The effect of selective cerebral perfusion on cerebral versus somatic tissue oxygenation during aortic coarctation repair in neonates and infants

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Abstract

Background: Suboptimal tissue perfusion and oxygenation may be the root cause of certain perioperative complications in neonates and infants having complicated aortic coarctation repair. Practical, effective, and real-time monitoring of organ perfusion and/or tissue oxygenation may provide early warning of end-organ mal-perfusion.

Methods: Neonates/infants who were scheduled for aortic coarctation repair with cardiopulmonary bypass (CPB) and selective cerebral perfusion (SCP) from January 2015 to February 2017 in Children’s Hospital of Nanjing Medical University participated in this prospective observational study. Cerebral and somatic tissue oxygen saturation (SctO₂ and SstO₂) were monitored on the forehead and at the thoracolumbar paraspinal region, respectively. SctO₂ and SstO₂ were recorded at different time points (baseline, skin incision, CPB start, SCP start, SCP end, aortic opening, CPB end, and surgery end). SctO₂ and SstO₂ were correlated with mean arterial pressure (MAP) and partial pressure of arterial blood carbon dioxide (PaCO₂).

Results: Data of 21 patients were analyzed (age = 75±67 days, body weight = 4.4±1.0 kg). SstO₂ was significantly lower than SctO₂ before aortic opening and significantly higher than SctO₂ after aortic opening. SstO₂ correlated with leg MAP when the measurements during SCP were included (r = 0.67, p < 0.0001) and were not included (r = 0.46, p < 0.0001); in contrast, SctO₂ correlated with arm MAP only when the measurements during SCP were excluded (r = 0.14, p = 0.08 vs. r = 0.66, p < 0.0001). SCP also confounded SctO₂/SstO₂’s correlation with PaCO₂; when the measurements during SCP were excluded, SctO₂ positively correlated with PaCO₂ (r = 0.65, p < 0.0001), while SstO₂ negatively correlated with PaCO₂ (r = -0.53, p < 0.0001).

Conclusions: SctO₂ and SstO₂ have distinct patterns of changes before and after aortic opening during neonate/infant aortic coarctation repair. SctO₂/SstO₂'s correlations with MAP and PaCO₂ are confounded by SCP. The outcome impact of combined SctO₂/SstO₂ monitoring remains to be studied.

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Introduction

Coarctation of the aorta (CoA) is a congenital narrowing of upper descending thoracic aorta adjacent to the site of attachment of ductus arteriosus just distal to the left subclavian artery. The reported prevalence of CoA is approximately 4 per 10,000 live births [1, 2] or 400 per million live births, [3] which accounts for ~4% of all congenital heart defects [3]. The preferred treatment for native CoA during childhood is surgical correction based on the considerations related to midterm and long-term outcomes in many children's hospitals [4, 5]. The optimal age for elective repair of aortic coarctation is controversial. Some centers perform elective aortic coarctation repair around 1.5 years of age [6]. However, surgery at a much earlier age may be required depending on the severity of the coarctation and the adequacy of the collateral flow.

CoA does not cause hemodynamic problems in utero, as two-thirds of the combined cardiac output flows through the patent ductus arteriosus (PDA) into the descending thoracic aorta, bypassing the site of constriction at the isthmus. During the neonatal period, when the PDA and foramen ovale begin to close, the cardiac output that must cross the narrowed aortic segment to reach the lower extremities steadily increases and the clinical consequences start to show. The central dilemma of this unique congenital malformation is the divergent hemodynamic patterns in the body parts that are perfused by the vasculature proximal and distal to the coarctation, respectively, i.e., systolic hypertension in the upper extremities while hypotension in the lower extremities.

We hypothesize that tissue beds perfused by the vasculature proximal and distal to the aortic coarctation have distinct oxygenation patterns during aortic coarctation surgery in neonates and infants. This study aims to compare SctO2 and SstO2 monitored on the forehead and at the paraspinal thoracolumbar region, respectively, and correlate SctO2/SstO2 with relevant physiological variables.

Methods

This prospective cohort study was approved by the Internal Review Board at Children's Hospital of Nanjing Medical University located in Nanjing, Jiangsu Province, China. Consent for study participation was obtained from the patient's guardians before surgery.

Patients

Neonates and infants undergoing complicated aortic coarctation repair surgery from January 2015 to February 2017 in the Children's Hospital of Nanjing Medical University participated in this study. The inclusion criteria were age < 1-year-old and coarctation surgery mandating CPB and SCP. The exclusion criteria were emergent surgery and refusal by the patient's guardians.

Anesthesia

After arriving in the operating room, patients were first sedated using intravenous fentanyl (2 mcg/kg) and midazolam (0.05 mg/kg). Standard electrocardiography, pulse oximetry, and non-invasive blood pressure monitoring, in addition to SctO2/SstO2 monitoring, were applied before anesthesia induction. Anesthesia was induced using intravenous administration of penehyclidine (0.01 mg/kg), fentanyl (10 mcg/kg), midazolam (0.1 mg/kg), and rocuronium bromide (0.6 mg/kg). All patients were intubated and mechanically ventilated with a tidal volume of 6-8 ml/kg, inspiratory to expiratory time ratio of 1.1.5-2, and inspired oxygen of 40%. The respiratory rate was adjusted per the level of end-tidal carbon dioxide which was maintained at 45-50 mmHg before CPB in patients with preductal patent ductus arteriosus. An
arterial catheter (22-24 GA) was placed in the right radial and femoral arteries to monitor the arterial blood pressure on the right arm and right leg, respectively. A central venous catheter (5 F) was placed through the right jugular vein for intravenous access and central venous pressure monitoring. Anesthesia was maintained using sevoflurane inhalation and intravenous infusion of Rocuronium bromide (0.1 mg/kg/h), in addition to the intermittent intravenous bolus of fentanyl (10-20 mcg/kg), and midazolam (0.1 mg/kg).

Tissue Oxygenation Monitoring
ScTO2 and SstO2 were monitored by a tissue oximeter (CASMED MC-2030 C, CAS Medical System, Branford, CT). ScTO2 was monitored with the pediatric sensor placed on the right forehead, while SstO2 was monitored with the pediatric sensor placed on the right paraspinal muscle at the T10-L2 level. The first set of ScTO2 and SstO2 measurements were obtained with the patient sedated but spontaneously breathing (i.e., before anesthesia induction). ScTO2 and SstO2 were then measured at the pre-determined time points throughout the surgery.

Surgery
A midline sternal incision was made for access. The ascending aorta and superior and inferior vena cava were cannulated in 20 patients. One patient with an interrupted aortic arch received additional pulmonary artery cannulation. Following heparinization, CPB was established using an artificial heart-lung machine (Maquet HL 20, MAQUET Cardiovascular, LLC, Wayne, NJ, USA) with a membrane oxygenator (D901, Sorin Group Italia S.r.l., Mirandola, Italy). The CPB started with moderate flow (100-150 ml/kg/min) and moderate to high flow rate (100-150 ml/kg/min). Following the clamping of the aorta and superior and inferior vena cava, the heart was arrested using histidine-tryptophan-ketoglutarate solution (Dr. Franz Köhler Chemie GmbH, Bensheim, Germany) infused at the aortic root. Following the correction of intracardiac malformation, the rectal temperature was further decreased to 18-20 °C for aortic arch repair. SCP was accomplished following the advancement of the aortic cannula into the innominate artery with a flow rate of 20-40 ml/kg/min. The successful coarctation repair was followed by aorta re-opening and then the termination of CPB. Patients were mildly hyperventilated, and the hemodynamics were normally supported using epinephrine 0.05-0.1 mcg/kg/min and milrinone 0.5 mcg/kg/min.

Data Collection
Physiological measurements including mean arterial pressure (MAP), partial pressure of arterial blood carbon dioxide (PaCO2), hematocrit, temperature, arterial blood oxygen saturation (SaO2), mixed venous blood oxygen saturation (SmvO2), ScTO2 and SstO2 were prospectively recorded at the pre-determined time points. These time points were baseline with the patient sedated and spontaneously breathing, skin incision, CPB start, SCP start, SCP end, aortic opening, CPB end, and surgery end. 1 ml of arterial blood and 1 ml of mixed venous blood were taken for blood gas analysis at each time point.

Statistical Analysis
Data were presented in mean ± SD. The difference between two variables at different time points was assessed using paired t-test. Pearson’s correlation coefficient was used to assess the correlation between different variables. A two-sided p-value < 0.05 was regarded as statistically significant.

Results
Among the 21 patients who participated in this study, 16 were males, 3 neonates (< 30 days old), and 18 infants (< 1-year-old). The average age was 75 ± 67 days (range = 12 to 333 days). The average body weight was 4.4 ± 1.0 kg (range = 2.8 to 6.5 kg) (Table 1). All patients had ventricular septal defect; 20 patients had patent ductus arteriosus; 16 had pulmonary hypertension; and 9 had an atrial septal defect.

The CPB, aortic clamping, and SCP time were 185 ± 101 min, 68 ± 17 min, and 23 ± 6 min, respectively. The length of hospital stay, ICU stay, and postoperative intubation time was 25 ± 8 days, 11 ± 2 days, and 6 ± 1 days, respectively.

The physiological measurements at different time points are presented in Table 2. SstO2 was consistently and significantly lower than ScTO2 at each time points before the aortic opening, including the baseline (Δ ≈ -12%), skin incision (Δ ≈ -12%), CPB start (Δ ≈ -12%), SCP start (Δ ≈ -40%), and SCP end (Δ ≈ -21%) (Δ = SstO2 – ScTO2). Following the aortic opening, this relationship was reversed with the SstO2 consistently and significantly higher than ScTO2 at each time point, including aortic opening (Δ ≈ +24%), CPB end (Δ ≈ +12%), and surgery end (Δ ≈ +8%). Overall, ScTO2 and SstO2 were significantly correlated (r = -0.57, p < 0.0001, Fig. 1 A); however, the correlation became weaker after exclusion of the measurements during SCP (r = -0.22, p = 0.01, Fig. 1B). The correlation between ScTO2 and SstO2 was at its strongest when only considering the data before SCP (r = 0.81, p < 0.0001, Fig. 1 C) and weakest when only considering the data after SCP (r = 0.009, p = 0.94, Fig. 1D).

The correlation between ScTO2 and SmvO2 was stronger than that between SstO2 and SmvO2. ScTO2 was significantly correlated with SmvO2 with the
measurements during SCP considered \((r = 0.80, p < 0.0001, \text{Fig. 2 A})\) and not considered \((r = 0.69, p < 0.0001, \text{Fig. 2B})\). \(\text{SstO}_2\) and \(\text{SmvO}_2\) were significantly correlated only when the measurements during SCP included \((r = -0.35, p < 0.0001, \text{Fig. 2 C})\), not excluded \((r = 0.06, p = 0.54, \text{Fig. 2D})\).

\(\text{SctO}_2\) and \(\text{MAP}\) measured on the arm were not correlated with all measurements considered \((r = 0.14, p = 0.08, \text{Fig. 3 A})\); however, they became significantly correlated with the measurements during SCP excluded \((r = 0.66, p < 0.0001, \text{Fig. 3B})\). In contrast, \(\text{SstO}_2\) and \(\text{MAP}\) measured on the leg were significantly correlated with
Fig. 1 Correlations between cerebral tissue oxygen saturation ($SctO_2$) and somatic tissue oxygen saturation ($SstO_2$). The correlations were based on all data (A), data with the measurements during selective cerebral perfusion (SCP) excluded (B), only data before SCP (C), and only data after SCP (D), respectively. The red dotted lines are trend lines and the data points in green dotted circle are measurements during SCP.

Fig. 2 Correlations between mixed venous blood oxygen saturation ($SmvO_2$) and cerebral tissue oxygen saturation ($SctO_2$) (A and B) and between $SmvO_2$ and somatic tissue oxygen saturation ($SstO_2$) (C and D). The correlations were based on all data (A and C) and data with the measurements during selective cerebral perfusion (SCP) excluded (B and D), respectively. The red dotted lines are trend lines and the data points in green dotted circles are measurements during SCP.
measurements during SCP included ($r = 0.67$, $p < 0.0001$, Fig. 3 C) and excluded ($r = 0.46$, $p < 0.0001$, Fig. 3D).

SctO$_2$ and PaCO$_2$ were not correlated with all measurements considered ($r = -0.04$, $p = 0.63$, Fig. 4A); however, they became significantly correlated with the measurements during SCP excluded ($r = 0.65$, $p < 0.0001$, Fig. 4B). SstO$_2$ and PaCO$_2$ were not correlated with all measurements considered ($r = 0.02$, $p = 0.83$, Fig. 4C); however, they also became significantly correlated with the measurements during SCP excluded ($r = -0.53$, $p < 0.0001$, Fig. 4D). Of note, SctO$_2$ positively (Fig. 4B), while SstO$_2$ negatively (Fig. 4D), correlated with PaCO$_2$ after the exclusion of the measurements during SCP.

**Discussion**

Our study showed that the measurements of SctO$_2$ and SstO$_2$ is surgical stage-dependent in neonates and infants undergoing aortic coarctation repair. SstO$_2$ was significantly lower than SctO$_2$ before aortic opening; however, following aortic opening, SstO$_2$ was significantly higher than SctO$_2$. SctO$_2$ and SstO$_2$ have distinct correlations with MAP, PaCO$_2$, hematocrit, and temperature. SstO$_2$ consistently correlates with leg MAP; however, the correlation between SctO$_2$ and arm MAP is confounded by the measurements during SCP. The measurements during SCP also confound the correlations between SctO$_2$ and PaCO$_2$ and between SstO$_2$ and PaCO$_2$. SctO$_2$, not SstO$_2$, is significantly correlated with SmvO$_2$.

Aortic cross-clamping is a well-known risk factor for cerebral, spinal cord, pulmonary, renal, and visceral injuries [10–12]. The disturbance of systemic and regional blood flow threatens organ perfusion, with the resultant tissue hypoperfusion and overzealous perfusion likely being the root cause of certain perioperative complications. Practical, effective, and real-time monitoring of organ perfusion and/or tissue oxygenation may provide early warning of end-organ mal-perfusion and thereby improve patient outcomes.

Tissue NIRS was originally used to monitor cerebral tissue bed. The recent technological advancement made the monitoring of non-cerebral tissue beds possible [8]. The combined monitoring of both cerebral and non-cerebral tissue beds has the potential to further improve outcomes because the brain and non-brain organs have different schemes of metabolic demands and compensatory mechanisms during hemodynamic instability. Hoffman et al. pioneered the clinical application of multisite tissue oxygenation monitoring in pediatric cardiac patients. They monitored both cerebral oxygenation and renal oxygenation (with the sensor placed over the kidney region) in neonates undergoing stage 1 palliation for hypoplastic left heart syndrome [13]. Berens et al.
investigated the clinical application of the same multsite monitoring protocol in 26 pediatric patients (11 neonates, 5 infants, and 10 children) undergoing aortic coarctation repair [14]. They reported that the decline in $S_{stO2}$ during aortic cross-clamping was larger in neonates and infants than children, which was attributed to a better established collateral circulation around the incomplete aortic obstruction in older patients. However, they did not specifically compare $S_{ctO2}$ and $S_{stO2}$ at different time points and correlate $S_{ctO2}/S_{stO2}$ with different physiological parameters.

The significantly lower $S_{stO2}$, compared with $S_{ctO2}$, before aortic opening reflects the hypoperfusion of the tissue beds that were perfused by the vasculature distal to the aortic stenosis. The start of CPB led to simultaneous decreases of both $S_{ctO2}$ and $S_{stO2}$, likely secondary to decreased global tissue oxygen delivery (delivery = flow*hemoglobin*arterial blood oxygen saturation) assuming tissue oxygen consumption remained unchanged. The start of SCP led to a distinct increase of $S_{ctO2}$ while a decrease of $S_{stO2}$, which reflects the effectiveness of SCP in increasing cerebral oxygen delivery and the corresponding worsening of peripheral oxygen delivery. The discrepancy between $S_{ctO2}$ and $S_{stO2}$ was lessened toward the end of SCP, which was likely secondary to the adjustment of regional vascular resistance and flow redistribution. The aortic opening led to a remarkable increase of $S_{stO2}$ while a remarkable decrease of $S_{ctO2}$, a distinct change in the oxygenation pattern that is likely caused by the hyperperfusion of the distal tissue beds and the simultaneous relative hypoperfusion (or a “steal” phenomenon) of the proximal tissue beds (in relevance to the aortic stenosis). The remarkable $S_{ctO2}$ decrease may also relate to the rewarming-related increase in cerebral tissue oxygen consumption. The discrepancy between $S_{ctO2}$ and $S_{stO2}$ was gradually minimized thereafter which is likely, again, secondary to the adjustment of the vascular resistance of different tissue beds over time.

The consistent correlation between leg MAP and $S_{stO2}$ reflects the chronic vasodilation and pressure-passive flow in the tissue beds that are perfused by the vasculature distal to the aortic stenosis. The confounding of the correlation between arm MAP and $S_{ctO2}$ by the measurements during SCP reflects the overriding effect of SCP on cerebral perfusion [15]. The sloped and linear relationship between arm MAP and $S_{ctO2}$ may be a reflection of the loss of cerebral autoregulation in this patient population undergoing the described type of open cardiac surgery [9, 16].

$S_{ctO2}$ positively correlated with $PaCO_2$, while $S_{stO2}$ negatively correlated with $PaCO_2$ when the
measurements during SCP are excluded (not included), which again highlights the following: (1) carbon dioxide is a predominantly cerebral vasodilator and hypercapnia leads to increased cerebral perfusion, (2) SCP has an overriding effect on cerebral perfusion, and (3) the correlations between SctO2/SstO2 and PaCO2 are confounded during SCP.

Our study demonstrated a significant correlation between SctO2 and SmvO2, which is supported by some previous reports [17] and refuted by others [18]. We also showed that SctO2 is more consistently correlated with SmvO2 than SstO2. Tissue oxygen saturation is tissue bed specific and measures the hemoglobin saturation of mixed arterial, capillary, and venous blood, while SmvO2 is the hemoglobin saturation of the pooled venous blood coming from a variety of tissue beds. These two parameters are different but related. The stronger correlation of SctO2 compared with SstO2 with SmvO2 reflects the dominance of cerebral metabolism and the dominant contribution of cerebral venous blood to the mixed venous blood in this patient population.

Our study has limitations that highlight the need for future studies. One of the important goals of a clinical monitor is to improve patient outcome via monitor-guided care. This is normally done based on randomized controlled trials to understand if the proposed monitor-guided intervention is better than the conventional approach. In order to do so, an interventional protocol needs to be first established. An intervention protocol needs to specify the tissue dys-oxygenation thresholds beyond which corrective measures need to be instituted. It also needs to establish the intervention algorithm with details of when and how to intervene and the priorities, especially considering that tissue oxygenation is determined by multiple yet integrated variables. However, our study neither specifically studied the intervention guided by SctO2/SstO2 monitoring nor correlated SctO2/SstO2 measurements with patient outcomes. In addition, future studies need to address the tissue beds that should be prioritized for monitoring and the details of intervention based on multisite monitoring. The sample size of our study is small. Large-scale studies are needed to validate our findings, establish the intervention protocol, and prove the outcome benefits.

Conclusions
In summary, SctO2 and SstO2 have distinct patterns of change during neonate and infant aortic coarctation repair. SctO2 and SstO2 measurements are surgical stage dependent. The correlations of tissue oxygenation with MAP and PaCO2 are confounded during SCP. The distinct changes in SctO2 and SstO2 and their correlations with MAP and PaCO2 suggests the potential value of multisite tissue oxygenation monitoring during high-risk pediatric cardiac surgeries.

Abbreviations
CoA: Coarctation of the aorta; CPB: Cardiopulmonary bypass; MAP: Mean arterial pressure; NIRS: Near-infrared spectroscopy; PaCO2: Arterial blood carbon dioxide tension; PDA: Patent ductus arteriosus; SCP: Selective cerebral perfusion; SctO2: Cerebral and tissue oxygen saturation; SstO2: Somatic and tissue oxygen saturation; SmvO2: Mixed venous blood oxygen saturation.

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Authors’ contributions
L. Zhang: conceptualization, methodology, data collection and checking, interpretation of data, writing original draft preparation. L. Liu, ZQ. Zhong: data collection and checking, interpretation of data, reviewing original draft preparation. HF. Jin, J. Jia: interpretation of data, statistical analysis, reviewing original draft preparation. L. Meng: conceptualization, methodology, data collection and checking, interpretation of data, writing original draft preparation. XM. Mo: interpretation of data, reviewing original draft preparation. XH. Shi: conceptualization, methodology, interpretation of data, statistical analysis, reviewing original draft preparation. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations
Ethics approval and consent to participate
This prospective cohort study was approved by the Institutional Ethics Committee of Children’s Hospital of Nanjing Medical University with approval number 20151003-1. The patient’s guardian provided verbal consent. All methods were carried out in accordance with Declaration of Helsinki.

Consent for publication
Not Applicable.

Competing interests
Lingzhong Meng received lecture fees from the previous CAS Medical Systems, Inc (now acquired by Edwards Lifesciences). The other authors declare no conflicts of interest.

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