Original Article

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Analysis of haemodynamics surrounding blood transfusions after the arterial switch operation: a pilot study utilising real-time telemetry high-frequency data capture

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Abstract

Background: Packed red blood cell transfusions occur frequently after congenital heart surgery to augment haemodynamics, with limited understanding of efficacy. The goal of this study was to analyse the hemodynamic response to packed red blood cell transfusions in a single cohort, as "proof-of-concept" utilising high-frequency data capture of real-time telemetry monitoring. *Methods:* Retrospective review of patients after the arterial switch operation receiving packed red blood cell transfusions from 15 July 2020 to 15 July 2021. Hemodynamic parameters were collected from a high-frequency data capture system (Sickbay™) continuously recording vital signs from bedside monitors and analysed in 5-minute intervals up to 6 hours before, 4 hours during, and 6 hours after packed red blood cell transfusions—up to 57,600 vital signs per packed red blood cell transfusions. Variables related to oxygen balance included blood gas co-oximetry, lactate levels, near-infrared spectroscopy, and ventilator settings. Analgesic, sedative, and vasoactive infusions were also collected. *Results:* Six patients, at 8.5[IQR:5-22] days old and weighing 3.1[IQR:2.8-3.2]kg, received transfusions following the arterial switch operation. There were 10 packed red blood cell transfusions administered with a median dose of 10[IQR:10-15]mL/kg over 169[IQR:110-190]min; at median post-operative hour 36[IQR: 10-40]. Significant increases in systolic and mean arterial blood pressures by 5-12.5% at 3 hours after packed red blood cell transfusions were observed, while renal near-infrared spectroscopy increased by 6.2% post-transfusion. No significant changes in ventilation, vasoactive support, or laboratory values related to oxygen balance were observed. *Conclusions:* Packed red blood cell transfusions given after the arterial switch operation increased arterial blood pressure by 5-12.5% for 3 hours and renal near-infrared spectroscopy by 6.2%. High-frequency data capture systems can be leveraged to provide novel insights into the hemodynamic response to commonly used therapies such as packed red blood cell transfusions after paediatric cardiac surgery.

Introduction

Post-operative management of children with CHD is primarily focused on maintaining tissue oxygenation while allowing cardiac recovery and adaptation to a new physiologic state.[1,2] Outcome expectations for CHD have drastically improved to ~ 3% mortality in the modern era thanks to advances in surgical technique and available medical therapies and modalities.[3] Post-operative recovery following surgery, however, continues to be a high-risk period for this population, with 30-day survival of the most complex lesions utilised as a benchmark for hospital performance.[3–7] Accurate assessments of cardiac output and oxygen delivery are necessary to optimise global organ perfusion and provide therapeutic targets to guide titration of mechanical ventilation, vasoactive, analgesic, and sedative infusions, as well as volume repletion.[1,2,8]

Packed red blood cell transfusions are frequently utilised to increase oxygen-carrying capacity for oxygen delivery and maintain intravascular volume for cardiac output, with more than 70% of congenital heart surgery patients receiving a transfusion in the perioperative period.[9] In addition to high rates of packed red blood cell transfusion exposure, the unique physiologies associated with complex CHD such as shunt dependent blood flow, and intracardiac mixing in univentricular circulation place them at high risk for transfusion-related complications including circulatory overload, ventricular dysfunction, elevated vascular resistance, and allo-sensitisation.[10–13]

In 2018, the Transfusion and Anemia Expertise Initiative published guidelines specific to CHD, recommending packed red blood cell transfusions "if haemoglobin (Hb) <7 g/dL after biventricular repair and if >9 g/dL after staged single ventricle palliation for the patient with stable haemodynamics and adequate oxygenation (*weak recommendation, low quality evidence*)".[12] The rationale for this strategy, based on the "growing body of literature illustrating a strong association between transfusion and worse clinical outcomes in patients with paediatric heart disease", consists of three small retrospective studies of transfusions given during cardiopulmonary bypass, not post-operatively, with duration of mechanical ventilation and length of stay the only outcome variables affected, not survival.[10,14,15]

However, two subsequent meta-analyses comparing "restrictive" and "liberal" packed red blood cell transfusion strategies during paediatric cardiac surgery found no significant difference in risk of in-hospital mortality, infection, blood loss, duration of mechanical ventilation, or length of stay.[16,17] Furthermore, subgroup analysis of patients with cyanotic CHD treated with "liberal" transfusion strategy demonstrated a significantly *shorter* duration of post-operative mechanical ventilation.[16]

Regarding efficacy, outcome measures focusing on oxygen delivery biomarkers such as lactate and mixed venous oxygen saturation (SvO_2) have failed to find consistent benefit from packed red blood cell transfusion transfusion after paediatric cardiac surgery. Reasons for this are likely multifactorial, including high baseline Hb levels at time of transfusion and failing to account for the concomitant effects supplemental oxygen, mechanical ventilation, vasoactive support, analgesics, and neuromuscular blockade have on overall oxygen balance.[11,13,18,19] In addition to impaired oxygen delivery, patients after paediatric cardiac surgery are at significant risk of low cardiac output due to varying degrees of systolic and diastolic ventricular dysfunction, valvular regurgitation, and myocardial inflammation depending on type of surgery and CPB exposure.[20,21] Strategies to improve cardiac output after paediatric cardiac surgery include balancing systemic and pulmonary vascular resistance, which packed red blood cell transfusions are known to affect.[22–24]

Two recent studies of oxygen delivery response to packed red blood cell transfusions after single ventricle palliation reported drastically conflicting results, highlighting the need for further in-depth investigation, including leveraging developing HFDC technology to guide patient-specific care.[25] Loomba, et al. determined packed red blood cell transfusions "may be a useful intervention to increase systemic oxygen delivery" based on a significant decrease in lactate from ~ 5 to 4 mmol/L and an increase in PaO_2/FiO_2 ratio from ~ 85 to 100, which equals ~ 5% reduction in FiO_2 requirement; however, they did not control for other variables related to oxygen delivery.[9] Meanwhile, Savorgnan, et al. concluded there was "surrogate evidence of coronary ischaemia" during packed red blood cell transfusions based solely on increased ST segment-vector variability from baseline during the transfusion period, despite significantly decreased HR and increased diastolic pressures.[26] Not only were no oxygen delivery biomarkers included in this study, but the ST segment-vector significance was determined using an advanced HFDC algorithm unique to that institution that has not been validated elsewhere.[26]

Sickbay™ (Medical Informatics Corp, Houston, TX) is one such HFDC platform that continuously records numeric and waveform vital sign data across multiple standard monitoring and therapeutic devices.[25,27] In addition to allowing real-time, second-to-second analysis, this platform has provided novel insights into patient response to therapy, such as time to arrhythmia cessation with IV sotalol and hypotension associated with IV acetaminophen.[28,29] Even routine bedside procedures such as vasoactive infusion syringe pump exchanges-performed by the bedside nurse every 24-72 hours, have been shown to significantly alter subsequent patient haemodynamics.[30]

Accordingly, we sought to leverage the Sickbay™ system to describe the real-time hemodynamic response to packed red blood cell transfusions in dextro-transposition of the great arteries (d-TGA) patients after the ASO. We chose this cohort for our pilot study given their relative homogeneity in preoperative diagnosis, demographics, and perioperative clinical course, in effort to minimise confounding variables affecting oxygen balance at time of transfusion.[31–33] By leveraging HFDC analysis of haemodynamics in addition to controlling for variables related to oxygen delivery, we may better understand the effect packed red blood cell transfusions have on cardiac output and oxygen delivery after paediatric cardiac surgery.

Patients and methods

Study structure and data sources

The study was approved by the Institutional Review Board at The University of Texas at Austin (STUDY00001279, approved 11 November 2021). This is a retrospective review of d-TGA patients who underwent ASO and received a post-operative packed red blood cell transfusions at Dell Children's Medical Center from 15 July 2020 to 15 July 2021. Our cardiac care unit utilises Philips© telemetry monitors (Koninklijke Philips N.V., Amsterdam, Netherlands) to display HR calculated from electrocardiogram leads, oxygen saturations from pulse oximetry (SpO_2), and systolic, diastolic, and mean arterial blood pressures (ABP-S, ABP-D, and ABP-M) from invasive arterial catheter measurements. Both numeric and waveform data are captured by Sickbay™ at 0.5 to 2-Hz fidelity and stored for future analysis. Continuous vital sign data were collected by Sickbay™ up to 6hr prior to packed red blood cell transfusions, during packed red blood cell transfusions (up to 4h), and 6hrs after packed red blood cell transfusions, except for cerebral and renal NIRs, due to lack of monitor capture by Sickbay™ at our institution.

Binary pre-and-post-packed red blood cell transfusion markers of oxygen delivery from arterial blood gas analysis were collected within 4h of packed red blood cell transfusions, with data closest to transfusion time used for analysis. Standard practice at our institution includes hourly post-operative arterial blood gas, while venous co-oximetry is only performed at the discretion of the provider team and thus was not able to be included for comparative analysis peri-transfusion. All patients had post-operative transesophageal echocardiograms, allowing documentation of ventricular function at time of transfusion.

Continuous sedative, analgesic and neuromuscular blockade infusion doses, and vasoactive inotropic scores were collected hourly from medical records for the study period duration. As per our standard institutional practice, no other volume resuscitation was given at the time of transfusion.

Statistical analysis

Descriptive statistics were used for clinical demographics and categorical laboratory values. Continuous variables were reported as median [interquartile range (IQR)]. For hourly recorded data, the mean values over the 6hrs pre- and post-packed red blood cell

transfusions were compiled, and a mean difference was calculated, while median pre- to post-packed red blood cell transfusion labs were compared using Wilcoxon signed rank test.

Sickbay™ data analysis was performed using previously published methods.[28,30] Data were cleaned by filtering out all packed red blood cell transfusions/time pairs with missing data. The time axis for each packed red blood cell transfusions was standardised so that time "0-min" corresponded to the recorded packed red blood cell transfusion starting time. Pre-transfusion baselines were taken to be their average values prior to packed red blood cell transfusions, excluding the 10 minutes leading up to the packed red blood cell transfusions to account for possible error between documented and actual start time. A non-overlapping, 5-minute moving average was applied to the time series for each event to filter out monitor "noise". Hemodynamic variables in these intervals were converted into percentage changes relative to their packed red blood cell transfusions-specific baseline. Aggregated hemodynamic data were then plotted along with 95% confidence intervals (95%CI). Additionally, to provide additional context, binary comparisons of baseline hemodynamic values 1 hour prior to packed red blood cell transfusions compared to hemodynamic values at 3hr and 6hr after packed red blood cell transfusions using paired Wilcoxon signed rank tests. All statistical analyses were performed using R and RStudio (https://www.R-project.org).

Results

Patient population and clinical course

There were six patients who underwent ASO at median 8.5[IQR: 5-22] days and 3.1[IQR:2.8-3.2]kg and received a total of 10 packed red blood cell transfusion post-operatively (Table 1). One patient had prior pulmonary artery banding at day of life 4 at 3.4 kg because of challenging ventricular septal and coronary anatomy. That patient underwent ASO, at 3 months of age, weighing 4.85 kg. Median packed red blood cell transfusion prescriptions were 10[IQR:10-15]mL/kg, over 169[IQR:110-190]min at median 36[IQR:10-40] hours post-procedure. At the time of transfusion, 50% of patients had mild-to-moderately depressed left ventricular function. Indications for packed red blood cell transfusions were at the discretion of the clinical care team. There were no adverse events directly related to packed red blood cell transfusions. All patients survived to discharge, with zero 30-day readmissions.

Hemodynamic analysis

Leveraging HFDC system allowed for analysis of up to 57,600 continuous data points (1 data point per second over the 16hr study period) per vital sign for each packed red blood cell transfusion exposure. Figure 1 displays aggregated mean change in HR and SpO_2, and Figure 2 displays the aggregate change in ABP-S, ABP-D, and ABP-M over time for all packed red blood cell transfusions events. After packed red blood cell transfusion initiation, all three ABP parameters crossed 95%CI at ∼ 3hr by 7-12.5%, with return to baseline by 6hr. HR trended downward after packed red blood cell transfusions, though never crossing 95%CI. To determine if these trends were statistically different, comparison of baseline hemodynamic values were compared to those at 3hr and 6hr. At 3hr, there was a 5.1 ± 2.2% (p = 0.039) increase in ABP-S and 5.4 ± 2.1% (p = 0.039) increase in ABP-M, but no significant changes in HR, ABP-D, or SpO_2 at 3hr and no changes in any hemodynamic parameters compared to baseline at

Table 1. Baseline demographics and transfusion characteristics (n = 6)

Demographics	Value
Median age at surgery (days) [IQR]	8.5 [5-22]
Median weight at surgery (kg) [IQR]	3.1 [2.8-3.2]
Female (%)	33%
Anatomic diagnosis (%)	
d-TGA with ventricular septal defect	67%
d-TGA with intact ventricular septum	33%
Left ventricular function at time of transfusion (%)	
Normal ventricular function	50%
Mild-to-moderately depressed function	50%
Median hospital length of stay (days) [IQR]	39 [24-43]
Survival to discharge (n)	6 (100%)
Median pRBCTx dose (mL/kg) [IQR]	10 [10-15]
Median pRBCTx duration (min) [IQR]	169 [110-190]
Median post-operative hour until pRBCTx [IQR]	36 [10-40]

Key: IQR = interquartile range; pRBCTx = packed red blood cell transfusion.

6hr after packed red blood cell transfusions (Table 2). Concurrently, there were no significant changes in ventilator support, doses of sedative, analgesia, or vasoactive infusions throughout the study period (Table 3). No patients were under neuromuscular blockade at time of transfusion.

Markers of oxygen delivery

Pre-to-post-packed red blood cell transfusions we appreciated an increase in median Hb from 10.4[IQR: 9-11] to 12[IQR: 11.6-12.3] (p = 0.021) and median haematocrit from 31.5[IQR: 26.5-33.4] to 35.5[IQR: 34.6-36.6] (p = 0.027), but there were no differences in markers of oxygen delivery, such as PaO_2 or lactate (Table 3). Hourly renal and cerebral NIRS, a surrogate marker of end-organ oxygenation and venous saturations, are plotted in Figure 3. Renal NIRS showed an overall increasing trajectory, with a significant increase of 6.2% (from 67.4% before packed red blood cell transfusions to 73.6% after packed red blood cell transfusions, p = 0.039). Cerebral NIRS increased by 6% but did not reach statistical significance (p = 0.055).

Discussion

To the authors' knowledge, this represents the first report of the hemodynamic response of CHD patients to packed red blood cell transfusions utilising HFDC analysis. This pilot study functions as proof-of-concept for the feasibility to leverage Sickbay as a clinical research platform. We found a significant increase in ABPs of 5-12.5% from baseline at roughly 3hr after packed red blood cell transfusions with a subsequent return to baseline at 6hr as well as a sustained 6% increase in renal NIRS. This was despite 50% of the cohort having mild-to-moderately depressed left ventricular function at the time of transfusion.

During the entire study period, there were no significant changes in ventilator support, vasoactive inotropic scores, or doses of analgesic and sedative medications that contributed to oxygen balance. These data, which require further validation, describe real-
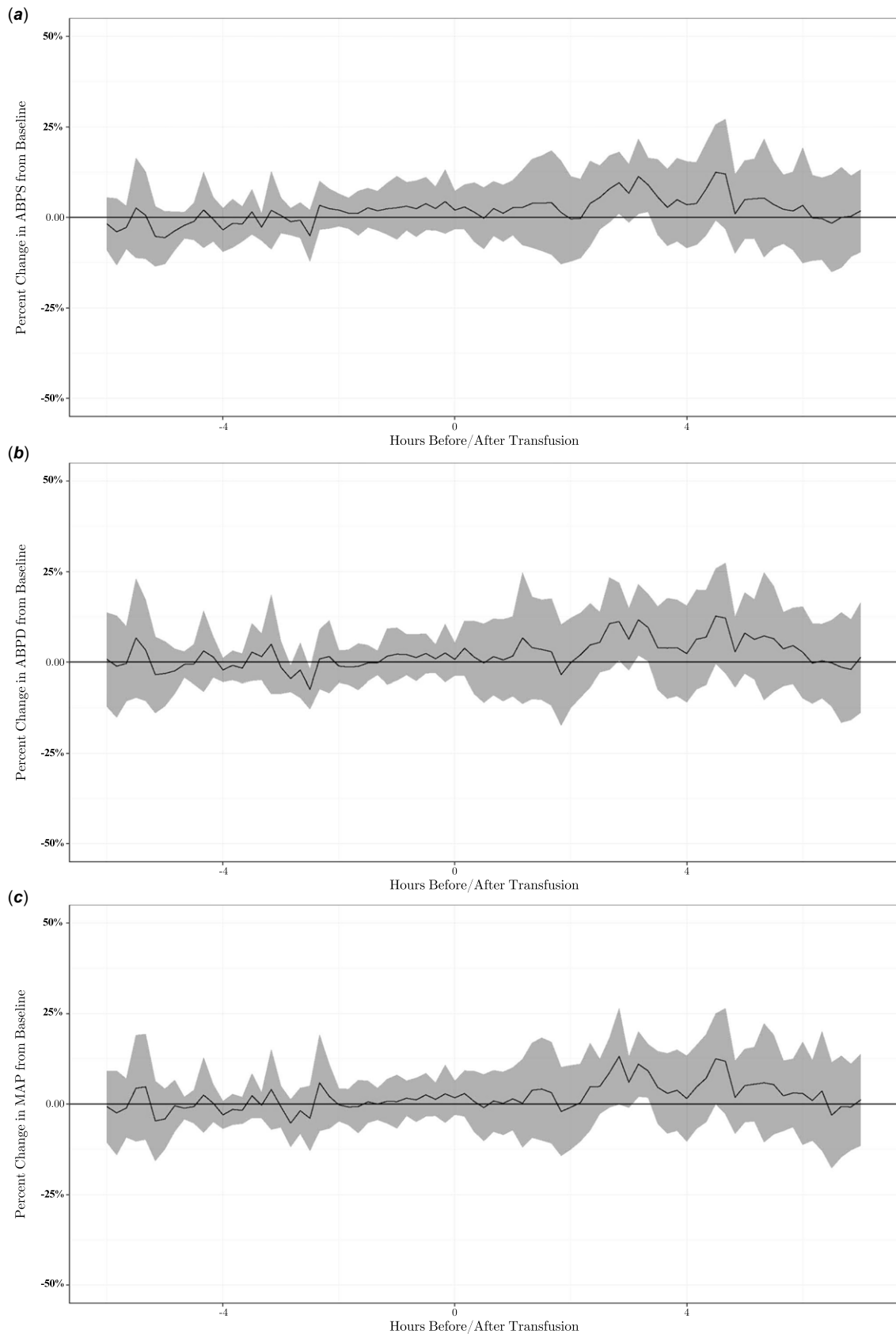
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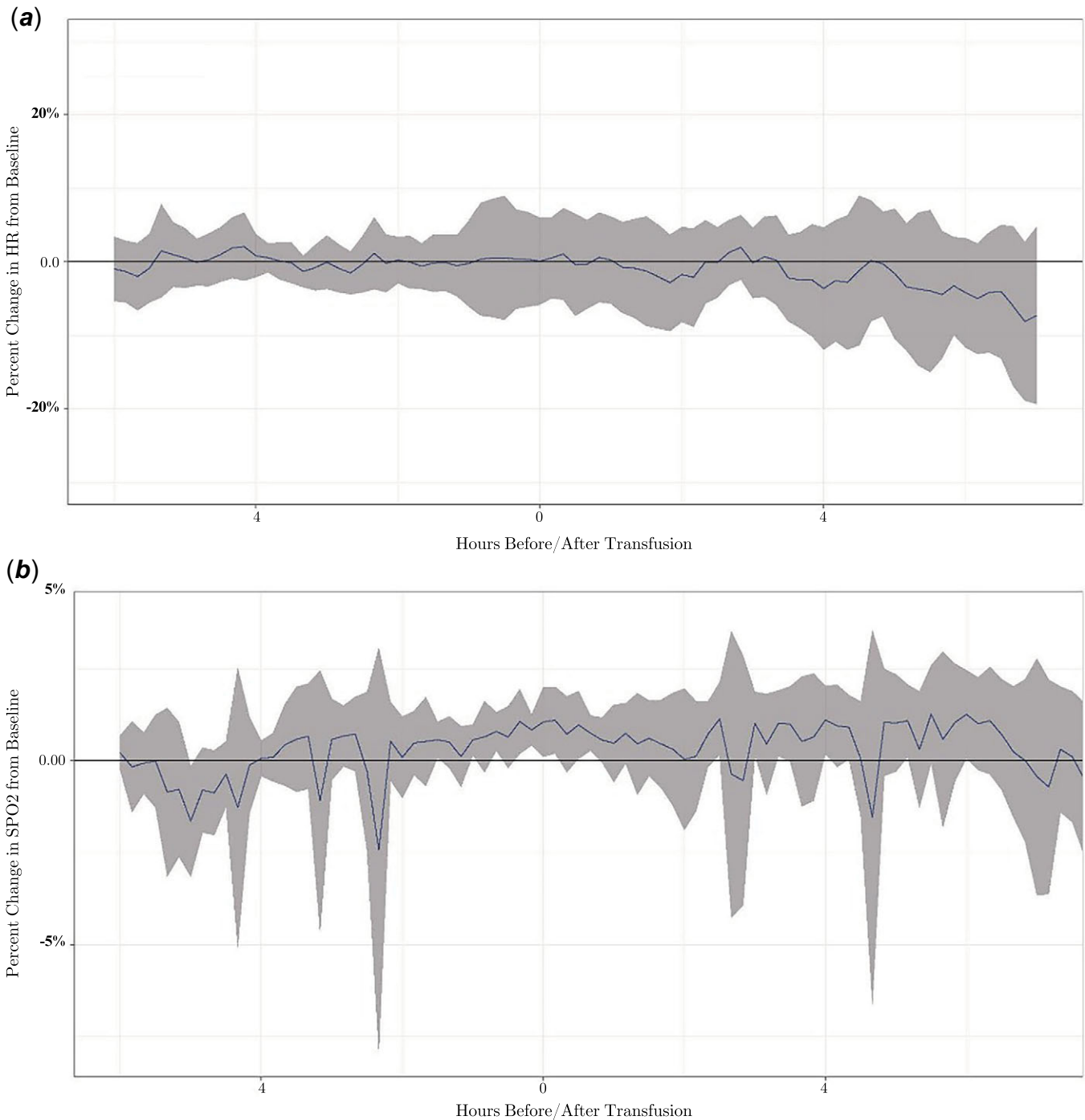
Figure 1. Sickbay™ Aggregate Percent Change from Baseline – HR (1a) and SpO$_2$ (1b). The central line represents the aggregate percent change from baseline of all nine red blood cell transfusion using 1 data point per second per red blood cell transfusion with the surrounding grey area representing the 95% confidence interval. HR trends began declining at 3hr after red blood cell transfusion but never eclipse 95% confidence interval. Key: HR—heart rate; SpO$_2$—oxygen saturations.

time augmentation of cardiac output during packed red blood cell transfusions after paediatric cardiac surgery while controlling for other variables of oxygen delivery. Leveraging HFDC systems can help create nuanced, patient-specific care plans by allowing better understanding of hemodynamic responses to frequently utilised therapies such as packed red blood cell transfusions.

For a term neonate status post ASO with ABP-M of 35-40mmHg, a 5-12.5% increase would correspond to a 2-5mmHg improvement, providing a considerable increase in overall perfusion pressure. The ability to augment haemodynamics with packed red blood cell transfusions—perhaps instead of interventions such as increasing vasoactive or ventilator support—could have significant clinical implications for many CHD patients. Especially for those who cannot tolerate high ventilator airway pressures, FiO$_2$ or vasoactive infusion doses, packed red blood cell transfusions may offer another therapeutic option for augmentation of cardiac output during surgical recovery.

Figure 2. Sickbay™ Aggregate Percent Change from Baseline – ABP-S (2a), ABP-D (2b), and ABP-M (2c). The central line represents the aggregate percent change from baseline of all nine pRBCTx using 1 data point per second per red blood cell transfusion with the surrounding grey area representing the 95% confidence interval. The 95% confidence interval is eclipsed at roughly 3hr after red blood cell transfusion corresponding to 7-12.5% increase from baseline with decrease to original baseline at 6 hr. Key: ABP-D—diastolic arterial blood pressure; ABP-M—mean arterial blood pressure; ABP-S—systolic arterial blood pressure.

Table 2. Comparisons of hemodynamic parameters pre- and post-red blood cell transfusion*

Measure	Baseline (mean ± SD)	3 Hours (mean ± SD)	% Change at 3 Hours (% ± SE)	p-value	6 Hours (mean ± SD)	% Change at 6 Hours (% ± SE)	p-value
HR (bpm)	137.5 ± 6.3	136.0 ± 6.9	−1.3 ± 1.1%	0.38	132.3 ± 7.4	−5.1 ± 2.6%	0.2
ABP-S (mmHg)	80.1 ± 5.2	83.8 ± 5.0	5.1 ± 2.2%	**0.039**	79.1 ± 4.6	−2 ± 4.5%	0.38
ABP-D (mmHg)	41.0 ± 2.7	43.1 ± 3.1	5.2 ± 2.4%	0.078	42.7 ± 3.5	−1.3 ± 4.3%	0.64
ABP-M (mmHg)	56.8 ± 3.6	59.7 ± 3.6	5.4 ± 2.1%	**0.039**	58.6 ± 3.8	0.5 ± 4.1%	0.84
SpO$_2$ (%)	99.4 ± 0.3	99.3 ± 0.33	−0.1 ± 0.3%	0.67	99.3 ± 0.2	−0.2 ± 0.3%	0.8

Key: ABP-S/D/M = arterial blood pressure-systolic/diastolic/mean; HR = heart rate; SD = standard deviation; SE = standard error; SpO$_2$ = oxygen saturations.
*p-values are computed from a paired Wilcoxon signed rank test, comparing change at 3 hours to baseline and 6 hours to baseline, respectively.

Table 3. Laboratory and clinical variables affecting DO$_2$

| Lab value	Pre-transfusion (median [IQR])	Post-transfusion (median [IQR])	p-value
Haemoglobin (g/dL)	10.4 [9-11]	12 [11.6-12.3]	**0.021**
Haematocrit (%)	31.5 [26.5-33.4]	35.5 [34.6-36.6]	**0.027**
Arterial pH	7.39 [7.39-7.40]	7.38 [7.34-7.39]	0.313
P$_a$CO$_2$ (mmHg)	37.7 [35.8-40.1]	37.4 [36.0-42.5]	0.383
P$_a$O$_2$ (mmHg)	130.3 [124.4-157.6]	125 [82.7-144.3]	0.25
HCO$_3^-$ (mEq/L)	22.1 [20.7-22.8]	21.9 [21.3-22.5]	0.78
Lactate (mmol/L)	1.24 [1.16-1.34]	1.38 [1.11-1.90]	0.74
Factor	**Pre-transfusion (mean)**	**Post-transfusion (mean)**	**p-value**
Near-infrared spectroscopy			
Renal (%)	67.4	73.6	**0.039**
Cerebral (%)	66.3	72.3	0.055
Ventilator			
FiO$_2$ (%)	43.1	39	0.353
Tidal volume (mL)	29	28.1	0.181
PEEP (cmH$_2$O)	5	5	>0.999
Medications			
Dexmedetomidine (mcg/kg/min)	0.3	0.3	>0.999
Epinephrine*100 (mcg/kg/min)	2.9	2.8	0.834
Vasopressin*10000 (units/kg/min)	1.2	1.2	>0.999
Calcium chloride (mEq/mL/min)	6.8	6.3	0.59
Vasoactive-inotrope score	4.3	4.2	0.722

p-value considered significant < 0.05.

Given the paucity of existing evidence, leveraging HFDC to elucidate the effects of packed red blood cell transfusions from a hemodynamic perspective may help provide justification to guide packed red blood cell transfusions after paediatric cardiac surgery. With HFDC, we demonstrate a significant increase in ABP and renal NIRS post-transfusion, with a non-significant downward trend in HR. This is consistent with the findings of elevated ABP-D and lowered HR reported by Savorgnan, et al.[26]

Regarding oxygen delivery effect, there were minimal confounding variables during the peri-transfusion period. This was in effort to isolate the effect of packed red blood cell transfusions on outcome measures, including patients being at a similar clinical time course (~36 hours post-procedure). Given the baseline Hb of 10.4 as well as concomitant cardiopulmonary support at time of packed red blood cell transfusions, it is not surprising there was no effect on oxygen delivery. In contrast to Loomba et al's study cohort, our patients did not have baseline hyperlactatemia and were already receiving mechanical ventilation at the time of transfusion.[9]

There were several limitations to this pilot study, designed as proof-of-concept for feasibility of leveraging HFDC integration
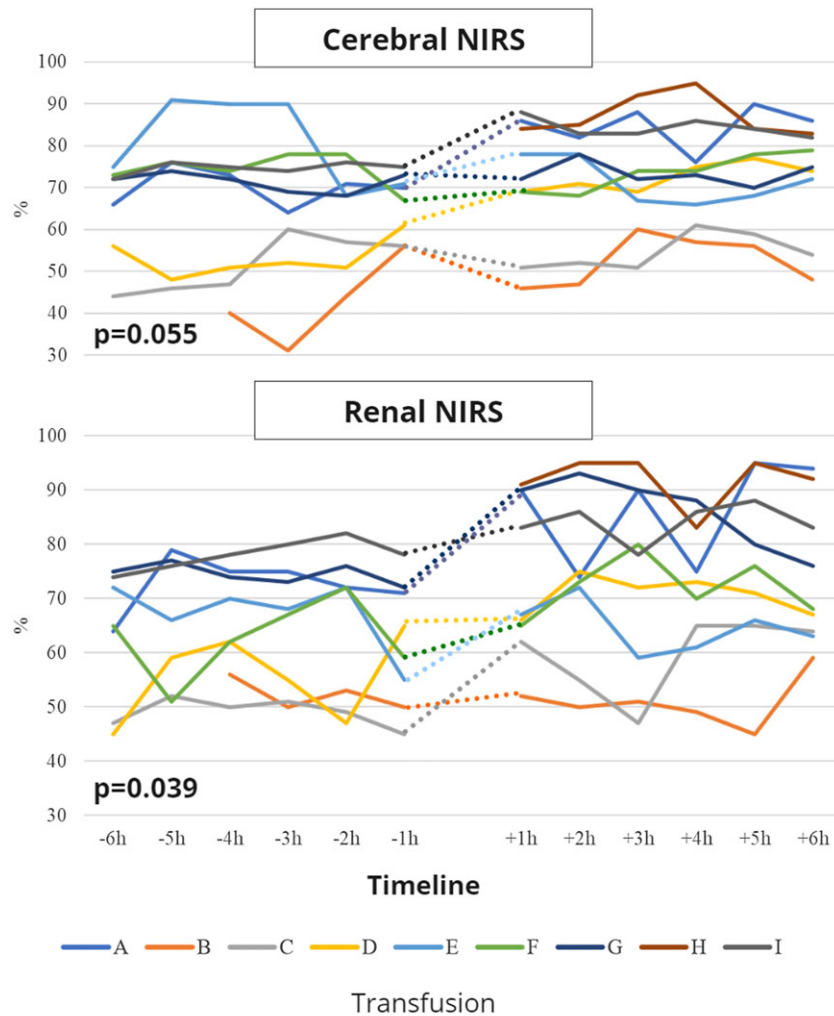
Figure 3. Cerebral and Renal NIRS Over Time. Lines correspond to hourly data from each of the red blood cell transfusion events included in final analysis. Key: NIRS—near-infrared spectroscopy.

into transfusion medicine research. This was performed as a retrospective review at a single centre, on a small, homogeneous patient cohort. packed red blood cell transfusion prescription dose and duration were at the discretion of the clinical team and vary by provider within our institution. Indication for transfusion could not be assessed from the medical record due to lack of documentation. Sickbay data capture at our institution at the time of study was limited to the telemetry monitor recordings of HR, SpO_2, and ABP. For NIRS, ventilator settings and medication dosages, we relied on manually entered data from the electronic medical record, which is prone to errors and a lag-time between occurrence and documentation.[34]

Conclusion

In this pilot study investigating high-fidelity, real-time hemodynamic parameters surrounding packed red blood cell transfusions after ASO, packed red blood cell transfusions resulted in short-term increases in ABP-M and ABP-S by 5-12% relative to baseline without significant changes in vasoactive or ventilator support. Future studies should be prospective in nature and powered to detect significant changes in CO relative to hemodynamic markers such as vasoactive inotropic scores in

addition to standard vital signs. Future cohorts should be expanded to include other index lesions, univentricular defects, and patients with varying degrees of ventricular function to assess hemodynamic response to transfusion in different clinical settings. HFDC should continue to be leveraged for this research to develop patient-specific management strategies after paediatric cardiac surgery.

Informed consent. This study was approved under the auspice of the Institutional Review Board at The University of Texas at Austin (STUDY00001279, approved on 11 November 2021).

Meeting Presentation. The abstract from this work was presented at the Pediatric Cardiac Intensive Care Society Annual Meeting, Miami, FL, 15-18 December 2022.

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