vector variability. The ST segment variability does not appear to be the result of unfavorable changes in hemodynamics, as it occurred without a decrement in diastolic blood pressure. There was no change in myocardial oxygen demand, as the RPP did not increase significantly, a variable that correlates strongly and positively with changes in myocardial oxygen demand (13, 14). Furthermore, the ST segment vector variability increased temporally related to the accumulation of transfused RBCs.

It is intriguing that the BTS group experienced statistically significant ST segment vector variability, and the RVPAS group only shows trending toward significance. It would seem logical that if the transfusion had an adverse effect on coronary vascular function and myocardial oxygen delivery, the BTS group would be more susceptible to this phenomenon than the RVPAS group. In contrast to the RVPAS, the BTS allows for pulmonary artery diastolic run-off, leading to diastolic hypotension and “coronary steal” (15). It is this physiologic phenomenon that provided the impetus for the single ventricle reconstruction trial, which evaluated the impact of shunt type on outcomes following the NP (16).

We assessed for myocardial ischemia by evaluating the ST segment. However, the ECG obtained from infants with single ventricle anatomy is highly variable

in appearance. There is often ST segment elevation or depression at baseline in univentricular hearts due to cardiac conduction abnormalities either native to the patient or following surgery (17, 18). For these reasons, we used a signal processing algorithm that captures the movement of the ST segment from multiple leads, generating a 3D ST vector (11, 12). Previous studies have demonstrated that the variability of this ST vector is associated with cardiopulmonary arrest in univentricular hearts (11, 12). We used this ST segment vector and associated variability as a surrogate indicator of coronary ischemia.

Numerous studies of critically ill adults and children have found an association between RBC transfusions and increased mortality and morbidity (1–4). Although the storage lesion has been well documented for some time and our understanding of the mechanisms involved have increased substantially over the last several years, its role in disease and the clinical consequences remain to be determined (5–8).

This is a retrospective study with a relatively small sample size from a single center. The age of transfused blood in our patient group was not determined, and the extent to which the RBC storage lesion may have contributed to these findings was not established. Another limitation relates to the lack of information concerning the baseline levels of electrolytes in each patient. This may have a confounding effect that we did not account for. Finally, positioning of ECG leads may not be uniform for all patients; however, each patient served as their own control, and findings of ST segment variability were determined based on changes from the transfusion to pretransfusion state.

A future prospective study may address the above limitations and assess the persistence of the increase in ST segment variability beyond the 120-minute window. This would have to be carefully designed to avoid the introduction of additional confounders due to the ongoing clinical interventions over a longer window of time.

CONCLUSIONS

We found a significant increase in ST segment vector variability and evidence of myocardial ischemia temporally related to RBC transfusions in neonates following the NP. It also appears that the BTS is more susceptible to the adverse effects of RBC transfusion than the RVPAS, as the degree of ST segment vector variability was significantly greater with this shunt

type. Whether these findings are the result of a transient decrease in NO bioavailability and the clinical consequences remain to be determined.

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The authors have disclosed that they do not have any potential conflicts of interest.

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