Aortic atresia is associated with an inferior systemic, cerebral, and splanchnic oxygen-transport status in neonates after the Norwood procedure

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Abstract

Objective: Aortic atresia (AA) is a risk factor for mortality after the Norwood procedure. The mechanisms remain unknown. We compared the profiles of systemic, cerebral, and splanchnic oxygen transport in neonates with hypoplastic left-heart syndrome with AA or aortic stenosis (AS) after the Norwood procedure.

Methods: Systemic oxygen consumption (VO2) was measured using respiratory mass spectrometry for 72 h in 17 neonates (nine in the AA group, eight in the AS group). Cardiac output (CO), systemic vascular resistance (SVR), oxygen delivery (DO2), and oxygen extraction ratio (ER02) were calculated combining with blood gases and pressures at 2—4-h intervals. Cerebral (ScO2) and splanchnic (SsO2) oxygen saturations were measured by near-infrared spectroscopy. The doses of dopamine, milrinone, phenoxybenzamine, and vasopressin were recorded. Preoperative echocardiographic left-ventricular morphology and ejection fraction ratio were measured.

Results: Compared with the AS group, the AA group had lower CO (p = 0.03), higher SVR (p = 0.002), lower DO2 (p = 0.07), VO2 (p = 0.003), and ScO2 (p = 0.07) during the first 40 h. SsO2 was insignificantly lower. Despite a similar ERO2, the AA group had higher lactate (p = 0.01). The AA group received higher doses of milrinone (p < 0.0001), vasopressin (p = 0.005), and phenoxybenzamine (p = 0.02), and lower higher doses of dopamine (p = 0.07). Vasopressin adversely correlated with systemic oxygen-transport variables and SsO2 (p < 0.05). The AA group had thicker left-ventricular posterior wall (p = 0.05) that was negatively correlated with CO (p = 0.02). Conclusions: AA is associated with an inferior status of systemic, cerebral, and splanchnic oxygen-transport after the Norwood procedure. Aggressive use of vasopressin may worsen systemic oxygen transport and decrease splanchnic perfusion.

Keywords: Hypoplastic left-heart syndrome; The Norwood procedure; Aortic atresia; Oxygen transport

1. Introduction

Controversy remains with regard to aortic atresia (AA) as a risk factor for mortality in patients with hypoplastic left-heart syndrome undergoing the Norwood procedure. Although some reported that AA was associated with a higher early and late mortality as compared with those with aortic stenosis (AS) [1,2], others did not [3]. More recently, it has been shown that the pathological change of left ventricle—subepicardial coronary artery communications occurs frequently in a subgroup of AA patients in association with mitral stenosis, and is attributable to increased mortality [2]. Clear identifications of risk factors and underlying mechanisms are important in the care of this challenging group of patients, who are associated with important morbidities mainly involving cardiovascular and neurological systems as well as splanchnic organs [4—6]. While all the previous studies have used the ‘hard’ clinical endpoints of death to compare the outcomes, we aimed in the present study, first, to obtain physiological comparison of early postoperative systemic, cerebral, and splanchnic oxygen transport between the AA and AS groups in relation with left-ventricular morphology and function in order to obtain understanding of the underlying mechanisms for the outcomes. The second aim of the study was to compare clinical management with regard to the dosages of vasoactive drugs including dopamine, milrinone, phenoxybenzamine, and vasopressin between the two groups, and, further, to examine their influences on the systemic and regional oxygen-transport balance.

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2. Materials and methods

2.1. Patients

This study was approved by the Research Ethics Board at the Hospital for Sick Children, Toronto, Canada. Consent was obtained from the parents of 17 neonates with hypoplastic left-heart syndrome undergoing a classic Norwood procedure before termination of CPB. A pulmonary venous line was inserted into the orifice of the right upper pulmonary vein. The chest was routinely left open in all the patients.

2.2. Intra-operative procedures

All patients were intubated with cuffed endotracheal tubes (Microcuff GmbH, Weinheim, Germany). General anesthesia was maintained with inhaled isoflurane, intravenous fentanyl, and pancuronium bromide. A standard Norwood procedure with a right ventricle to pulmonary artery shunt (three patients), and a Blalock—Taussig shunt, because of the introductions of the hybrid procedure (six patients) and the modified Norwood procedure with a right ventricle to pulmonary artery shunt (three patients). The latter was part of a multicenter clinical trial. Additionally, data obtained from this group of patients have been used to report the findings of other aspects of the Norwood physiology [7—9].

2.3. Postoperative management

Sedation consisted of a continuous intravenous infusion of morphine and lorazepam as required. Intermittent doses of a muscle relaxant (pancuronium bromide) were given. The esophageal temperature was maintained between 36 and 37 °C. Time-cycled pressure control/pressure support ventilation was used with ventilation volume and rate adjusted to control PaCO₂ ranging from 45 to 55 mmHg and peak airway pressure at around 20 mmHg. Arterial oxygen saturation was maintained between 70% and 85%, and hemoglobin between 14 and 16 mg dl⁻¹. Dopamine (5—10 μg kg⁻¹ min⁻¹) or epinephrine (0.01—0.04 μg kg⁻¹ min⁻¹), milrinone (0.33—0.66 μg kg⁻¹ min⁻¹), phenoxymenzamine (0.5—2 μg kg⁻¹ day⁻¹), and vasopressin (0.0001—0.0008 unit kg⁻¹ min⁻¹) and volume infusions (5% albumin or packed red blood cells) were administered based on clinical indications to maintain a mean arterial pressure of 40—45 mmHg with systolic pressure in the range of 55—65 mmHg and a heart rate in the range of 140—150 beats/min according to our standard protocol. Sternal closure was performed on postoperative days 4—5. None of the patients received peritoneal dialysis [9].

2.4. Methods of measurements

2.4.1. Systemic hemodynamic and oxygen-transport variables

Systemic oxygen consumption (VO₂) was measured continuously using respiratory mass spectrometry. This is a highly sensitive and accurate method for continuous gas analysis...
that allows simultaneous measurements of multiple gas fractions. An Amis 2000 quadrupole mass spectrometer (Innovision A/S, Odense, Denmark) was adapted for use in patients ventilated with the Servo ventilator 300. VO₂ was measured by using the mixed expiret inert gas (argon) dilution method [10]. This requires analysis of inspired and expired gases, together with the collection of all expired gas. Details are described elsewhere [9]. Blood samples were taken from the arterial, superior vena cava, and pulmonary venous lines to measure blood gases and arterial lactate. Systemic hemodynamics and oxygen-transport variables were then calculated using the standard equations according to the direct Fick principle using VO₂ and the blood gases and pressures (Table 2) [9].

### 2.4.5. Data analysis

Post hoc analysis was performed in the data obtained from a prospective study. Data are expressed as mean ± standard deviation. Unpaired two-tailed t-test was used to compare the clinical demographic data and left-ventricular size and ejection fraction data between the two groups. For those without a normal distribution (the duration of mechanical ventilation, circulatory arrest, and cerebral perfusion), Wilcoxon test was used for comparison between the groups and indicated in the text. Mixed linear regression analysis for repeated measures was used to determine the nature of any time trend over the 72-h study period, and to compare the differences in levels and trends between the groups with analysis of the effects of group interaction between time and group. The parameter estimates and p values of the group effect indicate the difference in the overall levels of each variable between the two groups. The parameter estimates and p values of the interaction of time and group indicate the difference in trends of each variable between the groups. For some measures, various transformations of time (logarithmic and polynomial) were tested regarding the best fit for the time course as indicated by the smallest value of log likelihood in fit statistics. Mixed linear regression analysis for repeated measures was also used to analyze correlations between the variables with regard to time and group, as well as the correlations between left-ventricular measurements and CO. All data analysis was performed using SAS statistical software version 9.2 (SAS Institute, Inc., Cary, NC, USA). A p value < 0.05 was considered significant.

### 3. Results

#### 3.1. Patients

There was no significant difference in age, body weight, and body surface area between the two groups. The durations of CPB (p = 0.04), aortic cross-clamp (p = 0.17), and circulatory arrest (p = 0.02) were shorter in the AA group as compared with the AS group. The duration of selective cerebral perfusion was similar between the two groups (Table 1). There were no episodes of circulatory collapse during the 72-h study period. One patient (patient 8 in the AA group) required extracorporeal membrane oxygenation (ECMO) and died on the 25th day of stay (22 days in the AA and AS groups, respectively, p = 0.10 by Wilcoxon test) and hospital stay (22 ± 4 and 30 ± 13 days in the AA and AS groups, respectively, p = 0.10) were not significantly different. Milrinone (0.33–0.99 mcg kg⁻¹ min⁻¹) was used in all the patients over the study period. Dopamine (5–10 mcg kg⁻¹ min⁻¹) was given at the termination of CPB and stopped within the first 48 h in all the patients except one (patient 11 in the AS group), who was given throughout the study period. One patient (patient 8 in the AA group) received epinephrine (0.01–0.04 mcg kg⁻¹ min⁻¹) in 22–72 h. Phenoxybenzamine (0.5–2.0 mg kg⁻¹ day⁻¹) was used in 14 patients (eight in the AA group and six in the AS group). Vasopressin (0.0001–0.0008 unit kg⁻¹ day⁻¹) was used in 11 patients (six in the AA group and five in the AS group), and among them, it was used.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qp (l min⁻¹ m⁻²)</td>
<td>VO₂/(CpO₂ − CaO₂)</td>
</tr>
<tr>
<td>Qs (l min⁻¹ m⁻²)</td>
<td>VO₂/(CpvO₂ − CvO₂)</td>
</tr>
<tr>
<td>CO (l min⁻¹ m⁻²)</td>
<td>Qp + Qs</td>
</tr>
<tr>
<td>SVR (Wood unit m²)</td>
<td>(mPa − mPv)/Qs</td>
</tr>
<tr>
<td>DO₂ (ml min⁻¹ m⁻²)</td>
<td>Qs × CaO₂</td>
</tr>
<tr>
<td>ERO₂</td>
<td>VO₂/DO₂</td>
</tr>
</tbody>
</table>
during phenoxybenzamine infusion in 10 patients, and before the initiation of phenoxybenzamine in three patients within the first 2–4 h after the arrival in the ICU. Additionally, the diameters of aortic annulus and ascending aorta were 2.6 ± 0.7 and 3.1 ± 0.4 mm, respectively, in the AA group, and 4.9 ± 1.7 and 5.8 ± 0.8 mm, respectively, in the AS group (p < 0.001 for both). An antegrade flow was observed in all the patients in the AS group.

3.2. Comparison of the profiles of systemic hemodynamics and oxygen transport, cerebral and splanchnic oxygen saturations, and left-ventricular size and ejection fraction between the AA and AS groups

When compared with the AS group, the AA group showed no significant difference in heart rate, systolic, diastolic, and mean arterial pressures in the first 24 h (p > 0.10 for all). However, thereafter, heart rate showed a slower decrease (p = 0.04), systolic and diastolic arterial pressures showed a slower increase (p = 0.01 for both) in the AA group. The AA group had a significantly higher systemic vascular resistance (SVR; p = 0.002), lower CO (p = 0.03) and DO2 (p = 0.07) in the first 32 h with a faster decrease in SVR (p < 0.0001) and a faster increase in CO (p < 0.0001) and DO2 (p = 0.0001) over time. The AA group also had a lower VO2 in the first 32 h (p = 0.003) with a slower decrease over time (p < 0.0001). As a result, ERO2 was not significantly different between the AA and AS groups. However, arterial lactate level was significantly higher in the AA group throughout the 72 h (p = 0.01). ScO2 was lower in the AA group (p = 0.07) with a faster increase (p = 0.006). So2 showed a lower trend in the AA group, but without achieving statistical significance due to the small number of patients in whom the measures were obtained (Table 3 and Fig. 1).

The AA group received higher doses of milrinone throughout the 72 h (p < 0.0001), with an increase in the first 40 h (p < 0.0001), followed by a gradual decrease (p < 0.0001). They trended to receive slightly higher phenoxybenzamine in about 40 h (p = 0.10), followed by a faster decrease thereafter (p = 0.02) (Table 3 and Fig. 1). The AA group received higher vasopressin in the first 24 h (p = 0.005), followed by a faster decrease (p < 0.0001). In more details, a dose as high as 0.0008 unit kg−1 min−1 was used in our patients, and was ≥0.0004 unit kg−1 min−1 in four out of nine patients in the AA group, but ≤0.0002 in all the patients in the AS group. The AA group received slightly less dopamine but one of them received epinephrine, making a true comparison inadequate. When these drugs were included in the statistical model, the differences in systemic oxygen-transport variables and ScO2 between the AA and AS groups remained significant (Table 4).

The left-ventricular images were assessable in 15 patients (except for patients 5 and 8 in the AA group). The left-ventricular posterior wall was significantly thicker in the AA

### Table 3. Statistical results of the comparison of systemic hemodynamics and oxygen transport, and cerebral and splanchnic oxygen saturations during the 72-h study period between AA and AS groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Parameter estimate</th>
<th>p value</th>
<th>Time Parameter estimate</th>
<th>p value</th>
<th>Time × Group Parameter estimate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat/min)</td>
<td></td>
<td>−6</td>
<td>0.33</td>
<td>−4</td>
<td>&lt;0.0001</td>
<td>2</td>
<td>0.04</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td></td>
<td>4.8</td>
<td>0.28</td>
<td>4.5</td>
<td>&lt;0.0001</td>
<td>−1.8</td>
<td>0.01</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td></td>
<td>0.52</td>
<td>0.75</td>
<td>0.02</td>
<td>0.10</td>
<td>−0.08</td>
<td>0.58</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td>3.3</td>
<td>0.12</td>
<td>1.9</td>
<td>&lt;0.0001</td>
<td>−1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>SVR (Wood unit m −2)</td>
<td></td>
<td>26.5</td>
<td>0.002</td>
<td>0.72</td>
<td>0.12</td>
<td>−3.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CO (l min−1 m−2)</td>
<td></td>
<td>−0.9</td>
<td>0.03</td>
<td>0.12</td>
<td>0.05</td>
<td>0.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DO2 (ml min−1 m−2)</td>
<td></td>
<td>58.7</td>
<td>0.07</td>
<td>3.3</td>
<td>0.0001</td>
<td>1.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>VO2 (ml min−1 m−2)</td>
<td></td>
<td>−31.0</td>
<td>0.003</td>
<td>−7.7</td>
<td>&lt;0.0001</td>
<td>8.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ERO2</td>
<td></td>
<td>0.03</td>
<td>0.48</td>
<td>−0.03</td>
<td>&lt;0.0001</td>
<td>0.003</td>
<td>0.71</td>
</tr>
<tr>
<td>Lactate (mmol l−1)</td>
<td></td>
<td>0.58</td>
<td>0.01</td>
<td>−0.49</td>
<td>&lt;0.0001</td>
<td>−0.002</td>
<td>0.37</td>
</tr>
<tr>
<td>ScO2 (%)</td>
<td></td>
<td>−4.7</td>
<td>0.07</td>
<td>1.6</td>
<td>0.002</td>
<td>1.9</td>
<td>0.06**</td>
</tr>
<tr>
<td>So2 (%) (n = 7 in the AA group, n = 3 in the AS group)</td>
<td></td>
<td>2.6</td>
<td>0.61</td>
<td>−0.001</td>
<td>0.96</td>
<td>−0.06</td>
<td>0.12</td>
</tr>
<tr>
<td>Dopamine (µg kg−1 min−1)</td>
<td></td>
<td>−1.4</td>
<td>0.13</td>
<td>−1.2</td>
<td>&lt;0.0001</td>
<td>0.39</td>
<td>0.07</td>
</tr>
<tr>
<td>Milrinone (µg kg−1 min−1)</td>
<td></td>
<td>0.07</td>
<td>p &lt; 0.0001</td>
<td>0.00030</td>
<td>0.45</td>
<td>Group × time</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Phenoxybenzamine (mg kg−1 day−1)</td>
<td></td>
<td>0.10</td>
<td>0.71</td>
<td>0.25</td>
<td>&lt;0.0001</td>
<td>Group × time</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Vasopressin (unit kg−1 min−1)</td>
<td></td>
<td>0.0002</td>
<td>0.005</td>
<td>−1.5E–6</td>
<td>0.84</td>
<td>−0.0004</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

DAP: diastolic arterial pressure; MAP: mean arterial pressure; SAP: systolic arterial pressure; ScO2 and SsO2: cerebral and splanchnic oxygen saturation, respectively. Other abbreviations are the same as in Table 2.

Data was entered after logarithmic transformation of time.

" After polynomial transformation, with time indicating the coefficient of the early trend, and time² indicating the later trend, as shown in Fig. 1.

¹ Parameter estimate of group effect indicates the difference in the overall levels of each variable between the two groups: ‘+’ indicates a higher level, and ‘−’ indicates a lower level in the AA group as compared with the AS group.

² Parameter estimate of time effect indicates the change of each variable over time. ‘+’ indicates an increase, and ‘−’ indicates a decrease during the study period.

³ Parameter estimate of the interaction of time and group indicate the difference in trends of each variable between the groups. ‘+’ indicates a faster increase, and ‘−’ indicates a faster decrease over time in the AA group as compared with the AS group.
group as compared with the AS group (0.58 ± 0.14 and 0.43 ± 0.15 cm, respectively, \( p = 0.049 \)), left-ventricular ejection fraction was lower in the AA group as compared with the AS group, but did not achieve statistical significance (0.34 ± 2.1 and 0.16 ± 0.19, respectively, \( p = 0.14 \)). There was no significant difference in inter-ventricular septum thickness (0.43 ± 0.15 and 0.43 ± 0.12 cm, respectively, \( p = 0.93 \)), left-ventricular internal diameter (0.62 ± 0.19 and 0.62 ± 0.20 cm, respectively, \( p = 0.96 \)), left-ventricular area in diastole (0.50 ± 0.27 and 0.37 ± 0.29 cm², respectively, \( p = 0.11 \)), and in systole (0.39 ± 0.15 and 0.31 ± 0.24 cm², \( p = 0.40 \)).

3.3. Correlations of vasoactive drugs and left-ventricular size with systemic hemodynamics and oxygen transport, cerebral and splanchnic oxygen saturations

In addition to the group effect, these drugs showed varied correlations with oxygen-transport variables. Vasopressin did not correlate with arterial pressure, but significantly negatively correlated with CO (\( p = 0.02 \)), DO₂ (\( p = 0.005 \)), and VO₂ (\( p = 0.02 \)), positively correlated with SVR (\( p = 0.03 \)), ERO₂ (\( p = 0.002 \)), and lactate (\( p = 0.0008 \)). It did not correlate with ScO₂, but significantly and negatively correlated with SsO₂. Dopamine significantly and positively correlated with systolic and mean arterial pressure (\( p = 0.04 \) and 0.01, respectively), but not with SVR (\( p = 0.68 \)). It significantly and positively correlated with CO (\( p = 0.003 \)), DO₂ (\( p = 0.005 \)), VO₂ (\( p < 0.0001 \)), and ERO₂ (\( p < 0.0001 \)), as well as ScO₂ (\( p < 0.0001 \)), but not with lactate (\( p = 0.22 \)) or SsO₂ (\( p = 0.81 \)). Milrinone significantly and positively correlated with VO₂ (\( p = 0.003 \)), but not with other variables. Phenoxybenzamine showed a negative correlation with SVR (\( p = 0.008 \)), but not with other variables (Table 4).

Among the left-ventricular measurements, left-ventricular posterior wall significantly and negatively correlated with CO (parameter estimate = -4.1, \( p = 0.02 \)) (Fig. 2), Qs (parameter estimate = -2.2, \( p = 0.02 \)) and Qp (parameter estimate = -2.4, \( p = 0.04 \)), and a trend to negatively correlate with DO₂ (parameter estimate = -206, \( p = 0.08 \)) and positively correlate with ERO₂ (parameter estimate = 0.01, \( p = 0.09 \)) but not with other variables. There were no significant correlations of left-ventricular ejection fraction (\( p = 0.20 \)) or other variables with CO and other oxygen-transport variables.

4. Discussion

This study demonstrates that the presence of AA was associated with an inferior status of early postoperative
systemic, cerebral, and splanchnic oxygen transport in neonates with hypoplastic left-heart syndrome after the Norwood procedure. Compared with the AS group, the AA group had an elevated SVR, diminished CO and DO₂, and reduced VO₂. The insignificant difference in ERO₂ between the two groups indicates a similar degree of oxygen-transport balance at the systemic level. However, the significantly higher arterial lactate level throughout the first 72 h in the AA group reflects a poorer balance of oxygen transport at the regional and tissue levels. This is supported by the finding that left-ventricular posterior hypertrophy is nega-

![Fig. 2](image-url)

Fig. 2. The negative correlation between the thickness of left-ventricular posterior wall (LVPW) and total cardiac output in 15 patients during the first 72 h after the Norwood procedure. The confidence limit was 70% as indicated by the two thin lines.

### Table 4. Statistical results of the effects of the presence of aortic atresia and vasoactive and inotropic drugs on systemic hemodynamics and oxygen transport, cerebral and splanchnic oxygen saturations during the 72-h study period in neonates after the Norwood procedure.

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Group × Time</th>
<th>Vasopressin (unit kg⁻¹ min⁻¹)</th>
<th>Dopamine (µg kg⁻¹ min⁻¹)</th>
<th>Milrinone (µg kg⁻¹ min⁻¹)</th>
<th>Phenoxybenzamine (mg kg⁻¹ day⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter estimate</td>
<td>Parameter estimate</td>
<td>Parameter estimate</td>
<td>Parameter estimate</td>
<td>Parameter estimate</td>
<td>Parameter estimate</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>6.6</td>
<td>5.2</td>
<td>–2.3</td>
<td>–1765</td>
<td>0.46</td>
<td>0.04</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>2.0</td>
<td>0.55</td>
<td>–0.63</td>
<td>–1384</td>
<td>0.11</td>
<td>3.58</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>5.8</td>
<td>2.5</td>
<td>–1.5</td>
<td>–1783</td>
<td>0.33</td>
<td>1.9</td>
</tr>
<tr>
<td>SVR (Wood unit m⁻²)</td>
<td>12.4</td>
<td>1.2</td>
<td>–3.4</td>
<td>6964</td>
<td>0.07</td>
<td>–3.4</td>
</tr>
<tr>
<td>CO (l min⁻¹ m⁻²)</td>
<td>–0.94</td>
<td>0.17</td>
<td>0.31</td>
<td>–1054</td>
<td>0.07</td>
<td>0.13</td>
</tr>
<tr>
<td>DO₂ (ml min⁻¹ m⁻²)</td>
<td>–57</td>
<td>3.8</td>
<td>1.4</td>
<td>–131377</td>
<td>4.2</td>
<td>26</td>
</tr>
<tr>
<td>VO₂ (ml min⁻¹ m⁻²)</td>
<td>–25.6</td>
<td>–4.2</td>
<td>7.2</td>
<td>–16500</td>
<td>3.5</td>
<td>15.2</td>
</tr>
<tr>
<td>ERO₂</td>
<td>–0.008</td>
<td>–0.02</td>
<td>0.03</td>
<td>143</td>
<td>0.01</td>
<td>–0.01</td>
</tr>
<tr>
<td>Lactate (mmol l⁻¹)</td>
<td>0.56</td>
<td>–0.48</td>
<td>–0.02</td>
<td>1083</td>
<td>–0.02</td>
<td>–0.02</td>
</tr>
<tr>
<td>ScO₂ (%)</td>
<td>–0.63</td>
<td>3.0</td>
<td>0.85</td>
<td>–2791</td>
<td>0.53</td>
<td>0.11</td>
</tr>
<tr>
<td>SsO₂ (%)</td>
<td>–1.82</td>
<td>0.04</td>
<td>–0.07</td>
<td>–8571</td>
<td>–0.05</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Abbreviations the same as Tables 2 and 3.

* Data was entered after logarithmic transformation of time.
* Entered after quadric transformation of time.
* Parameter estimate of group effect indicates the difference in the overall levels of each variable between the two groups: ‘+’ indicates a higher level, and ‘−’ indicates a lower level in the AA group as compared with the AS group.
* Parameter estimate of time effect indicate the change of each variable over time. ‘+’ indicates an increase, and ‘−’ indicates a decrease during the study period.
* Parameter estimate of the interaction of time and group indicate the difference in trends of each variable between the groups. ‘+’ indicates a faster increase, and ‘−’ indicates a faster decrease over time in the AA group as compared with the AS group.

Data was entered after logarithmic transformation of time.

Higher doses of vasoactive drugs were used in attempt to counter hemodynamic instability, but aggressive use of vasopressin worsened systemic and splanchnic oxygen-transport status as shown in the AA group.

Because the AA group had shorter durations of CPB, aortic cross-clamp, and circulatory arrest, the inferior status of systemic and regional oxygen transport is unlikely attributable to the intra-operative factors and secondary systemic inflammatory response, but rather likely to AA per se. Previous studies have suggested that AA as a postoperative risk factor might be related to the reduced myocardial perfusion due to the lack of antegrade aortic flow and abnormal coronary artery flow patterns [1,2]. This may be supported by the finding that patients with smaller ascending aortas are associated with worse outcomes [6]. In our patients, the AA group had a significantly smaller aortic annulus and ascending aorta as compared with the AS group. This may be also supported by the finding that left-ventricular posterior hypertrophy is negatively associated with cardiac output [11], and left-ventricular...
hypertrophy is significantly more severe in patients with AA as compared with those with AS. Interestingly, left-ventricular ejection fraction trended to be lower in the AA group as compared with the AS group. However, no significant correlation was found between left-ventricular ejection fraction and cardiac output, likely due to the difficulties in obtain precise measurements of left-ventricular areas, which were not the focus in the original clinical echocardiograms in hypoplastic left-heart syndrome. Furthermore, it has been reported that the pathological change of left ventricle—subepicardial coronary artery communications occurs in about half of a subgroup of AA patients in association with mitral stenosis, attributable to the increased mortality [2]. Only three patients in our study came under in this subgroup, and no echocardiographic images were available about the subepicardial coronary artery communications, thus insufficient to provide comparative data on oxygen-transport variables to the other subgroup of AA patients with mitral atresia. Nonetheless, the myocardial pathological changes may be the main elements contributing to the diminished CO and DO2 in the AA group as compared with the AS group.

Similarly, it is unlikely to attribute the higher SVR in the AA group to any difference in the circulating levels of vasoconstrictive compounds, that is, catecholamines, angiotensin II, and arginine-vasopressin that are increased after CPB [12,13], although no measurements of these compounds were obtained in the present study. The higher SVR in the AA group may have resulted partly from the lower CO that is intrinsically associated with AA [14], which may reduce CO as a negative feedback. The dynamic interaction between the ventricle and afterload, the so-called ventricular—vascular coupling, plays a fundamental role in determining CO [15]. This may be particularly crucial in the Norwood circulation, where SVR is the most important determinant to systemic blood flow and DO2 [9]. For this reason, it has become an important part of our routine clinical management to use the vasodilators of phenoxybenzamine and milrinone during the early postoperative period after the Norwood procedure [9]. Phenoxybenzamine is an irreversible and long-acting α-adrenergic receptor blocker that results in a relatively low and stable SVR and thereby to optimize DO2 [16]. Milrinone does so through inhibition of phosphodiesterase-3, resulting in increased levels of cyclic adenosine monophosphate in vascular smooth muscle and myocardium to decrease SVR and increase myocardial contractility, respectively [17]. In our patients, despite the higher doses of milrinone and phenoxybenzamine in the AA group, SVR was still significantly higher as compared with the AS group. The ventricular—vascular coupling may be an additional element contributing to the diminished CO and DO2.

Is the lower VO2 in the AA group a result of the lower CO and DO2, or vice versa? The significantly higher level of lactate in the AA group throughout the 72-h study period supports the notion of the former. In other words, VO2 was inhibited by the critically low CO and DO2 to a greater degree in the AA group, leading to more severe cellular hypoxia and increased lactate production. Therefore, the phenomenon of pathological dependence of VO2 on DO2, which has been extensively demonstrated in animal experiments, may have well occurred in our patients, but this cannot be fully revealed by the present study design with mathematical coupling when DO2 was calculated from VO2. It should be noted that ERO2, as a result of the proportionately reduced DO2 and VO2 in the AA group, was similar to that of the AS group. Thus, it seems that the balance, or rather the imbalance, of oxygen transport was at a similar degree between the two groups at the systemic level. However, it cannot be overemphasized that the balance of systemic oxygen transport does not necessarily reflect the balance at the regional and tissue levels. Some organs and tissue beds, such as brain and splanchnic organs, are particularly vulnerable to small changes in the precarious balance between oxygen delivery and oxygen consumption [18,19]. This is supported by the significantly lower ScO2 and the trend of a lower SsO2 in the AA group, despite a similar ERO2 as compared with the AS group in our study.

In an attempt to counter the poor hemodynamic status, more vasoactive drugs were given to the AA group in our clinical practice, including milrinone, phenoxybenzamine, and vasopressin. The comparison of dopamine dosage was difficult, as one of the AA patients was administered epinephrine at increasingly high doses. These drugs are commonly used as 'cocktail' in children after CPB. Their effects on oxygen transport are complex because of the dynamic interactions between myocardial and vascular function [15], and between oxygen delivery and oxygen consumption at both systemic and regional levels, as well as the varied circulating levels of endogenous catecholamines and vasopressin after CPB [13,20]. An important part of our study was to examine the influences of these drugs on systemic and regional oxygen transport in neonates after the Norwood procedure. Further analysis was performed to include the drugs into the statistical model in order to examine both the group and drug effects on oxygen-transport variables. The statistical results showed that the inferior systemic and cerebral oxygen-transport status remained significant in the AA group even when the drugs were included in the analysis, confirming the intrinsic adverse effects of AA. Furthermore, our data demonstrate significant adverse effects of dopamine and vasopressin on systemic and regional oxygen transport. Further supporting our previous report [21], dopamine negatively affects the overall balance of systemic oxygen transport by a greater stimulation of VO2 relative to CO and DO2. The reason for the significant positive correlation between dopamine and ScO2 is unclear.

More importantly, our data demonstrate the significant adverse effects of vasopressin on all the systemic oxygen-transport variables and splanchnic oxygenation, including a decrease in CO, DO2, VO2, and ScO2, and an increase in SVR, ERO2, and lactate in the Norwood circulation. Vasopressin has an inotropic effect via V1 receptor stimulation. The potent vasoconstrictive effect of vasopressin does not act through the α-adrenergic receptor and has a relatively short half-life. Largely for the latter reason, it has become part of our management strategy to use vasopressin to reverse prolonged vasodilatation that is caused by phenoxybenzamine as an irreversible adrenergic receptor blockade [22]. Vasopressin is commonly and effectively used to treat critically ill patients with vasodilatory shock, such as septic shock [23]. Vasopressin was also used frequently to counter hemodynamic instability in our clinical practice. However, aggressive
use of vasopressin may worsen the balance of systemic and splanchnic oxygen transport in patients after the Norwood procedure, as demonstrated in our AA group. Previous studies have shown that the inotropic effect of vasopressin is diminished after CPB; at the same time, endogenous vasopressin and catecholamines are increased, resulting in an elevated SVR [12]. Furthermore, vasopressin has specific gut effect to reduce splanchnic perfusion and induce splanchnic lactate release and arterial hyperlactatemia [24]. This is evidenced by our data of the significant negative correlation of vasopressin with So2 and arterial lactate level. As the gut is often referred to as the ’motor’ of the systemic inflammatory response syndrome, any reduction in splanchnic perfusion has important implications, particularly in neonates after the Norwood procedure. In these neonates, splanchnic blood flow is reduced even before operation and worsened postoperatively [25]. Splanchnic complications may occur in about 40% and increase the risk of death [5]. Therefore, the use of vasopressin should be with caution in neonates during the early postoperative period after the Norwood procedure. Further, the routine use of vasopressin was mainly to counter the excessive vasodilation induced by phenoxybenzamine. Our data show that this treatment strategy may cause certain difficulties and complications in the care of these patients. As such, other afterload reduction agents with a short half-life, such as nitric oxide donor nitroprusside, and α-blockade phentolamine, which are used in some centers, may be considered.

5. Limitations

There are several limitations to our study. First, a small number of patients were studied involving many confounding factors. Recent reports have shown a higher risk of mortality in a subgroup of AA patients with mitral stenosis as compared with AA with mitral atresia [1,2]. There were only three and six in each of the subgroups, respectively, insufficient to provide comparative data as mentioned above. Second, near-infrared spectroscopy was used to estimate cerebral and splanchnic oxygen transport. This technique measures oxygen saturation in the mixture of arteries, capillaries, and veins in a small part of underlying cerebral tissue, thus may not precisely reflect overall balance of oxygen transport of the whole organ. It does not differentiate oxygen consumption from oxygen delivery, thus limiting the information about the mechanisms of the effects of the vasoactive drugs on the two components of oxygen transport at the regional level. So2 was only measured in seven patients in the AA group and three in the AS group, therefore, insufficient for a group comparison. Nonetheless, when putting the data of the two groups together, the negative correlation between vasopressin and So2 was significant. Third, hemodynamic and oxygen-transport data obtained from this relatively small group of patients have been repeatedly used to examine other aspects of the Norwood physiology [7–9]. This may introduce the potential bias that might exist in these data across these reports. This limitation will be overcome with further studies that are being carried out in neonates after the modified Norwood procedure with the right ventricle to pulmonary artery shunt in a different center. Finally, the hemodynamic and oxygen-transport parameters were mostly calculated using VO2, according to the direct Fick principle, which would induce a certain degree of mathematical coupling in the relationships between VO2, CO, DO2, and ERO2. However, our present study did not aim to examine the relationship between VO2 and DO2; rather, we sought to compare the profiles of oxygen transport between the AA and AS groups, which should not be affected by the applied methods of calculations. This limitation was, to some degree, compensated by the independent measurements of regional oxygen transport using near-infrared spectroscopy.

6. Conclusions

The presence of AA is associated with an inferior status of systemic, cerebral, and splanchnic oxygen transport in neonates after the Norwood procedure. Vasopressin may worsen systemic oxygen-transport status and decrease splanchnic perfusion, thus high doses should be avoided. Postoperative management strategies should be directed to improve both systemic and regional oxygen-transport balance in this very challenging group of patients.

References


