Neurodevelopmental Outcome of Infants Supported With Extracorporeal Membrane Oxygenation After Cardiac Surgery

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ABSTRACT. Objectives. To evaluate the long-term neurodevelopmental outcome of infants who underwent cardiac surgery and required extracorporeal membrane oxygenation (ECMO) support, and to examine variables that predict death or disability in these patients.

Methods. We studied all infants who had congenital heart disease and were supported postoperatively with ECMO from 1990 to 2001 at our institution (n = 53). Medical records were reviewed retrospectively to obtain clinical variables. Neurologic and age-appropriate developmental examinations occurred at ages 1, 1.5, 2.5, and 4.5 years. Median age at follow-up was 55 months (9–101). Cognitive outcome was defined as suspect when scores were between 1 and 2 SD below the mean for age and abnormal when scores were >2 SD below mean for age. Neuromotor outcome was defined as suspect when the patient manifested clumsiness, tremor, or mild tone and reflex changes without functional limitations, and abnormal when there were functional limitations.

Results. In-hospital survival was 17 (32%) of 53. Of survivors, 14 (88%) of 16 are living and 1 patient was lost to follow-up. Of the 53 patients, 7 survived completely intact (13%). Seven (50%) of 14 patients had a normal cognitive outcome, 3 (21%) had a suspect cognitive outcome, and 4 (29%) were abnormal. Ten (71%) of 14 patients had a normal neuromotor outcome, 1 (7%) patient had a suspect neuromotor outcome, and 3 (21%) were abnormal. No survivor with an aortic cross-clamp time >40 minutes had a normal cognitive outcome. Nonsurvivors were more likely than survivors to have had cardiac arrest as an indication for ECMO (31% vs 6%), to have had a longer aortic cross-clamp time (mean 73 minutes vs 32 minutes), and to have required continuous arteriovenous hemofiltration (78% vs 35%). The age and weight at cannulation, gender, cardiac diagnosis, interval from surgery to ECMO, cardiopulmonary bypass time, diagnosis of sepsis or mediastinitis, and duration of ECMO were not significantly associated with survival.

Conclusions. Although mortality was 68% in infants who had congenital heart disease and were treated with ECMO postoperatively, of those who survive to hospital discharge, 75% have a normal neuromotor outcome and 50% have a normal cognitive outcome. These high rates of mortality and disability suggest that increased attention be paid to neuroprotection in these complex disorders. Pediatrics 2003;111:e671–e675. URL: http://www.pediatrics.org/cgi/content/full/111/6/e671; congenital heart disease, extracorporeal membrane oxygenation, neurodevelopmental outcome.

ABBREVIATIONS. ECMO, extracorporeal membrane oxygenation; CHD, congenital heart disease; CPB, cardiopulmonary bypass; SD, standard deviation; CAVH, continuous arteriovenous hemofiltration; MRI, magnetic resonance imaging.

Postoperative support with extracorporeal membrane oxygenation (ECMO) for infants with congenital heart disease (CHD) has not met the same survival success rate as ECMO for respiratory indications, and the neurodevelopmental outcome of these patients is not well described. Previous reports have described the neurodevelopmental outcome in patients with CHD1–5 and the neurodevelopmental outcome after cardiopulmonary bypass (CPB).6–9 These studies reveal that significant neurodevelopmental abnormalities are present in newborns with CHD before surgical repair, and length of circulatory arrest and periods of low perfusion or acidosis peroperatively are associated with poor outcome. Previous studies have also addressed the neurodevelopmental outcome after ECMO for respiratory and cardiac indications,10–18 describing similar neurodevelopmental outcomes as compared with “near-miss” controls, with severe cognitive impairment occurring in approximately 10%. Few studies, each with significant limitations, have investigated the neurodevelopmental outcome of infants who had CHD and were supported postoperatively with ECMO.19–22 Our objective was to evaluate the long-term neurodevelopmental outcome in a cohort of newborns who had CHD and were supported with ECMO postoperatively and to identify clinical characteristics that are associated with survival and better neurodevelopmental outcome.

METHODS

We studied 53 infants who had cardiac disease and were supported postoperatively with ECMO at our institution from 1990 to 2001. The details of ECMO have been described extensively elsewhere.23,24 Infants were included for review when they were younger than 1 year at the time of cannulation and when they had received cardiac surgery for a congenital heart lesion before the initiation of ECMO. Newborns were excluded when they required ECMO before surgical repair or when they had an associated CHD but their indication for ECMO was respiratory failure. Current institutional review board approval was obtained for the present study.

Clinical Data

Medical records of these children were reviewed retrospectively for demographics, diagnosis, indication for cannulation,
Neurodevelopmental Outcome

All infants who survive ECMO are eligible for follow-up in the University of California San Francisco intensive care nursery follow-up clinic. Complete physical, neurologic, and age-appropriate developmental examinations were performed on the children at 1, 1.5, 2.5, and 4.5 years’ chronological age. Three survivors (out of state) were not seen by us, but we were able to place the children in outcome categories using the Child Development Chart and Review (Behavioral Science Systems, Minneapolis, MN) to assess cognitive outcome and a pediatrician’s physical examination to assess neuromotor outcome. Outcome categories include normal, abnormal, or suspect. Neuromotor outcome was defined as suspect when the patient manifested clumsiness, tremor, or mild tone and reflex changes without functional impairment. Neuromotor outcome was defined as abnormal when there was cerebral palsy or abnormalities associated with functional impairment such as diplegias and hemiplegias. Cognitive outcome was determined by scores obtained on developmental testing, including the Bayley Scales of Infant Development II at 1 and 1.5 years of age, the Stanford Binet Intelligence Scale at age 2.5 years, and the McCarthy Scales of Children’s Abilities or Wechsler Scale of Intelligence at 4.5 years. 25–29 Cognitive outcome was defined as suspect when scores on the age-appropriate scale were between 1 and 2 standard deviations (SD) below the mean and as abnormal when scores were 2 SD or more below the mean (<–69).

Statistical Analysis

Statistical analysis was performed using Mann-Whitney U test for nonparametric continuous data and χ² and Fisher exact tests as appropriate for dichotomous variables.

RESULTS

Clinical Characteristics and Survival Predictors

The clinical characteristics and survival predictors of the study population are shown in Table 1. Fifty-three infants from 1990 to 2001 had CHD and underwent operative repair and were subsequently placed on ECMO. In-hospital survival was 17 (32%) of 53. Nonsurvivors were more likely than survivors to have had cardiac arrest as an indication for ECMO (31% vs 6%; P = .05), a longer aortic cross-clamp time (mean 73 minutes vs 32 minutes; P = .01), and require continuous arteriovenous hemofiltration (CAVH; 78% vs 35%; P = .01). These did not differ by diagnosis group. The age and weight at cannulation, gender, cardiac diagnosis, interval from surgery to ECMO, CPB time, diagnosis of sepsis or mediastinitis, and duration of ECMO were not significantly associated with survival. One infant died as a result of a circuit complication, 58% had support withdrawn, and the remainder died after decannulation but before hospital discharge. Reasons given for withdrawal of support were poor cardiac function (58%), neurologic complication (26%), and multorgan failure (16%). The specific cardiac lesions for survivors and nonsurvivors are given in Table 2.

Neurodevelopmental Outcome

Table 3 reveals the neurodevelopmental outcome for 14 survivors. Median age at most recent follow-up visit was 55 months (9–101 months; all but 1 were >12 months). Of survivors to hospital discharge, 15 (88%) of 17 are still living. One patient was lost to follow-up. Ten (72%) of 14 patients evaluated had a normal neuromotor outcome, 1 (7%) patient had a suspect neuromotor outcome, and 3 (21%) of 14 were abnormal. Seven (50%) of 14 patients had a normal cognitive outcome, 3 (21%) of 14 had a suspect cognitive outcome, and 4 (29%) of 14 had an abnormal cognitive outcome. Figure 1 is a flowchart of patient outcomes. Thus, of the 53 patients, 7 (13%) survived neurologically intact. Two (14%) of 14 survivors have microcephaly. One abnormal survivor has visual impairment, and 1 is deaf. Two patients carry the diagnosis of DiGeorge syndrome; 1 has an abnormal cognitive outcome, and 1 has a suspect cognitive outcome. One patient with an abnormal neurodevelopmental outcome has a seizure disorder. One patient with an abnormal neuromotor and cognitive outcome also experienced birth asphyxia. There was a trend toward statistical significance for length of aortic cross-clamp time and cognitive outcome (normal mean 23 minutes vs abnormal mean 47

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>17</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Weight (kg [range])</td>
<td>4.3 (3.5–6)</td>
<td>3.9 (2.1–7.9)</td>
<td>.37</td>
</tr>
<tr>
<td>Median age at cannulation (days; [range])</td>
<td>27 (1–362)</td>
<td>22 (1–314)</td>
<td>.66</td>
</tr>
<tr>
<td>Male/female</td>
<td>10/7</td>
<td>18/18</td>
<td>.76</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyanotic, decreased PBF</td>
<td>9 (41%)</td>
<td>13 (59%)</td>
<td>.46</td>
</tr>
<tr>
<td>Cyanotic, increased PBF</td>
<td>2 (17%)</td>
<td>10 (83%)</td>
<td></td>
</tr>
<tr>
<td>Left-sided obstruction</td>
<td>6 (33%)</td>
<td>12 (66%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Indication for ECMO</td>
<td></td>
<td></td>
<td>.05</td>
</tr>
<tr>
<td>Failure to wean from bypass</td>
<td>8 (38%)</td>
<td>13 (62%)</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>1 (8%)</td>
<td>11 (92%)</td>
<td></td>
</tr>
<tr>
<td>Slow deterioration</td>
<td>7 (37%)</td>
<td>12 (63%)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Interval from surgery to ECMO (h)</td>
<td>28.5 (0–242)</td>
<td>46.5 (0–504)</td>
<td>.33</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>214 (0–242)</td>
<td>285 (0–607)</td>
<td>.28</td>
</tr>
<tr>
<td>Aortic cross-clamp (min)</td>
<td>32 (0–73)</td>
<td>73 (0–260)</td>
<td>.01</td>
</tr>
<tr>
<td>CAVH (no. of patients)</td>
<td>6 (18%)</td>
<td>28 (82%)</td>
<td>.01</td>
</tr>
<tr>
<td>Duration of ECMO (h)</td>
<td>150 (39–504)</td>
<td>172 (8–840)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

PBF indicates pulmonary blood flow.
minutes; $P = .06$). No survivor with an aortic cross-clamp time $>40$ minutes had a normal cognitive outcome. Cardiac diagnosis, indication for ECMO, interval from surgery to ECMO, CPB time, need for CAVH, a diagnosis of sepsis or mediastinitis, and ECMO duration were not statistically different between normal and abnormal survivors. Neuroimaging results are shown in Table 3. Ten survivors had magnetic resonance imaging (MRI) in addition to head ultrasounds. Five of these patients had evidence of hypoxic-ischemic brain injury.\(^{30}\) Patients with a normal MRI had a normal outcome. Three of 4 patients with abnormal cognitive outcome had an abnormal MRI demonstrating white matter damage (1 of these 4 patients with abnormal cognitive outcome did not have an MRI).

### DISCUSSION

In this population of infants who had CHD and were supported with ECMO postoperatively, the mortality rate was high (68%). This is comparable to what has been previously published for similar populations.\(^{31–36}\) It is higher than reports from Aharon et al,\(^{37}\) Rogers et al,\(^{38}\) and Walters et al,\(^{39}\) although 2 of these 3 studies had an older patient population. The Extracorporeal Life Support Organization, a registry inclusive of ECMO centers worldwide, reported in January 2003 that the survival to hospital discharge rate was 37% for neonates who had cardiac disease and received ECMO and 42% for pediatric patients with cardiac disease.\(^{40}\)

Given the high mortality rate, the neurodevelopmental outcome of survivors to discharge is arguably favorable, with only approximately one quarter having a clearly abnormal outcome. Although previous studies have reported neurodevelopmental outcome for patients with CHD,$^{1–5}$ outcome after CPB,$^{6–9}$ and outcome of patients after ECMO,$^{10–18}$ it is difficult to assess which neurodevelopmental abnormalities might be attributable to cyanosis, to CHD, to CPB, or to ECMO when all are frequently combined in this population. Recent data have suggested that the prevalence of preoperative neurologic abnormalities in newborns is higher than 50%.\(^{5}\) These newborns and infants were not followed beyond the early postoperative period. Klein et al\(^{19}\) described a normal neurodevelopmental outcome in 9 (41%) of 22 patients with CHD after ECMO for postoperative support. This was an older cohort (mean age of ECMO: 13.6 months), and the length and formality of follow-up are unknown. Ibrahim et al\(^{21}\) conducted a telephone survey to assess follow-up on 25 pediatric cardiac survivors of ECMO; these results revealed moderate to severe neurologic impairment in 59% but were limited by the subjective design of a questionnaire study. The interpretation of another study, which found a normal neurologic outcome in 100% of survivors, is restricted by very small patient numbers ($n = 5$).\(^{20}\) Ziomek et al\(^{22}\) followed survivors to a mean age of only 7 months; 2 of 13 had mild developmental delays at that age. Although our study had sufficient patients to allow for certain clinical variables to predict survival status, our survivor number was too small to allow those clinical variables to predict neurodevelopmental outcome. Only length of aortic cross-clamp time was suggestive of an association with neurodevelopmental outcome.

Hemorrhagic or thrombotic events are often cited as the most frequent cause of neurologic complication of ECMO. Earlier eras in ECMO management often maintained much higher activated clotting times,\(^{24}\) putting patients at higher risk for hemorrhagic complications. Rather than finding exclusively hemorrhagic or thrombotic complications, we also found evidence for hypoxic-ischemic brain injury. Studies of neuroimaging (ultrasound and computed tomography) after ECMO have been conflicting as to correlation with neurodevelopmental outcome.\(^{10,11,16,41}\) Our neuroimaging results of the 4 patients who had a frankly abnormal cognitive outcome revealed no abnormality on head ultrasound in 1 patient (but no MRI done) and parenchymal or intraventricular hemorrhage followed by periventricular white matter injury in 3 patients. The 3 patients with an abnormal neuromotor outcome were these same 3 patients. The 1 surviving patient with an infarction (basal ganglia and thalamus) had a normal outcome. Accurate predictors of outcome in this population need additional refinement before any statistically significant conclusions can be drawn. Hemorrhagic neurologic complications are also often cited as a common reason for withdrawal of support. It accounted for approximately one quar-

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### TABLE 2. Cardiac Lesions in the ECMO Survivor and Non-survivor Groups

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanotic, decreased pulmonary blood flow</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>TOF/PA/MAPCAS</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>TOF/AV canal</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>TOF/absent pulmonary valve</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary atresia, intact septum</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>DORV/pulmonary atresia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Severe pulmonary stenosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Epstein's with pulmonary stenosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cyanotic, increased pulmonary blood flow</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>d-TGA</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>AV canal</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Left-sided obstruction</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>TAPVR</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hypoplastic left heart</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Taussig Bing, interrupted aortic arch</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Critical aortic stenosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Scimitar/anomalous pulmonary veins/lung hypoplasia</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

TOF indicates tetralogy of Fallot; PA, pulmonary atresia; MAPCAS, major aortopulmonary collateral arteries; AV, atrioventricular canal; DORV, double outlet right ventricle; TGA, transposition of the great arteries; TAPVR, total anomalous pulmonary venous return.
ter of the indications to withdraw support in this cohort, lower than 2 other cohorts.31,35

Statistically significant clinical differences between the survivor and nonsurvivor groups were cardiac arrest as an indication for ECMO, a longer aortic cross-clamp time, and need for CAVH. Of interest, the indication for ECMO in patients with CHD that is typically associated with the highest mortality rate is failure to wean from CPB.19,22,31,34,39,42 This was not a risk factor for mortality in our patients. Ibrahim et al21 and Duncan et al 43 described their intensified efforts to resuscitate quickly pediatric patients who experience a cardiac arrest with a rapid-response ECMO circuit. An ECMO circuit had not been available at our center in the past for rapid response, and this may reflect the poor survival rate in our cardiac arrest group. This has since changed at our institution, and, in fact, the philosophy has shifted from using ECMO for rescue only to more liberal indications for support, with a crystalloid primed circuit always available.

Aortic cross-clamp time was not found to be significantly associated with survival in Walter’s analysis of risk factors for in-hospital death, although they report that the cross-clamp time was longer in nonsurvivors (data not shown).19,39 Renal status (urine output, need for CAVH or dialysis) has been previously reported to predict survival.19,32,34,37,44

Our study is strengthened by the length and formality of neurodevelopmental follow-up. In all previous reports of neurodevelopmental outcome after ECMO, data were obtained retrospectively and the cohorts were small and heterogeneous. However, our surviving children were followed prospectively. Given the high mortality rate of patients who have CHD and require support of ECMO and the previous data suggesting a high prevalence of preoperative abnormalities, the normal neurodevelopmental outcome in approximately half of surviving infants is encouraging. As infants with CHD are receiving newer, complex interventions, examination of neuroprotection strategies and additional longer-term outcomes studies are warranted.

ACKNOWLEDGMENTS

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REFERENCES


PS indicates pulmonary stenosis; IVH, intraventricular hemorrhage; SEH, subependymal hemorrhage; PVWMI, periventricular white matter injury.


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