Hyperglycaemia after Stage I palliation does not adversely affect neurodevelopmental outcome at 1 year of age in patients with single-ventricle physiology


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Abstract

Objective: Hyperglycaemia has been associated with worse outcome following traumatic brain injury and cardiac surgery in adults. We have previously reported no relationship between early postoperative hyperglycaemia and worse neurodevelopmental outcome at 1 year following biventricular repair of congenital heart disease. It is not known if postoperative hyperglycaemia results in worse neurodevelopmental outcome after infant cardiac surgery for single-ventricle lesions. Methods: Secondary analysis of postoperative glucose levels in infants <6 months of age undergoing Stage I palliation for various forms of single ventricle with arch obstruction. The patients were enrolled in a prospective study of genetic polymorphisms and neurodevelopmental outcomes assessed at 1 year of age with the Bayley Scales of Infant Development-II yielding two indices: mental developmental index (MDI) and psychomotor developmental index (PDI). Results: Stage I palliation was performed on 162 infants with 13 hospital and 15 late deaths (17.3% 1-year mortality). Neurodevelopmental evaluation was performed in 89 of 134 (66.4%) survivors. Glucose levels at admission to the cardiac intensive care unit and during the first 48 postoperative hours were available for 85 of 89 (96%) patients. Mean admission glucose value was 274 ± 91 mg d l−1; the maximum was 291 ± 90 mg d l−1, with 69 of 85 (81%) patients having at least one glucose value >200 mg d l−1. Only two patients had a value <50 mg d l−1. Mean MDI and PDI scores were 88 ± 16 and 71 ± 18, respectively. There were no statistically significant correlations between initial, mean or maximum glucose measurements and MDI or PDI scores. Only delayed sternal closure resulted in a statistically significant relationship between initial, minimum and maximum glucose values within the context of a multivariate analysis of variance model. Conclusions: Hyperglycaemia following Stage I palliation in the neonatal period was not associated with lower MDI or PDI scores at 1 year of age.

Keywords: Congenital heart disease; Hyperglycaemia; Patient outcomes; Postoperative care

1. Introduction

Advances in both surgical techniques and perioperative care have led to improved survival for neonates undergoing surgery for single-ventricle congenital heart defects (CHDs) such as hypoplastic left heart syndrome (HLHS). There has long been a concern about neurodevelopmental outcomes after the Norwood operation. With increased survival there have also been improvements in the neurodevelopmental outcomes [1]; however, their outcomes still fare worse than other forms of CHD. Microcephaly, structural brain abnormalities, decreased cerebral blood flow, low cardiac output, prolonged hypoxaemia, multiple operations and longer duration of stay in intensive care unit and length of hospital stay are felt to contribute to compromised neurological outcomes in these infants [2–6]. We previously evaluated the relative effects of underlying genetic factors and current management strategies on the neurodevelopmental outcomes after staged palliation for HLHS at 1 year of age [1] and identified that the presence of a genetic syndrome, younger gestational age and the need for preoperative intubation also negatively affected neurological outcomes.

Hyperglycaemia and impaired glucose control are modifiable risk factors which in adults have been associated with worsened outcomes following myocardial infarction and acute coronary syndromes [7,8], stroke [9], postoperative wound infections [10] and severe traumatic brain injury [11]. Insulin...
protocols and use of a glucose—insulin—potassium solution to ensure tight glucose control following cardiac surgery in adults have been associated with lower mortality, lesser renal failure, improved haemodynamics and decreased need for re-opera-
tions [12,13]. Although postoperative hyperglycaemia is a modifiable risk factor in other forms of critical illness, a recent study from our institution found no association of early postoperative hyperglycaemia with worse neurodevel-
mental outcomes following biventricular repair in infancy of a variety of CHDs [14]. Factors that may not impact on infants with two-ventricle defects may influence those with single-
ventricle lesions, who likely have less reserve and face greater physiological stress with potential for longer periods of low cardiac output, a greater degree of prolonged hypoxaemia and longer length of stay. Compared with infants undergoing biventricular repair, the Norwood procedure or stage 1 palliation (S1P) typically requires longer cardiopulmonary bypass (CPB) and results in a palliative circulation, with ongoing hypoxaemia, lower cardiac output and less physiolo-
gical reserve. Consequently, this study was undertaken to determine if early postoperative hyperglycaemia after S1P in neonates with HLHS and variants is associated with a worse neurodevelopmental outcome at 1 year of age.

2. Materials and methods

This study constitutes a secondary analysis of a subgroup of patients enrolled in a prospective trial assessing the effects of polymorphisms of the apolipoprotein E (APOE) gene on neurodevelopmental disabilities [15]. Risk factors for neurodevel-
mental outcomes for this cohort have been previously reported but did not include an analysis of hyperglycaemia [1]. The study was approved by the Institutional Review Board at The Children’s Hospital of Philadelphia. Informed consent was obtained from the parent or legal guardian.

3. Patient population

Patients born between April 1998 and March 2003 with HLHS or variants were eligible. Entry criteria included all patients with single-ventricle physiological features and systemic outflow obstruction undergoing staged palliation. Exclusion criteria before surgical intervention included: (1) multiple congenital anomalies; (2) recognisable genetic or phenotypic syndrome other than chromosome 22q11 microdeletions at birth or (3) language other than English spoken at home. Patients who were diagnosed as having chromosomal or phenotypic syndromes after their initial operation or at the time of 1-year neurodevelopmental testing were included. Anatomic diagnoses included (1) HLHS with a combination of mitral stenosis or atresia and aortic stenosis or atresia and (2) variants including single ventricles (right or left) with systemic outflow obstruction.

Five surgeons, with a dedicated team of cardiac anaes-
thesiologists, performed the operations. All patients under-
went CPB and deep hypothermic circulatory arrest (DHCA) was used at the discretion of the surgeon. Alpha-stat blood gas management was used. Methylprednisolone (30 mg kg−1) was added to the pump prime. Glucose containing fluids were administered in the perioperative period. Modified ultrafiltra-
tion was performed in all patients. Postoperatively, patients were managed by a dedicated team of cardiologists and intensivists in a dedicated Cardiac Intensive Care Unit (CICU). Inotropic drugs were used as clinically indicated to support cardiac output in the immediate postoperative period. Insulin was not given to manage any level of hyperglycaemia. Neonates were maintained on a 10% dextrose solution until they were able to tolerate enteral feeding. Total fluids were limited to approximately 100 ml kg−1 day−1 for the first 24 h postoperatively and then advanced appropriately. Parental nutrition was not routinely started until after the sampling period.

4. Glucose measurements

Blood glucose values included both whole blood bedside glucometer (Surestep Flexx, Lifescan, Milpitas, CA, USA) and chemistry laboratory serum glucose values (Vitros 950, Ortho-Clinical Diagnostics, Rochester, NY, USA). These measurements were obtained as part of the clinical care of the patient and not as a part of a pre-designed protocol. Blood glucose values were retrieved from the electronic data warehouse at the Children’s Hospital of Philadelphia. Initial glucose measurement was defined as the first glucose obtained by either measurement instrument after arrival in the CICU from the operating room. All glucose measure-
ments during the first 48 h postoperatively were recorded. The minimum and maximum glucose values within the first 48 postoperative hours were identified. Hypoglycaemia was defined as a glucose measurement of <50 mg dl−1. Hyper-
glycaemia was defined as a glucose measurement of >200 mg dl−1. The mean glucose value was the average of all the available values for a patient during the study period.

5. Neurodevelopmental examination

The protocol for the neurodevelopmental examination has been previously described [15]. Briefly, children were evaluated at 12 months of age ±2 weeks, adjusted as necessary for prematurity. Development was assessed by the Bayley Scales of Infant Development-II (BSIDII), which yields scores in two areas: psychomotor and mental development. The psychomotor development index (PDI) assesses control of gross motor function, fine motor skills, use of writing instruments and imitation of hand movements. The mental development index (MDI) evaluates memory, problem sol-
ving, early number concepts, generalisation, vocalisations, and language and social skills. Both the PDI and MDI yield a standard score. PDI and MDI population mean scores are 100 with a standard deviation (SD) of 15. The 1-year evaluation also included an interim medical history, growth measure-
ments including head circumference, detailed neurological examination and evaluation by a genetic dysmorphologist. The ethnicity of the child and the familial socioeconomic status (SES) were also documented. Ethnicity was classified as Asian/Pacific, Black, Hispanic, Native American, Other, or White as reported by the parent. SES was assessed by parental report using the Hollingshead scale [16].
6. Statistical analysis

Data analysis proceeded in three discrete steps. First, descriptive statistics for all variables in the data set were computed using both parametric and non-parametric statistical techniques, with particular attention given to glucose and neurodevelopmental status variables. In addition, two specific measures of neurodevelopmental status (MDI and PDI scores) were compared with normative data using one-sample t-tests and extreme scores, specifically to see how the current sample compared with the general population. Comparisons between children with and without genetic syndromes and chromosomal abnormalities were conducted for selected variables (e.g., birth weight, gestational age, use of ECMO, total CPB time, total DHCA time) to verify comparability of sub-samples for inclusion in the current study.

Second, four specific sets of glucose values were summarised across the initial 48-h postoperative period (i.e., initial, minimum, maximum and mean). In an effort to understand better the relationship between glucose and neurodevelopmental status, four different Pearson’s correlation coefficients were computed and tested for statistical significance between the four aforementioned glucose values and MDI and PDI, respectively.

Third, nine different multivariate linear regression models were specified and tested to estimate the relationship among three different glucose measures (initial, minimum and maximum), collectively, and selected patient-related, operative and postoperative variables (see Table 2 for a listing of variables). Multivariate models were deemed necessary due to the highly correlated nature of the summary glucose measures. Mean glucose values were not included in this phase of the analysis due to the linearly dependent nature of mean values on the other three values. For covariates that were continuous in nature, multivariate regression was used as the test of choice while for covariates that were dichotomous in nature, a regression-based multivariate analysis of variance model was deemed appropriate. Multivariate normality was assumed based on the linear nature of the univariate q plots. Three specific outliers were identified and evaluated but not deemed detrimental to the normality of the data. Roy’s maximum root test statistic was used as the criterion for statistical significance for all nine models due to the concentrated structure of the data. Hypothesis-wise error rates were adjusted using Tukey, Ciminera and Heyse’s adjustment for multiple comparisons. All data were analysed using SAS v9.1.

7. Results

Between October 1998 and April 2003, 162 patients enrolled in the primary study met inclusion criteria for the secondary analysis. Hospital mortality was 8% (13/162). There were 15 late deaths after hospital discharge before 1 year of age (1-year survival: 82.7%). Neurodevelopmental evaluation was performed in 89 of 134 (66.4%) of the surviving cohort. Glucose data were available for 85 of 89 (96%) of those who had undergone neurodevelopmental evaluation. Comparative statistics for the preoperative and intra-operative characteristics for the 89 patients who returned and the 45 patients who did not return for 1-year follow-up and the 28 patients enrolled who did not survive have been previously published [1]. At the time of neurodevelopmental testing, the median age was 1.01 years (±0.03 years), the median weight was 8.49 kg (±1.08 kg) and the median head circumference was 45.63 cm (±1.66 cm). A genetic syndrome or chromosomal abnormality was confirmed or suspected for 27 patients (32%), and these patients were not significantly different with respect to birth weight, birth head circumference, gestational age, preoperative intubation, use of ECMO, use of delayed sternal closure, and length of CPB or DHCA. They did differ from those without a definite or suspected genetic syndrome, in that they had a longer postoperative length of stay following S1P (22 ± 19 vs 13 ± 9.5 days; p = 0.02).

For the entire cohort, the mean PDI was 70.6 (±16; median: 90; range: 50–117) and the mean MDI was 88.3 (±16; median: 90; range: 50–129). There was significant deviation from the normative data with PDI scores <70 (2 SDs below the mean) in 47% (p < 0.01) of the patients and MDI scores <70 in 12% (p < 0.01). Previous multivariate analysis by Tabbutt et al. [1] identified the presence of a confirmed or suspected genetic syndrome, and preoperative intubation as risk factors for significantly lower PDI. Similarly, multivariate analysis for MDI identified the presence of a confirmed or suspected genetic syndrome, preoperative intubations and younger gestational age as risk factors for significantly lower MDI. Hyperglycaemia was not evaluated in the previous analysis and was therefore evaluated in this study.

The mean initial postoperative blood glucose for the entire cohort was 274 ± 91 mg dL⁻¹ (range: 73–532 mg dL⁻¹). The mean of all the glucose measurements over the 48-h period was 152 ± 40 mg dL⁻¹. The mean values of the maximum and minimum glucose levels were 291 ± 90 mg dL⁻¹ (range: 109–557 mg dL⁻¹) and 88 ± 23 mg dL⁻¹ (range: 47–172), respectively. Two patients had documented hypoglycaemia (glucose <50 mg dL⁻¹). Sixty-nine of 85 (81%) of patients had at least one glucose measurement greater than 200 mg dL⁻¹ and 11 had measurements in excess of 400 mg dL⁻¹. Glucose values varied widely but tended to decrease over the 48-h immediate postoperative period (Fig. 1). Only two patients had glucose
values greater than 200 mg dl$^{-1}$ at the 48-h postoperative time point.

There were no statistically significant correlations between initial, mean, minimum or maximum glucose measurements and MDI or PDI scores using the adjusted alpha (see Table 1). In addition, no statistically significant relationships were observed among the three glucose measurements, when taken together, and other patient-related (birth weight, genetic exclusion and gestational age), operative (use of ECMO, preoperative intubation, total CPB time and total DHCA time) or postoperative (postoperative length of stay) variables. The lone exception to this finding was delayed sternal closure ($p < 0.01$; see Table 2). Statistically significant differences were observed at initial ($p < 0.01$) and for minimum glucose values ($p = 0.03$), but not for maximum glucose values ($p = 0.11$). With respect to initial glucose level, children with delayed sternal closure had significantly lower glucose values than children without delayed sternal closure (221 vs 290 mg dl$^{-1}$). However, the pattern reversed itself for minimum glucose, as children with delayed sternal closure (221 vs 290 mg dl$^{-1}$) had significantly lower glucose values than children without delayed sternal closure ($p = 0.03$).

Hyperglycaemia in the early postoperative period was not a predictor of worse neurodevelopmental outcomes at 1 year of age following staged reconstructive surgery for HLHS. There was no association of hyperglycaemia with lower scores for either the MDI or the PDI. Specifically, there were no statistically significant correlations between initial, mean, minimum or maximum glucose measurements and PDI or MDI scores.

### Table 1

<table>
<thead>
<tr>
<th>Neurodevelopment</th>
<th>Glucose</th>
<th>$r$</th>
<th>$C_{0.95}$</th>
<th>$p$-value</th>
</tr>
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<tbody>
<tr>
<td>MDI</td>
<td>Initial</td>
<td>0.28</td>
<td>0.07, 0.47</td>
<td>&lt;0.01</td>
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<tr>
<td></td>
<td>Minimum</td>
<td>-0.10</td>
<td>-0.30, 0.12</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>0.21</td>
<td>0.01, 0.41</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>0.15</td>
<td>-0.07, 0.35</td>
<td>0.18</td>
</tr>
<tr>
<td>PDI</td>
<td>Initial</td>
<td>0.25</td>
<td>0.04, 0.44</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>-0.26</td>
<td>-0.45, -0.05</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>0.23</td>
<td>-0.02, 0.2</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>-0.02</td>
<td>-0.23, 0.20</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Note. $n = 85$. Significance values reported here were rounded to two decimal places for consistency and ease of reporting. The criterion for statistical significance for all eight analyses was set at the $e_{ADJ} > 0.0076$ level due to the multiplicity of moderately correlated endpoints.

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>RMR</th>
<th>$p$-value</th>
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</thead>
<tbody>
<tr>
<td>Class</td>
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<tr>
<td>Patient-related</td>
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<td></td>
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<tr>
<td>Birthweight</td>
<td>0.20</td>
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</tr>
<tr>
<td>Gestational age</td>
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<td></td>
</tr>
<tr>
<td>Genetic exclusion</td>
<td>0.74</td>
<td></td>
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<tr>
<td>Operative</td>
<td></td>
<td></td>
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<tr>
<td>Delayed sternal closure (y/n)</td>
<td>-0.01</td>
<td></td>
</tr>
<tr>
<td>Use of ECMO/LVAD (y/n)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Pre-operative intubation (y/n)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Total CPB time</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Total DHCA time</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative LOS</td>
<td>0.37</td>
<td></td>
</tr>
</tbody>
</table>

Note. $n = 85$. RMR = Roy’s Maximum Root test statistic.

### 8. Discussion

Neurodevelopmental outcomes for infants undergoing staged reconstructive surgery for HLHS have improved significantly. Early reports from our institution [17] suggested a high incidence of neurodevelopmental disability, while more recent reports [1] are more encouraging.

Nonetheless, early neurodevelopmental outcomes remain inferior to those for infants with many other types of CHD which require cardiac surgery in the neonatal period. In this analysis of neonates undergoing S1P, we found no adverse effect of early postoperative hyperglycaemia on neurodevelopmental outcome, as assessed by the BSID-II, at 1 year of age.

The interest in tight glucose control in congenital heart surgery stems from the adult cardiac surgery literature. Infectious, renal and cardiopulmonary morbidity has been reported to be increased in uncontrolled diabetic patients undergoing cardiac surgery [18]. Additionally, cognitive deficits have been reported in 50% of adults after coronary artery bypass grafting associated with hyperglycaemia [19]. However, recent paediatric evidence suggests that hypoglycaemia, rather than hyperglycaemia, may be more predictive of worse outcome, with an increased incidence of adverse events in the immediate postoperative period [20]. In prior work, investigators from The Boston Circulatory Arrest study failed to demonstrate any relationship of intra-operative hypoglycaemia or hyperglycaemia to short-term neurological evaluation or mid-term neurodevelopmental testing at 1, 4 and 8 years of age [21]. Our previous report about patients with two-ventricle cardiac defects also found no adverse effect of immediate postoperative hyperglycaemia on 1 year neurodevelopment or length of stay [14]. However, it is unclear if this early postoperative hyperglycaemia, which may be an immediate response to stress and administered steroids, is comparable to later hyperglycaemia where the mechanisms for and the effects of which may be different.

The mechanisms by which blood glucose levels modulate the risk of brain injury following hypoxic ischaemic insult have not been fully elucidated. There is convincing clinical evidence that hyperglycaemia worsens outcome following brain injury in adults [11]. The current study and others suggest that hyperglycaemia has no adverse effect following hypoxic ischaemia of the immature brain, and in some cases may be neuroprotective [22]. Maturational changes in glucose metabolism by the brain may explain some of the divergent findings [23]. In adults, hyperglycaemia leads to lactic acid production and subsequent neuronal death secondary to metabolic acidosis. In the immature brain, lactic acid production during hyperglycaemia is less and lactic acid clearance may be enhanced, resulting in a decrease in the severity of the metabolic acidosis [24]. In neonates the maturational differences in glucose metabolism and susceptibility to hypoxic injury of immature oligodendrocytes and developing glial cells may explain the differing...
effects of hyperglycaemia on brain injury between adults and children. The current study evaluated only neonates undergoing S1P for HLHS and variants in contrast to other studies that have included a wider age range of patients. The findings of this study and our previous report support that hyperglycaemia following hypoxia–ischaemia is not deleterious and that tight control of glucose in the early postoperative period after infant cardiac surgery may not be warranted. The findings of our current study are in contrast to a recent report from Yates et al. that suggested higher morbidity and mortality following paediatric cardiac surgery for CHD with postoperative hyperglycaemia. In that study, however, the relationship of hyperglycaemia to adverse outcomes were based on the duration of hyperglycaemia and peak glucose levels over 10 days, a much longer time period which may make it difficult to compare directly with our current data and that previously published.

This study is subject to limitations of a retrospective analysis. The glucose values were obtained by the care team in a non-standardised fashion and the glucose infusion rate for each patient was not standardised or related to the degree of hyperglycaemia. The effects of inotropic drugs, low cardiac output or other physiological stressors were not systematically evaluated in this study. The interim effects of additional interventions were not included in the analyses. In addition, neurodevelopmental evaluation at 1 year of age has limited predictive validity for many later outcomes in childhood. Finally, the tertiary referral patterns for our institution limited the number of patients available for the 1-year neurodevelopmental evaluation.

In conclusion, the current study does not demonstrate an adverse effect of early postoperative hyperglycaemia on morbidity, mortality or neurodevelopmental outcome at age 1 year in infants after S1P for HLHS and variants. In contrast to adult patients undergoing cardiac surgery, the findings of this study in combination with the known adverse effects of hypoglycaemia may suggest that perhaps tight glucose control is not indicated in the early postoperative period following S1P and may in fact have risk. This is in concert with basic science studies as well as our previous report in neonates and infants following biventricular repair of complex CHD which suggest no adverse effect of hyperglycaemia in the immature brain.

Continued follow-up of neurodevelopmental outcomes are necessary in this population to confirm these findings over the long term.

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Appendix A. Conference discussion

Dr J. Rubay (Brussels, Belgium): I have read your paper with particular interest since, as you may know, I’m involved in a protocol of normothermia, and we are currently assessing late neurodevelopment status of our patients.

You are, in Philadelphia, along with the Boston group, leaders in many aspects, but particularly in trying to identify all the factors which might have a negative impact on late neurodevelopment. And as you mentioned, to the contrary, in adult patients in whom hyperglycaemia has been demonstrated to be associated with worse neurologic outcome, you have beautifully showed that this is not the case for children, confirming that our population of patients are not just adults in small size. And you have chosen the most difficult patients, those who survived Stage I palliation for HLHS.

My two questions will be very simple.

First, do you have any explanation for the two patients who developed hypoglycaemia although they were perfused with dextrose 10%?

And the second question is related to any correlation you might have found between the use of adrenaline and hyperglycaemia.

Dr Ballweg: To answer your first question, the two patients who had documented hypoglycaemia were not any different than the other patients that we looked at. I couldn’t find anything that made them stand out. They were not smaller, they were not younger, they were not more sick preoperatively.

The majority of the patients who underwent Stage I palliation were not on hyperalimentation prior to surgery, and I did not have the opportunity to go back and look at glucose infusion rates. I suppose there could have been a difference there. However, since it’s not standardised for the entire group, I can’t certainly say that it was related to that for only two patients.

Dr Rubay: Any relation between the use of adrenaline and hyperglycaemia?

Dr Ballweg: Postoperatively?

Dr Rubay: Yes.

Dr Ballweg: Quite honestly, we had very few patients that required epinephrine infusions postoperatively. Our general practice is to use the inotropes of milrinone and dopamine. I did not go back and look to see if certain patients who had more hyperglycaemia were on epinephrine.

Dr W. Mrowczynski (Poznan, Poland): It was already well documented that children with such severe congenital heart defects are already born with certain problems of central nervous system. Can you correlate this potential congenital neurological problem with rather high variability of your neurological scores?

And the second question, did you screen your patients for some neurological problems?

Dr Ballweg: Certainly at our center right now there are many people that are looking at the neurodevelopmental outcomes, and one of our neurologists in particular has looked at some of the infants preoperatively with MRI. We know that there is a certain percentage of patients who do have PVL preoperatively and have brain injury in utero. He has recently presented his data, which has found that the brain of many of these infants is about 4 weeks delayed in maturation. So certainly, they’re vulnerable. They’re vulnerable to the intra-operative and the postoperative complications that probably potentiate the underlying mechanisms of injury that they already have.

Your second question?

Dr Mrowczynski: If you screen your patients for some substrate?

Dr Ballweg: We don’t standardly screen. Certainly some cardiologists will do a head ultrasound on all patients that are single ventricle, but it’s not standardised through our institution.