Increasing duration of circulatory arrest, but not antegrade cerebral perfusion, prolongs postoperative recovery after neonatal cardiac surgery

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Objective: Deep hypothermic circulatory arrest (DHCA) and antegrade cerebral perfusion (ACP) are 2 cardio-pulmonary bypass techniques applied in aortic arch repair. In recent literature, cerebral effects of both techniques have received most attention, whereas the consequences for other organs have not been thoroughly investigated. Therefore, in this study, the impact of duration of DHCA and ACP on postoperative recovery was analyzed in a cohort of neonates undergoing aortic arch reconstruction.

Methods: All consecutive neonates who underwent aortic arch reconstruction from 2004 to 2009 were included in this retrospective study. Length of stay on the intensive care unit (ICU-LOS), duration of mechanical ventilation, inotrope score, and areas under the curve (AUC) for lactate and creatinine were compared with respect to durations of DHCA and ACP, respectively. Correction for confounders was performed using multivariable linear regression.

Results: Eighty-three neonates were included, with a 30-day mortality of 4.8%. Longer duration of DHCA was associated with longer ICU-LOS both in univariable and multivariable analyses. Similarly, duration of mechanical ventilation and lactate and creatinine AUCs increased with duration of DHCA. Inotrope score was only associated with DHCA duration in univariable analysis. Duration of ACP did not affect any of the outcome parameters.

Conclusions: Increasing duration of DHCA, but not ACP, during neonatal aortic arch reconstruction prolongs short-term postoperative recovery. This suggests all efforts should be made to reduce the duration of DHCA to the shortest period possible, which may be achieved by exclusive use of ACP or a combination of the 2 perfusion techniques. (J Thorac Cardiovasc Surg 2012;143:375-82)

As mortality rates are steadily decreasing in pediatric cardiac surgery, focus is shifting toward improving associated morbidity and outcome. Large studies have identified neonates with complex congenital heart defects as being most at risk for a prolonged recovery in the intensive care unit (ICU) after surgery.1,2 Therefore, it is important to identify modifiable perioperative strategies to improve outcome in this group.

Controversy still exists on the use of deep hypothermic circulatory arrest (DHCA) versus antegrade cerebral perfusion (ACP). Initially, DHCA was frequently used for various intracardiac procedures in small infants. Nowadays, it is used less often; one of the most common indications is during aortic arch reconstructions, where standard cardiopulmonary bypass (CPB) techniques are not feasible. ACP is a more recent technique that aims to selectively perfuse the brain during aortic arch reconstruction. A combination of the 2 techniques is also possible to shorten the duration of DHCA. In recent literature, the neurologic consequences of both techniques have received most attention, although this has not resulted in consensus on the superiority of DHCA or ACP.3-5

Little is known about the impact of DHCA or ACP on other vital organs, that is, heart, lungs, and abdominal viscera. In ACP, either the CPB cannula is advanced into the innominate artery or else perfusion may be provided via a shunt sewn to the innominate artery, at flows lower than full-flow CPB. An additional advantage of this technique may be that other organs also receive partial perfusion via collaterals. Various studies have found indications of this phenomenon during ACP, either by near infrared spectroscopy or by arterial flow in abdominal regions.5-8 Studies investigating whether this indeed has a favorable effect on postoperative morbidity have either homogeneous but small cohorts or else adequately sized but heterogeneous groups, in which the use of DHCA merely marks the most complex cases.2,9 Others have intended to compare perfusion techniques between groups but ultimately are
testing the change in management protocols over the years. Studies in adult cardiac surgery are less hampered by these issues and report that ACP, compared with DHCA, results in substantially shorter postoperative lengths of stay (LOS) in the ICU with less renal dysfunction. However, as the degree and form of collateralization may differ between adults and infants, the results cannot simply be translated into the current population.

In this study, we retrospectively analyzed a recent cohort of neonates undergoing aortic arch reconstruction and investigated the relationship between duration of DHCA and ACP, respectively, with regard to postoperative recovery in the ICU. We hypothesized that increasing duration of DHCA would be associated with a longer ICU-LOS, whereas ACP duration would have less impact.

PATIENTS AND METHODS

Patient Population

Retrospectively, data were collected by medical chart review from all consecutive infants under the age of 2 months who underwent aortic arch reconstruction with the use of CPB between July 2004 and October 2009 at the Wilhelmina Children’s Hospital, University Medical Center Utrecht, The Netherlands. Patients with both univentricular and biventricular physiology were included. Patients with biventricular physiology and concomitant intracardiac anomalies in which primary correction was not possible (ie, pulmonary artery banding) were excluded from this study. The local institutional review board waived the need for informed consent.

Surgical Procedures

In all patients, surgery was performed through a median sternotomy and all patients received 1 mg/kg of dexamethasone before CPB. Standard cannulation techniques were applied, except for cases of interrupted aortic arch, where double cannulation of the distal ascending aorta and the truncus pulmonalis was performed. CPB was initiated with a minimum of 20 minutes of cooling to a nasopharyngeal temperature of 18°C. Regarding pH strategy, arterial oxygen tension was kept between 45 and 55 mm Hg and pH strategy was used. Scores were calculated during the postoperative ICU stay was used. Scores were calculated using the following formula (\(\mu g\cdot kg^{-1}\cdot min^{-1}\)): dopamine + dobutamine + (15 \times milrinone) + (100 \times epinephrine) + (100 \times norepinephrine). Renal function was estimated by the AUC of postoperative creatinine in micromoles per liter times days. This was calculated by subtracting daily maximum creatinine values from the preoperative value and subsequently multiplying this by the number of postoperative days that the daily value exceeded the preoperative value.

Statistical Analyses

Data are shown as median (interquartile ranges) or number of patients (percentage of group). Univariable and multivariable linear regression analyses were performed with ICU-LOS, duration of mechanical ventilation and AUCs of lactate and creatinine as outcome variables. All outcome variables were log-transformed to attain a normal distribution. Preoperative and intraoperative confounders were identified for each of the analyses, based both on literature and on those showing a linear relationship with the outcome variables in univariable linear regression (P < .1). Postoperative variables were not included in the analyses because they cannot influence duration of DHCA. Age at operation, univentricular repair, Aristotle score, and total CPB duration were considered important confounders. Weight at surgery was omitted from the analyses inasmuch as it showed a weaker association than age with the outcome variables. Relationships between independent and outcome variables were verified for assumptions of linearity, normality, and homogeneity of variances using residual plots. Associations between outcome variables are described using the Pearson correlation.

SPSS version 15.0 (SPSS, Inc, Chicago, Ill) was used for statistical analyses.

RESULTS

Patient Characteristics and Intraoperative Data

A total of 87 consecutive infants underwent aortic arch repair between July 2004 and October 2009. Four patients...
were excluded owing to palliative procedures in biventricular physiology (ie, pulmonary artery banding), which left 83 infants available for analysis. Eight (9.4%) patients had a genetic syndrome, including DiGeorge (n = 3), Down (n = 2), and Pierre Robin, Ivemark, or Kabuki syndrome (all n = 1). Twenty-four patients had noncardiac comorbidities, which included small for gestational age (n = 5), gestational age under 37 weeks (n = 4), renal abnormalities (n = 4), congenital hypothyroidism (n = 3), infant respiratory distress syndrome (n = 2), clavicular fracture (n = 2), hemolytic disease of the newborn (n = 1), nitric oxide for pulmonary hypertension (n = 1), third-degree congenital heart block (n = 1), and duodenal atresia (n = 1). Patient characteristics and intraoperative data are depicted in Table 1. Specific diagnoses and surgical procedures with median DHCA and ACP durations are listed in Table 2.

Regarding choice of perfusion technique, 35 (42%) of the infants underwent the procedure with ACP only and 14 (17%) infants with DHCA only. The remaining 34 (41%) infants received a combination of the 2 perfusion techniques.

**TABLE 1. Patient characteristics and intraoperative and postoperative data**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>All patients (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>54 (65)</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>39.6 (38.7-40.1)</td>
</tr>
<tr>
<td>Genetic syndrome</td>
<td>8 (9.6)</td>
</tr>
<tr>
<td>Noncardiac comorbidity</td>
<td>24 (29)</td>
</tr>
<tr>
<td>Preoperative mechanical ventilation</td>
<td>48 (58)</td>
</tr>
<tr>
<td>Age at operation (d)</td>
<td>12.0 (9.0-18.5)</td>
</tr>
<tr>
<td>Weight at surgery (kg)</td>
<td>3.4 (3.0-3.8)</td>
</tr>
</tbody>
</table>

**Intraoperative data**

- Univentricular repair: 30 (36)
- Aristotle score: 14.5 (10.0-14.5)
- Surgery duration (min): 332 (298-379)
- Total CPB duration (min): 167 (137-193)
- Myocardial ischemia duration (min): 71 (53-92)
- DHCA duration (min): 13 (0-29)
- ACP duration (min): 34 (24-49)
- Lowest nasal temperature (°C): 17.0 (16.0-18.0)

**Postoperative data**

- Mortality (<30 d): 4 (4.8)
- ICU-LOS (d): 7 (5-11)
- Hospital length of stay (d): 17 (11-27)
- Mechanical ventilation (d): 5 (4-9)
- AUC lactate (mmol/L × d): 2.8 (0.9-6.8)
- Inotrope score: 28.5 (19.6-67.4)
- AUC creatinine rise (μmol/L × days): 29 (11-69)
- Dialysis: 3 (3.6)

Values expressed as number of patients (% of group) or median (interquartile range). 

**TABLE 2. Cardiac diagnoses and procedures**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Median DHCA duration (min)</th>
<th>Median ACP duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biventricular repair</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>Hypoplastic aortic arch/CoA, plus:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No intracardiac procedures</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>VSD</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>ASD</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>cAVSD</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>TGA</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ebstein's malformation</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Interrupted aortic arch, plus:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSD, ASD</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Severe LVOTO (Norwood-Rastelli procedure)</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Common arterial trunk</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TGA</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Aortopulmonary window</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Hypoplastic left heart complex</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Univentricular repair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>Double inlet left ventricle</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>DORV, IAA, severe LVOTO</td>
<td>1</td>
<td>49</td>
</tr>
</tbody>
</table>

Values expressed as number of patients (% of group) or median (interquartile range). 

**Postoperative Results**

Data concerning the postoperative recovery of the cohort are listed in Table 1. The 30-day mortality rate was 4.8%. Two infants died of sepsis and multiorgan failure 3 weeks postoperatively (after 23 minutes of DHCA and no ACP, and 6 minutes DHCA and 20 minutes ACP, respectively), 1 infant died 3 days postoperatively of low cardiac output syndrome and multiorgan failure (with no DHCA and 34 minutes of ACP), and 1 of a myocardial infarction on postoperative day 11 (with 18 minutes of DHCA and 30 minutes of ACP). Two patients required a cardiac reoperation during the ICU stay, 1 for a residual VSD and 1 for a revision of a modified Blalock-Taussig shunt. Extracorporeal membrane oxygenation was not used in any of the patients.

**ICU-LOS**

The results of the linear regression analyses for log-transformed ICU-LOS are shown in Figure 1. In univariable analysis, there was a significant relationship between DHCA duration and ICU-LOS. After adjusting for confounders (age at operation, preoperative ventilation, Aristotle score, CPB duration, and presence of noncardiac comorbidity), there was no significant relationship between DHCA duration and ICU-LOS.
comorbidities or a genetic syndrome), the relationship between DHCA duration and ICU-LOS remained significant. The percentage of variation ($R^2$) of ICU-LOS explained by DHCA duration alone was 24%, which increased to 50% in the multivariable analysis.

In univariable analysis, no significant relationship between ACP duration and ICU-LOS was determined and was not attempted.

Results of the multivariable analysis can be interpreted as follows: when DHCA duration increases with 10 minutes, ICU-LOS increases with 13% ($=\exp[0.012 \times 10]$). Therefore, for example, in an infant who would normally have an ICU-LOS of 7 days, and in whom 30 minutes of DHCA had been used, would then have an ICU-LOS of $7 + (7 \times 13\% \times 3) = 10$ days. In contrast, duration of ACP would not have any effect on ICU-LOS.

**Duration of Mechanical Ventilation**

The results of the linear regression analyses for log-transformed mechanical ventilation duration are shown in Figure 2. In univariable analysis, there was a significant relationship between DHCA duration and mechanical ventilation duration. This remained the case after adjustment for age at operation, preoperative ventilation, univentricular repair, Aristotle score, duration of CPB, and presence of a congenital syndrome. ACP duration was not associated with duration of mechanical ventilation in univariable analysis.

The Pearson correlation coefficient between duration of mechanical ventilation and ICU-LOS was 0.9. Interpretation of the multivariable analysis results in a 19% longer mechanical ventilation duration when duration of DHCA increases by 10 minutes. Therefore, in an infant who would have 5 days of postoperative mechanical ventilation and who had undergone surgery with 30 minutes of DHCA, this would result in a mechanical ventilation duration of $5 + (5 \times 19\% \times 3) = 8$ days. If ACP had only been used, the duration would remain 5 days.

**Lactate AUC**

As a parameter for hemodynamic function, the AUC for lactate higher than 2.5 mmol/L was investigated against duration of DHCA and ACP, respectively. Results are shown in Figure 3. Linear regression of DHCA duration revealed a significant relationship with log-transformed lactate AUC, both before and after adjustment for confounders (age at operation, univentricular repair, Aristotle score, and intraoperative myocardial ischemia duration). ACP duration was not associated with lactate AUC. The Pearson correlation coefficient of lactate AUC with ICU-LOS was 0.8.
Inotrope Scores

Univariable linear regression showed a significant relationship between DHCA duration and log-transformed inotrope score (regression coefficient 0.008 [95% confidence interval, 0.001-0.016]). However, this did not remain the case in the multivariable analysis (using the same confounders as for lactate AUC). ACP duration was not associated with log-transformed inotrope score in univariable or multivariable analysis. The Pearson correlation coefficient between inotrope score and ICU-LOS was 0.6.

CREATININE AUC

Three patients required peritoneal dialysis owing to poor renal function postoperatively (after 43 minutes of DHCA and no ACP, 53 minutes of DHCA and 34 minutes ACP, and 23 minutes of DHCA and no ACP, respectively). Owing to this low incidence, the AUC of creatinine above baseline values was used to compare renal function between patients, and results are shown in Figure 4. Linear regression of DHCA duration again showed a significant relationship with log-transformed creatinine AUC, both before and after adjusting for confounders (age at operation, congenital syndromes, univentricular repair, and CPB duration). Although the relationship between ACP duration and creatinine AUC in the graph gives the impression of a slightly inverse relationship, linear regression showed no significant relationship. The Pearson correlation coefficient between creatinine AUC and ICU-LOS was 0.4.

DISCUSSION

In this cohort of neonates undergoing aortic arch reconstruction, we observed that increasing duration of DHCA, but not of ACP, results in a longer postoperative recovery in the ICU. This is likely due to an adverse effect on various organ functions essential for successful recovery. The results remain significant after adjustment for important confounders such as univentricular surgery. Inasmuch as duration of DHCA is a potentially modifiable intraoperative factor, these results suggest all efforts should be made to reduce the duration of DHCA to the shortest period possible, which may be achieved by the use of ACP.

Known risk factors for prolonged ICU-LOS after pediatric cardiac surgery are neonatal age, preoperative ventilation, noncardiac comorbidities, higher surgical complexity, longer CPB duration, and occurrence of postoperative complications. This underlines the importance of investigating the current cohort of patients, which represents the most complex cases of pediatric cardiac surgery. In our study, only DHCA and CPB duration remained significantly associated with ICU-LOS in multivariable analysis.
However, only 50% of the variation in ICU-LOS ($R^2$) could be explained by our multivariable model, indicating other factors (most likely postoperative complications) also have an effect on ICU-LOS. As may be expected, the correlation between parameters of hemodynamic function and ICU-LOS was high. This means that the corresponding regression analyses cannot be considered independent of each other. Renal function, however, showed only a modest correlation with ICU-LOS.

Our results suggest that increasing duration of DHCA negatively impact respiratory, hemodynamic, and renal function, shown by an increase in the duration of mechanical ventilation and increased lactate and creatinine AUCs. In contrast, even “prolonged” ACP (>60 minutes) did not seem to affect the outcome variables. A number of mechanisms may play a role in the vast contrast in postoperative organ function between the 2 techniques. As has been suggested before, in ACP there may be partial perfusion via collaterals to organs other than the brain. ACP inherently induces whole-body ischemia and reperfusion, possibly either directly leading to damage or at least putting cells at greater risk for a “second hit.” Furthermore, the systemic inflammation, triggered by surgery and the use of CPB, seems enhanced by the use of DHCA.

Especially in the presence of endothelial dysfunction after DHCA, this can importantly impair end-organ perfusion. The combination of these factors may have led to the declining hemodynamic and renal function with increasing DHCA duration. Recent literature confirms our findings, as in adult aortic arch repair with DHCA, longer duration of DHCA results in more renal failure postoperatively. The washout of inflammatory mediators and metabolites after widespread ischemia may also have a direct cardiac depressant effect.

Although duration of mechanical ventilation and renal lactate AUC (regarded as “proxies” for hemodynamic function) increased with DHCA duration, inotrope scores did not. These were only associated with DHCA duration in univariable analysis and not in multivariable analysis. Although we can only speculate about the reason for this finding, it may be due to the fact that unlike other organs such as lungs and kidneys, the myocardium cannot receive partial perfusion via collaterals during ACP.

Limitations of this study are mainly due to the retrospective design and the heterogeneity of the cohort. To minimize the influence of any bias toward use of DHCA or ACP that may exist, we used multivariable analyses to adjust for important confounding variables as age at operation, surgical complexity, and univentricular or biventricular repair. However, we cannot exclude that other factors may play a role.

Another consequence of a retrospective study design is that one is limited to the data collected for clinical purposes.
Consequently, we could not assess other abdominal function than renal function (ie, intestinal or hepatic). Furthermore, a larger cohort may have permitted additional multivariable analyses for secondary outcomes as mortality or need for dialysis. On the other hand, an advantage of a (smaller) single-center study is that there are no differences in surgical and intensive care protocols between patients. Finally, this study does not directly compare DHCA and ACP only, inasmuch as in many patients a combination of the 2 techniques was used. However, by investigating whether the duration of either perfusion technique influences postoperative recovery, we have shown that efforts made to minimize DHCA, for instance by using ACP, are worthwhile in these patients.

CONCLUSIONS

This study indicates that increasing duration of DHCA during neonatal aortic arch reconstructions adversely affects postoperative recovery, whereas even prolonged duration of ACP is apparently without consequences. Although differences in neurologic outcome of both techniques still need to be clarified, these results suggest that the use of ACP to reduce DHCA duration improves short-term outcome in this high-risk patient group in pediatric cardiac surgery.

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References