Tissue Oxygenation During Treatment of Infant Congenital Heart Defects

Study design

This prospective observational study was approved by the Internal Review Board of Beijing Anzhen Hospital, Capital Medical University, Beijing, China (#2018009), registered at ClinicalTrials.gov (Identifier: NCT03941015), and performed from December 2018 to August 2020 at Beijing Anzhen Hospital, Capital Medical University, Beijing, China.

Participants

Infants between 1 and 12 months old and scheduled to undergo surgical repair of an isolated VSD involving CPB were eligible. The exclusion criteria were any of the following: 1) refusal to participate; 2) emergent or urgent surgery; 3) weight >10 kg; 4) preoperative renal dysfunction; 5) pulmonary failure requiring respiratory support; 6) digestive system failure requiring total parenteral nutrition; 7) chromosomal abnormalities; and 8) skin abnormalities precluding the application of the tissue oximetry probe. We excluded infants with a body weight > 10 kg because tissue oximetry may not be able to interrogate the renal tissue bed in heavier infants due to the limited penetrating capacity of near-infrared light.[18] Written informed consent was obtained from the infants' parents.

Anesthetic care

The anesthetic care was provided by the same team, comprising one attending anesthesiologist and four residents. The infants were allowed formula milk feeding until six hours before surgery, milk feeding until four hours before surgery, and water drinking until two hours before surgery. In the operating room, all infants received electrocardiography, pulse oximetry, noninvasive blood pressure, and temperature monitoring. Anesthesia was induced using 3-5% sevoflurane delivered over a fit face

mask. Midazolam (0.2 mg/kg), pipecuronium (0.2 mg/kg), and sufentanil (10 mcg/kg) were administered intravenously following the establishment of the peripheral access. All infants were endotracheally intubated and mechanically ventilated with a tidal volume of 8 mL/kg, a respiratory rate of 18-30 breaths/min, an inspiratory to expiratory time ratio of 1:1-1.5, and an inspired oxygen fraction of 50%. The end-tidal carbon dioxide was maintained at 35-45 mmHg. All infants received a radial or femoral arterial catheter for continuous arterial blood pressure monitoring and an internal jugular or femoral venous catheter for central venous pressure monitoring and intravenous access. Hemodynamics was monitored using a hemodynamic monitoring system based on arterial pressure waveform analysis (MostCare, Vytech, Padova, Italy). Anesthesia was maintained using a midazolam (0.2-0.4 mg/kg/h), pipecuronium (0.08-0.16 mg/kg/h), and sufentanil (2-4 mcg/kg/h) continuous infusion. Hemoglobin was maintained at ≥8 g/dL during CPB and ≥10g/dL before and after CPB. The CPB flow was maintained at 150-200 mL/kg/min and the mean arterial pressure was maintained at 30-50 mmHg. Hemodynamics was managed using crystalloid, dopamine, epinephrine, and/or milrinone before and after CPB. The core temperature was maintained at about 32-34°C during CPB; otherwise, it was maintained above 36°C before and after CPB. All infants received modified ultrafiltration following the weaning from CPB.

Ventricular septal defect repair

The procedure was performed through either an anterolateral fourth intercostal incision or a median sternotomy per the infant's condition and surgeon's preference. The VSD was closed using a patch through either a right atrium or right ventricle incision, depending on the location of the defect. All infants were admitted to the pediatric intensive care unit after surgery.

Renal tissue oxygen saturation monitoring

$SrtO_2$ was monitored using a tissue near-infrared spectroscopy oximeter (FORE-SIGHT ELITE, CASMED, Branford, Connecticut, USA; now acquired by Edwards Lifesciences, Irvine, California, USA). A biophotonic sensor was placed on the left flank at the level of T10-L2 to monitor $SrtO_2$.[3, 6, 18] A dedicated research personnel stayed in the operating room to ensure the proper function of the tissue oximeter. The patient care team was blinded to the monitoring because the $SrtO_2$ data were intended solely for research, not for clinical decision making, per the research protocol. The $SrtO_2$ data, generated by the tissue oximeter every 2 seconds, were extracted from the monitor at the end of the surgery.

Data collection

Demographic data including age, sex, height, weight, and body mass index (BMI) were recorded. Data based on the last echocardiography and laboratory results before surgery were collected. Intraoperative data including $SrtO_2$, systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, cardiac index, stroke volume index, stroke volume variation, body temperature, surgery time, CPB duration, aortic clamping time, urine output, estimated blood loss, and intravascular fluid repleted were recorded. Serum creatinine was recorded within one week before surgery and on postoperative days 1-3. The infant was dropped from the study if the $SrtO_2$ monitoring was interrupted for more than 5 minutes during surgery.

The baseline $SrtO_2$ and hemodynamics

The baseline $SrtO_2$ was defined as the median value of the data recorded over a 5-minute epoch when the infant was induced and mechanically ventilated and had a cardiac index ≥2.5 L/min/m^2, but before skin incision. The average cardiac index in infants weighing ≥4 kg is about 2.76 ± 0.41 L/min/m^2 (mean ± SD).[22] A previous study suggested an association between $SrtO_2$ and cardiac output.[23] In order to adopt a

baseline $SrtO_2$ that was not misleading due to an abnormally low cardiac output, we chose to use an $SrtO_2$ value that was measured when the infant's cardiac index was in the normal range. Blood pressure typically decreases following anesthesia induction and may or may not be accompanied by a reduction in cardiac output.[24] Therefore, we chose to consider cardiac output, instead of blood pressure, during the determination of the baseline level of $SrtO_2$. Similar to the determination of the baseline $SrtO_2$, the baseline systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, cardiac index, stroke volume index, and stroke volume variation were defined as the median value of the data recorded during a 5-minute epoch when the infant was anesthetized and mechanically ventilated and had a cardiac index $\geq$ 2.5 L/min/m^2, but before skin incision.

Renal desaturation and outcome measures

The exposure of this study was renal desaturation, defined as an at least 20% decrease in $SrtO_2$ from the baseline level for at least 60 consecutive seconds. The primary outcome was the incidence of AKI arising within postoperative days 1-3. AKI was diagnosed per the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[25] The secondary outcomes were the incidences of stages 1, 2, and 3 AKI per the KDIGO criteria.

Statistical analysis

The power analysis was based on the preliminary results of the first 50 infants. The ratio of infants with and without renal desaturation was about 1:6, and the incidences of AKI in infants with and without renal desaturation were about 50% and 25%, respectively. Hence, a total of 217 infants (i.e., 31:186) were needed to detect a 25% difference (i.e., 50% minus 25%) with a power of 80% using a two-side proportion test at an alpha level of 0.05. We aimed to recruit 242 infants, with the anticipation of a

drop-off rate of 10%.

The continuous variables that followed a normal distribution were presented as mean and standard deviation (SD); otherwise, they were presented as median and interquartile range (IQR). The normality of distribution was assessed using histograms and the Shapiro-Wilk test. The categorical variables were presented as frequency and percentage.

The primary analysis was the comparison of the incidences of AKI in infants with and without renal desaturation based on the propensity score-matched cohort. The matched pairs were identified using a one-to-three nearest neighbor caliper with a width of 0.1, accounting for demographics, echocardiography and laboratory data, baseline hemodynamics, and surgical information. The balance between the matched pairs was assessed using the standardized difference. The incidences of AKI in infants with and without renal desaturation were compared using conditional logistic regression. The effect size was quantified by the odds ratio (OR) and 95% confidence interval (CI). A two-sided P value of less than 0.05 was considered statistically significant for the primary outcome. The multiple testing for the secondary outcomes was adjusted using the Holm-Bonferroni method.

The Kaplan-Meier curves of the cumulative incidences of AKI in infants with and without renal desaturation based on the propensity score-matched cohort were constructed. The log-rank test was used to compare the distributions of cumulative AKI incidences in infants with and without renal desaturation. We then fitted a stratified Cox proportional-hazards model to analyze the association between renal desaturation and AKI. The effect size was quantified by the hazard ratio (HR) and 95% CI.

The incidences of AKI in infants with and without renal desaturation based on the original cohort were compared using multivariable logistic regression controlled for

confounders. This served as a sensitivity analysis to corroborate the primary analysis based on the propensity score-matched cohort. The confounders included the known risk factors for AKI (age, preoperative creatinine, preoperative hemoglobin, and CPB time) and the factors that had an imbalance (i.e., standardized difference ≥0.2) between infants with and without renal desaturation. To avoid collinearity, we included only one factor if two factors were correlated (i.e., Pearson's correlation coefficient >0.5).

Additionally, we explored the correlation between the duration of renal desaturation and the ratio of postoperative peak creatinine to preoperative baseline creatinine using the Spearman's rank correlation coefficient.

The statistical analyses were performed using R (version 3.5.3, R Foundation for Statistical Computing, Vienna, Austria) and SPSS software (version 17.0, SPSS, Chicago, IL, USA). A P value <0.05 was considered statistically significant for the primary hypothesis.