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Cognitive abilities of survivors of neonatal extracorporeal membrane oxygenation.

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COGNITIVE ABILITIES OF SURVIVORS OF NEONATAL EXTRACORPOREAL MEMBRANE OXYGENATION

by

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ABSTRACT OF DISSERTATION
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Extracorporeal membrane oxygenation (ECMO) is a medical technique that is used in the treatment of severe respiratory ailments. Used successfully since 1972 with adults, the first successful use of ECMO with neonates occurred in 1975. ECMO is now a commonly used technique for infants who fail to respond to less invasive treatments and would otherwise have a higher mortality rate. Although short-term follow up and survival rates have been impressively documented, the long-term follow up of these infants and the possible consequences of ECMO have not yet been thoroughly examined. A small number of reports exist that follow infants into childhood, and likewise reports that document the 1-year post-ECMO status have been published. However, to date, no study has looked intensively at the longer term follow up of a large number of infants. The current study examined the long-term follow-up data of 322 infants who received ECMO in the neonatal period at The Children's Hospital of Alabama in Birmingham over the past 16 years. Cognitive abilities, as measured by standardized developmental measures, were examined in order to determine the potential long-term side effects of ECMO treatment. Certain subgroups of children who received ECMO appear to experience difficulties with language skills. However, due to a large attrition rate and the lack of a true experimental design, it is difficult to state with certainty whether these problems are due to the ECMO treatment or to the conditions that made ECMO necessary for them

in the first place. Therefore, additional research is needed. However, this study contains one of the largest populations of ECMO survivors to date and has provided initial information on treatment outcome in these children.

DEDICATION

This dissertation is dedicated to my aunt, Karen Swann. Since day one, she has been my biggest fan and my inspiration. She is the reason I do what I do. Karen taught me more than I could ever learn in a graduate program. She is truly my hero.

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LIST OF ABBREVIATIONS

ANCOVA	analysis of covariance
BSID	Bayley Scales of Infant Development
BSID-II	Bayley Scales of Infant Development-Second Edition
CDH	Congenital Diaphragmatic Hernia
DAS	Differential Ability Scales
ECMO	Extracorporeal Membrane Oxygenation
F	Fisher's F ratio
GCA	General Conceptual Ability score
hr	hours
MAS	Meconium Aspiration Syndrome
n	number in a subsample
N	total number in a sample
p	probability
PFC	Persistent Fetal Circulation
PIQ	Performance IQ score
PPHN	Persistent Pulmonary Hypertension of the Newborn
RD	respiratory distress
SD	standard deviation
VA	venoarterial

VV	venovenous
WISC-R	Wechsler Intelligence Scales for Children-Revised
WISC-III	Wechsler Intelligence Scales for Children-Third Edition

INTRODUCTION

Extracorporeal Membrane Oxygenation (ECMO) is a prolonged cardiopulmonary bypass technique that is used in the medical treatment of severe respiratory problems. By artificially oxygenating the blood, ECMO allows the lungs to rest and recover without the potentially harmful side effects of high doses of oxygen and the use of high-frequency ventilators (Bartlett, 1989; Braden, 2002; Ortiz, Cilley, & Bartlett, 1987), because the use of conventional ventilation often increases risks for bronchopulmonary dysplasia due to the high pressures and oxygen used in treatment (Short, 1989; Wetzel & Gioia, 1987; Zwischenbeger and Bartlett, 1995). Wolfson (2003) described the key to the success of ECMO as allowing the lungs time to heal on their own while the patient's vital signs are maintained artificially. ECMO is a life-saving procedure and, with infants, is most often used as a measure of last resort.

Developed in the 1950s, ECMO was first used successfully with adult patients in 1972 (Hill et al., 1972). Soon after, the technique was applied to infants (see Dorson, 1969; Rashkind, Freeman, Klein, & Toft, 1965; White, Andrews, Risemberg, Mazur, & Haller, 1971). Although the technique was deemed successful in that it could be implemented with infants, all of the infants later died as a result of their preexisting conditions. Early trials of ECMO on premature infants with hyaline membrane disease also failed due to intracranial hemorrhage (Short, 1989). Bartlett reported the first successful use of ECMO in an infant with meconium aspiration syndrome (Anthony & Hardee, 2000; Bartlett, 1989; Short, 1989; see also Bartlett, 1997). By the late 1980s, ECMO had become

common practice for infants who failed to respond to aggressive nonsurgical management (i.e., ventilators) of their respiratory disorders.

Respiratory Distress in Newborns

Respiratory Distress (RD) is a combination of symptoms that, in infancy and newborns, can include tachypnea, cyanosis, and physical manifestations such as grunting, nasal flaring, and retractions of the chest wall upon inhalation. RD in newborns can occur due to a failure to transition to the external environment outside of the uterus, infections, or congenital defects of the cardiopulmonary system (Balsan & Holzman, 1997; Hagedorn, Gardner, & Abman, 2002). In RD, the oxygen and air that the infant or child is breathing are unable to pass from the lungs into the bloodstream. If left untreated, RD can lead to pneumothorax, intraventricular hemorrhage, brain damage, or death. Mortality rates from RD range from 12% to 75% (Somme & Liu, 2001).

The potentially reversible hypoxemia associated with RD has often been treated with ECMO when it fails to respond to conventional treatment. Persistent Pulmonary Hypertension of the Newborn (PPHN) is usually the resulting diagnosis in newborns who are experiencing RD, regardless of the initial diagnosis (Ortiz et al., 1987). PPHN was previously known as Persistent Fetal Circulation (PFC) because it is an incomplete transition to adult circulation from the fetal circulation route. In newborns, the symptoms of PPHN are severe pulmonary hypertension and elevated pulmonary artery pressure levels. When a healthy infant first breathes after delivery, a series of muscular contractions and increased alveolar oxygen tension causes the ductus arteriosus in the heart to close. The eustacian valve folds over and closes the foramen ovale in the heart, which allows for the blood to be circulated to the lungs where it will be oxygenated. In PPHN, this process

does not occur, and blood is shunted right to left through the foramen ovale and the ductus arteriosus (Batshaw, 1997; Hagedorn et al., 2002; Ortiz et al., 1987).

There are a number of conditions that can result in PPHN. Meconium Aspiration Syndrome (MAS) occurs when the newborn breathes in meconium (the first feces, composed of salts, liquor amnii, mucus, bile, and epithelial cells) prior to delivery. MAS often occurs when the fetus is in distress or may be asphyxiating (Balsan & Holzman, 1997; Batshaw, 1997; Taber's, 1997). Once aspirated, meconium can physically block structures in the airways, create inflammation, inhibit the development of surfactant needed for the lungs to develop, or, in approximately 33% of cases, result in PPHN (Hagedorn, Gardner, & Abman, 2002). Sepsis, which is a systemic infection of microorganisms or toxins in the blood stream, is another condition which can result in PPHN (Meyer & Jessen, 1997). Finally, Congenital Diaphragmatic Hernia (CDH), which occurs in 1 in 4,000 live births, occurs when the pleuroperitoneal canal does not close during pregnancy. The abdominal contents, including the intestines, migrate into the chest cavity through the hole in the diaphragm and end up compressing the developing lungs, resulting in the lungs being smaller than normal and/or abnormally developed (Batshaw, 1997; Hagedorn et al., 2002; Muratore & Wilson, 2000; Puri & Wester, 1997). CDH has been associated with the highest mortality rates among children who receive ECMO, probably due to the major physical anomaly that affects the child in addition to the respiratory problems (Roy, Rycus, Conrad, & Clark, 2000). Other less common diagnoses such as maternal blood aspiration or air leak syndromes can also result in PPHN.

Attempts are always made first to manage these conditions with standard, aggressive, less invasive medical treatment. Supplemental oxygen, mechanical ventilation, high-frequency oscillatory ventilation, liquid ventilation, and inhaled nitric oxide are

techniques that are usually attempted or considered (Baumgart, Hirschl, Butler, Coburn, & Spitzer, 2001; Hagedorn et al., 2002; National Institutes of Health, 1990; Somme & Liu, 2001; Wetzel & Gioia, 1987). However, if the infant does not respond to these therapies, then ECMO will often be considered. Estimates are that, across the United States and overseas, over 1,000 newborns per year receive ECMO therapy, although this number has been declining over the past decade (Extracorporeal Life Support Organization Registry, 2002; Hagedorn et al., 2002). In fact, since the introduction of therapies such as surfactant replacement, high-frequency oscillatory ventilation, and inhaled nitric oxide, the use of ECMO has decreased significantly (e.g., Hintz, Suttner, Sheehan, Rhine, & Van Meurs, 2000; Roy et al., 2000).

The ECMO Procedure

After conventional therapies have been exhausted, a number of criteria determine whether or not an individual will receive ECMO. Each ECMO center develops its own criteria; however, there is typically substantial overlap. ECMO is generally restricted to infants with a gestational age of 34 weeks or greater, although some centers have lowered this age to 32 weeks (the risk of intracranial hemorrhage increases significantly with decreased gestational age). Birth weight is recommended to be over 2000 grams. Infants with an intracranial hemorrhage (particularly of grade II or greater) are excluded, given the significant risk of bleeding. Intracranial hemorrhage of grade I is not thought to progress significantly to grade II or higher during ECMO and therefore is not considered to be a contraindication (Radack & Baumgart, 1994). Any other active bleeding or coagulation problems are a concern and are dealt with prior to ECMO initiation. Congenital anomalies, especially those considered to be associated with nonfavorable outcomes, are

usually a contraindication (Rais-Bahrami & Short, 2000). Some reports, for example, indicate that children with Down Syndrome, although they appear to be as likely to survive to the end of ECMO treatment as children without Down Syndrome, may have a higher mortality rate following treatment, perhaps due to other complications of the genetic disorder (e.g., Southgate, Annibale, Hulsey, & Purhoit, 2001). However, one report found that infants with Down Syndrome have been successfully treated with ECMO and had survival rates comparable to children without Down Syndrome following repair of congenital heart disease (Klein, Shaheen, Whittlesey, Pinsky, & Arciniegas, 1990). The overall numbers of children with Down Syndrome who are treated with ECMO therapy have been increasing since the beginning of the 1990s, which may reflect belief in the effectiveness of ECMO and/or a greater expectation for a positive quality of life for these children (Southgate et al., 2001).

Congenital heart disease should be ruled out prior to EMCO initiation. Infants are rarely considered for ECMO therapy if they have received more than 10-14 days of mechanical ventilation (Anthony & Hardee, 2000; Bartlett, 1989; Cullen, 1990; Hagedorn et al., 2002; National Institutes of Health, 1990; Ortiz et al., 1987; Rais-Bahrami & Short, 2000). Finally, a new study appears to suggest that pertussis may be a relative contraindication for ECMO treatment (e.g., Halasa, Barr, Johnson, & Edwards, 2003).

After these criteria have been evaluated, infants who display deterioration (as evidenced by criteria such as their oxygenation index), are suffering from potentially reversible respiratory problems, and are believed to have a very low survival rate (by some standards, an 80% mortality rate, based on their blood gases) despite the aggressive conventional therapies they have been receiving are considered for ECMO therapy (Hagedorn et al., 2002; Ortiz et al., 1987; Rais-Bahrami & Short, 2000).

The ECMO procedure has changed over the years. Initially, the approach was venoarterial (VA). In this procedure, a catheter is placed in the right internal jugular vein and is advanced to the right atrium. A second catheter is placed in the right common carotid artery and into the aortic arch. Following ECMO, the right carotid artery and right jugular vein are permanently ligated, because repair of the artery runs the risk of formation of clots that could proceed to the brain (Ortiz et al., 1987). Recently, a switch was made to using a venovenous (VV) approach, where a single double lumen catheter is placed into the right atrium via the right jugular vein. This approach has the advantage of sparing the carotid artery and maintaining the intactness of the jugular vein (it does not need to be tied off after ECMO is discontinued) and also maintains the normal blood flow (Cullen, 1990; Durandy, Chevalier, & Lecompte, 1989; Ortiz et al., 1987; Rais-Bahrami & Short, 2000; Sarioglu, McGahren & Rodgers, 2000; Shanley et al., 1994; Somme & Liu, 2001; Zahraa et al., 2000; Zwischenberger and Bartlett, 1995). Initial reports described comparable outcomes for VV versus VA despite longer times for operations and some complications (e.g., Klein, Andrews, Wesley, Toomasian, Nixon, Roloff, & Bartlett,1985). The use of VV ECMO increased significantly over the 1990s, as a study by Roy and colleagues demonstrated (2000). Comparison of the VV and VA procedures for infants with CDH by Dimmitt and colleagues (2001) suggested an increased incidence of neurological complications with VA yet similar survival rates. The VA procedure continues to be used when there is cardiac involvement (and often with older children and/or adults who are undergoing cardiac surgery).

Other changes to the general procedure of ECMO include an increase in the number of hours the child can be treated (which is believed to be most affected by diagnosis). What has not changed over the years has been the average gestational age of children

(about 38 weeks), age at start of ECMO (about 49 hr), and the oxygenation level/blood gas indices that are used to determine the need for ECMO (pH about 7.4, $paCO_2$ about 39; Roy et al., 2000).

Prior to insertion of the catheter, heparin administration is begun and continuously infused for the duration of the time the infant is on ECMO to prevent clotting (Muntean, 1999). Blood from the right atrium is passed out of the infant's body into a modified heart-lung machine. The ECMO machine consists of a blood pump, a membrane lung where carbon dioxide is removed and the blood is oxygenated, and a heater to return the blood to body temperature before it is returned to the infant's venous circulation (Ortiz et al., 1987). Drug-induced paralysis is begun prior to placement of the ECMO catheters; however, once the system is in place, the infant is allowed to awaken, and paralyzing agents are decreased. Medication for sedation and pain, as well as parenteral nutrition, are provided intravenously. Sedation is needed not only to keep the infant still but also to decrease the amount of oxygen required by the muscles during treatment. The amount of blood flowing through the ECMO machine (flow rate) is decreased gradually as the infant's condition improves. Blood work, administration of antibiotics, constant monitoring of vital signs, frequent ultrasounds of the brain to check for hemorrhages, and other necessary procedures are performed as deemed appropriate by the ECMO center (Bartlett, 1989; Braden, 2002; Rais-Bahrami & Short, 2000; Short, 1989; Zwischenberger & Bartlett, 1995). A photograph of a sample ECMO machine is shown in Figure 1.

Most infants will remain on ECMO for a period of several days (averaging 6-13 days, depending on their diagnoses). The flow of the blood from and into the body will gradually be decreased. Finally, a "trial" off of ECMO will be conducted to determine if the infant's lungs are ready to function independently. Following ECMO, most infants

are able to be weaned from mechanical ventilation (Rais-Bahrami & Short, 2000). The period of rest provided by ECMO allows for the ventilators to be turned down to a lower setting and provides a chance for the lungs to heal (Anthony & Hardee, 2000; Braden, 2002; Hagedorn et al., 2002; Ortiz et al., 1987; Short, 1989).

Potential Complications and Survival Rates

There are a number of complications that can arise during the ECMO procedure. Many of them are believed to be a result of the continuous use of heparin to prevent blood clots, but some complications may also be due to the ligation of the major blood vessels or a change in the blood flow (especially in the VA procedure) or a decrease in the number of blood platelets (thrombocytopenia).

Potential complications can include intracranial hemorrhage, hemorrhage elsewhere (especially at the site of the catheter or cannula), infection, seizures, failure to wean from ECMO (potentially due to an undiagnosed cardiac problem), renal failure (usually transient), cardiac arrest, hypertension, hearing loss, and complications resulting from the underlying diagnosis for which the infant was placed on ECMO. Jacobs and colleagues (1997) reported on one patient with a pseudoaneurysm of the carotid artery following ECMO. In addition to the complications listed above, mechanical failure can occur, including failure of the oxygenator and complications arising from placement or removal of the catheter (Bartlett, 1989; Becker, Short, & Martin, 1998; Bennett, Johnson, & Field, 2002; Cheung, Haluschak, Finer, & Robertson, 1996; Hagedorn et al., 2002; Muntean, 1999; Ortiz et al., 1987; Radack & Baumgart, 1994; Rais-Bahrami & Short, 2000; Short, 1989; Sweitzer, Lowry, Georgeson, Nelson, & Johnson, 1997; Rasheed, Tindall, Cueny, Klein, & Delaney-Black, 2001). Roy and colleagues (2000) examined

some of the overall rates of complications following ECMO for the years 1988 to 1998, using the Extracorporeal Life Support Organization Registry database. When looking at the absolute value of mortality rates, they discovered an increase (18%-22%) but determined that this reflected an increase in the number of children with CDH who were treated with ECMO. The percentages of children developing intracranial hemorrhages following ECMO remained constant. Wolfson (2003) reported an overall incidence of neurodevelopmental disabilities at 15-20%.

One other complication is not mentioned as frequently in the literature but is no less deserving of attention and consideration. In 2003, the number of ECMO centers was reported to be approximately 100, mostly in the United States (Wolfson, 2003). The scarcity of ECMO centers is due to the immense cost and training required-ECMO is a very complicated and laborious procedure and requires a significant amount of nursing and physician hours both before (training) and during (monitoring of infants is conducted around the clock; Goodridge, 1988). The small number of centers that perform ECMO often results in parents and children having to travel great distances to be together during the procedure. This results in great emotional, financial, and physical burdens on the family members (Cullen, 1990). The decision to approve ECMO for a child is often one that parents must make quickly, and the mother may still be hospitalized (Goodridge, 1988). Previous research has examined the health-related quality of life for children who received ECMO at The Children's Hospital of Alabama and quality of life of their parents. Findings suggested that the children's quality of life (as reported by their parents) ranked between children with chronic health conditions (i.e., diabetes or asthma) and that of typically developing same-age peers (Rector, 2003).

Of infants who received ECMO, survival rates are impressive. In fact, survival rates for infants versus pediatric patients or adults who received ECMO are usually much higher, given the lack of a chronic disease process prior to ECMO initiation (Thakar, Sinha, & Wenker, 2001). Bennett et al. (2002) reported on a randomized controlled trial comparing ECMO use with conventional care between the years of 1993-1995. Children in the ECMO group showed improved survival rates compared with controls as well as a lower proportion of disabilities. O'Rourke and colleagues (1989) conducted a prospective, randomized study of infants treated with ECMO versus conventional medical treatment (prior to the introduction of High Frequency Oscillatory Ventilation and inhaled Nitric Oxide) and found an increased rate of survival (97% versus 60%, respectively) for the ECMO group. One study conducted in Michigan described an association between increased use of ECMO in the 1980s and 1990s and a decreased neonatal mortality rate (Campbell, Braun, Schumacher, Bartlett, & Hirschl, 2003). In the state of Georgia, Southgate and colleagues predicted a decrease in infant mortality rate of 1.4% over a two year period (Southgate, Howell, & Kanto, 1990). The ECMO Registry (a database of all patients treated with ECMO), created and maintained by the Extracorporeal Life Support Organization, reported that between 1980 and 1995, there were 10,391 cases of neonatal ECMO. Of those cases, an 80% survival rate is reported. Wolfson (2003) reported an overall survival rate (of the 17,000 reported cases since 1974 to the time of his study) as 78%. Survival rates vary depending on the pre-ECMO diagnosis, and range from 94% for MAS to 58% for CDH (Extracorporeal Life Support Organization Registry, 2002). Reports elsewhere have yielded similar rates, with the lowest and highest rates for infants with CDH and MAS, respectively (Anthony & Hardee, 2000; P. J. Davis & Shekerdemian, 2001; Hagedorn et al., 2002; Muratore & Wilson, 2000; Ortiz et al., 1987; Rais-

Bahrami & Short, 2000; Roy et al., 2000; Shanley et al., 1994; Thakar et al., 2001; UK [United Kingdom] Collaborative ECMO Group, 1998; Wolfson, 2003).

Cognitive Abilities

Although numerous studies on neonatal EMCO provide survival statistics (e.g., the Extracorporeal Life Support Organization Registry), very few have examined long-term developmental outcomes, including cognitive abilities. Even fewer have used a large sample size. This may be due in part to the difficulty in tracking subjects following hospital discharge. In fact, prior to 1990, very few studies examined cognitive abilities at all (D. W. Davis, 1998).

A study conducted among 31 ECMO survivors at 6 months and 1 year of age found largely average scores on the Bayley Scales of Infant Development (BSID; 77% at 6 months and 86% at 12 months had scores in the average range; Lago et al., 1995). In the United Kingdom (UK Collaborative ECMO Group, 1998), 63 out of 92 children had survived to the age of 1year, and 57 of that number were scoring within the expected range on the Griffiths Mental Development Scales (i.e., a Developmental Quotient score of 85 or greater), compared with 34 of 92 who received conventional treatments (non-ECMO). Hofkosh and colleagues (1991) also conducted a study using the Bayley Scales and Stanford-Binet and found mean developmental scores within the average range.

Wildin, Landry, and Zwischenberger (1994) followed 22 infants who received ECMO through their second birthday. Significant differences were found between ECMO survivors and healthy controls on a language measure (the Sequenced Inventory for Communication Development) on both the Expressive and Receptive subtests. Scores

on the BSID for the ECMO survivors were within the average range; however, they were significantly lower than scores received by the healthy controls at the same age.

A study by Andrews and colleagues reported on 14 children ages 1 through 3 years old who had all survived ECMO (Andrews, Nixon, Cilley, Roloff, & Bartlett, 1986). Children were assessed with the BSID. Results indicated that 64% (n = 9) of the children scored within normal limits on the motor scale, and 71% (n = 10) scored within normal limits on the mental scale. Other studies assessing children under the age of 3 years found similar results (Adolph et al, 1990; Bennett, Johnson, Field, & Elbourne, 2001; D. W. Davis, 1998; Glass, Miller, & Short, 1989). However, although children who received ECMO were usually scoring within the expected ranges on developmental assessments, a general trend seems to be that they were often scoring below (sometimes significantly below) their healthy peers.

In one large study, Glass and colleagues (1995) assessed 102 five-year-olds who had received neonatal ECMO and found that the rate of major disability was 17%. Scores for the children who received ECMO on the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R) were within the expected range; however, they were significantly lower than 37 same-age healthy controls. In addition, parents indicated problems with behavior and increased risk of school failure. In a separate study, a sample of 7- to 9-year-olds suggested increased incidence of attention and memory problems (D. W. Davis, 1998). Langenbacher, Nield, & Kanne Poulson (2001) described a sample of 52 ECMO survivors who underwent extensive batteries of testing at age 5 years. Sixty-two percent of the sample received scores within the average range. However, there were potential subtle signs for later difficulties or future learning disabilities in 13 subjects, as evidenced by significantly lower subtests in areas testing nonverbal cogni-

tion. In addition, 11 of the children in the sample presented with significant behavioral concerns on at least one subscale of the Child Behavior Checklist. Recommendations were made that children who received neonatal ECMO should be reevaluated in the second or third grade, when it is generally easier to assess learning disabilities.

Rais-Bahrami, Short, Wagner, Coffman, and Glass (2000) also examined neurodevelopmental status in 5-year-olds who received neonatal ECMO ($n = 76$) and compared them to same-age peers who were considered for ECMO but did not receive it (near-miss ECMO; $n = 20$). Cognitive and behavioral outcomes were similar for both groups (mean estimated Full Scale IQ on WPPSI-R short form = 97 for ECMO survivors). Again, the recommendation was made to more closely follow these children as they enter grade school, because 38% were considered to be "at-risk" for school failure based on scores on the WPPSI-R or achievement testing.

A cross-sectional study of ECMO survivors between the ages of 6 months and 10 years of age found normal outcomes in 64% overall. Average cognitive or developmental scores were within the average range for all ages. However, the sample consisted of 47 infants (from 6-30 months of age), 10 preschoolers (2.7 to 4.11 years), and 10 school-aged children (5-10 years), and therefore statistical power was likely lacking for the older children (Hofkosh et al., 1991).

Ilke et al. (1999) reported on a group of children between the ages of 5 to 8 years. They found that 5 of 17 children in their study showed statistically significant discrepancies between Verbal IQ (VIQ) and Performance IQ (PIQ) scores (three had VIQ > PIQ; two had PIQ > VIQ). In addition, 12 children from their sample had subtest scores that differed significantly from the mean of their subtest scores. Separate studies have also

found similar results (i.e., discrepancies between VIQ and PIQ), as well as increased rates of scatter among subtest scores (Ilke et al., 1999).

One concern when evaluating the results of the above studies is that many of the subjects received VA ECMO, which requires ligation of the right common carotid artery and the jugular vein. This may result in a different pattern of results than the VV ECMO procedure. Overall, studies have found rates of disabilities in ECMO survivors to be around 20-40% (Davis, 1998; Rais-Bahrami, Short, Wagner, Coffman, & Glass, 2000; Wildin et al., 1994); however, it is not possible to know if one of the procedures differentially accounts for this rate. The studies mentioned above have also been hampered by relatively small sample sizes, which greatly limits statistical power and the ability to interpret findings.

Finally, few studies have separated subjects based on their initial diagnosis. One study that did do so found that children with CDH tended to have a greater number of developmental problems during the first year of life (Bernbaum et al., 1995). This study only followed the children to the age of 1 year, however.

Specific Aims of the Current Study

In this study, the cognitive abilities of survivors of ECMO were examined to determine if their pre-ECMO diagnosis (i.e., sepsis and MAS) resulted in a different pattern of cognitive abilities. Second, variables such as type of ECMO and length of time on ECMO were examined. The main goal of the study was to examine and describe the cognitive development of a large number of ECMO survivors, which has previously not been accomplished in the literature.

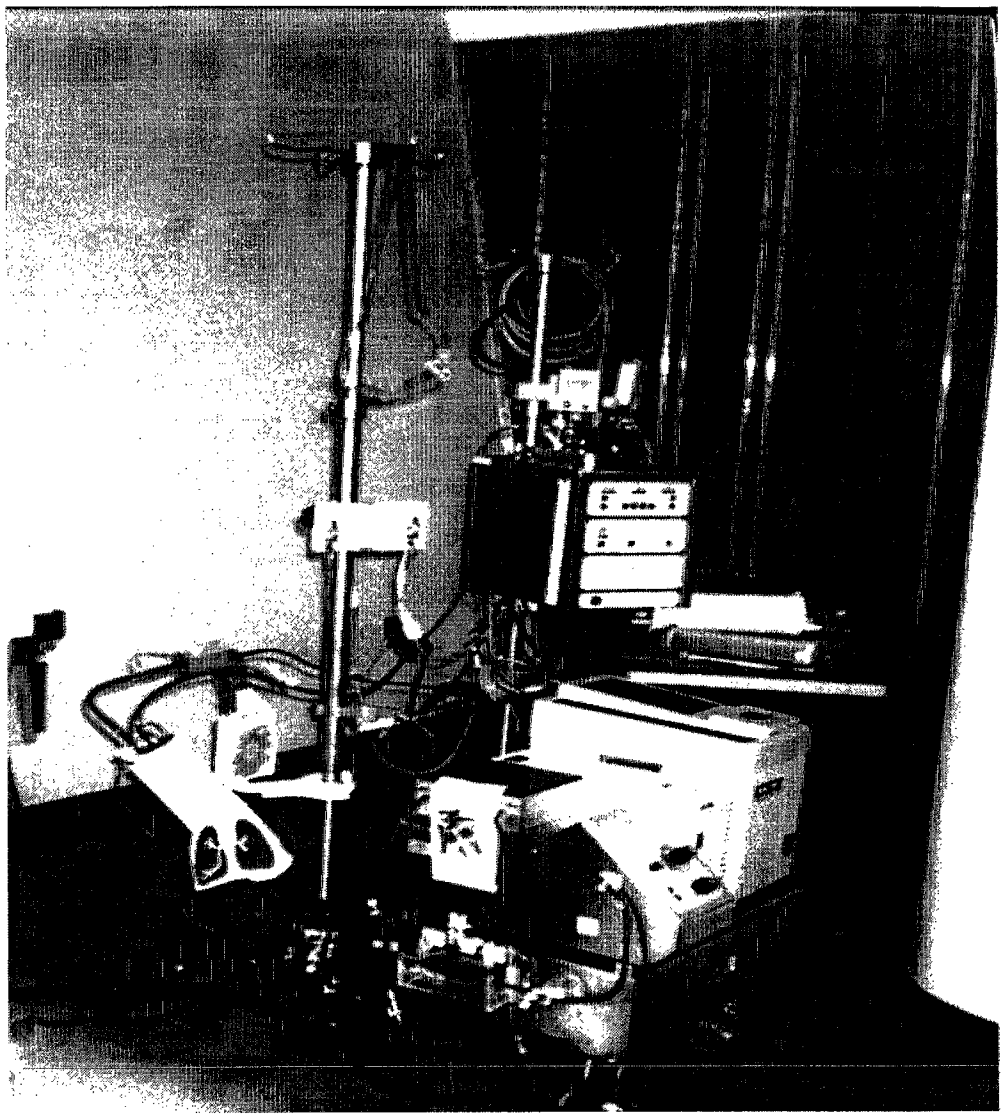

Figure 1. Sample Extracorporeal Membrane Oxygenation (ECMO) machine (blood pump, membrane lung, and heater).

METHODS AND DESIGN

Subjects

Subjects included 322 infants who were treated with ECMO at The Children's Hospital of Alabama in Birmingham throughout the past 16 years. Subjects were followed through the hospital's Newborn Follow Up Clinic, where they received periodic medical, developmental, occupational therapy, physical therapy, hearing, vision, and nursing screenings. Ages of subjects at the time of developmental assessments ranged from 12 months to 6 years. Racial and gender compositions of the sample at the time of each assessment are shown in Table 1.

Table 1

Racial and Gender Characteristics of Sample, by Age

	Race			Gender	
Age	Black	White	Other	Male	Female
1 year	102	135	3	134	106
2 year	48	69	1	68	50
4 year	41	51	1	51	42

Procedure

In accordance with guidelines established by the University of Alabama at Birmingham Graduate School, this study received expedited review from the University Institutional Review Board for Human Use (protocol X021220019) and was approved on

January 3, 2003. Reapproval was received on March 15, 2004. Forms for approval as well as the UAB Institutional Review Board for Human Use Approval of Waiver of Authorization/Waiver of Informed Consent are located in the Appendix.

This study analyzed cognitive and demographic data collected by the Newborn Follow Up Clinic from periodic visits made by the children and their caregivers. Cognitive tests administered include BSID-I or BSID-II at 1year of age (Bayley, 1969, 1993), the Differential Ability Scales (DAS) at 2½ and 4 years of age (Elliot, 1983), and either the Wechsler Intelligence Scale for Children–Revised Edition (WISC-R) or Third Edition (WISC-III) at 6 years of age (Wechsler, 1974, 1991).

Table 2

Measures Administered, by Age Group

Test administered	Age (years)
Bayley Scales of Infant Development	1
Differential Ability Scales	2½
Differential Ability Scales	4
Wechsler Intelligence Test for Children	6

The BSID is a standardized assessment designed to provide an overall view of a child's current developmental functioning. The BSID consists of two separate scales: the Mental Scale and the Psychomotor Scale. Administration of each scale results in a standard score (M = 100, SD = 15). The DAS is an individually administered, standardized measure of general cognitive ability and provides an estimate of global intellectual functioning, as well as information pertaining to specific abilities. Scores resulting from ad-

ministration of the DAS include the General Conceptual Ability standard score (GCA), a nonverbal score (Special Nonverbal Composite at 2½ years and Nonverbal Composite at 4 years), and a Verbal Composite at 4 years. The WISC-III (and WISC-R before it) is a standardized, individually administered assessment used in order to provide a measure of a child's general cognitive abilities. It yields an overall IQ standard score (Full Scale IQ) which is determined from the child's performance on a number of subtests which are each thought to measure a somewhat different aspect of intelligence. It also yields a PIQ which pertains to nonverbal skills, as well as a VIQ score which pertains to more verbal abilities.

Variables collected were coded as they were entered into the database. The variables of race and gender were coded as follows: for race, 1 = African-American or Other, 2 = Caucasian; for gender, 1 = male, 2 = female. Type of ECMO was coded as either 1 for VV ECMO or 2 for VA ECMO. Other variables such as mother's age, father's age, birth weight, and gestational age, were entered as both continuous and categorical.

Data Analysis

Preliminary Analyses

The general demographic information that was collected, including gestational age, apgar scores, birth weight, and parental age, is presented in Table 3.

Frequencies of ECMO by year of birth (through 2003) are presented in Figure 2. Socio-economic status was assessed by asking for household income in one of the following categories: < $5,000 ($n$ = 40), $5,000-$10,000 (n = 31), $10,000-$20,000 (n = 63), or > $20,000 ($n$ = 119). In addition, while subjects were attending follow-up clinic appoint

Table 3

Demographic Characteristics of the Sample

	N	Range	Mean
Mother's age (years)	284	13-46	26.36
Father's age (years)	230	12-59	28.62
Gestational age (weeks)	312	29-44	38.86
Birth weight (grams)	310	1193-5580	3343.15
1 min Apgar	288	0-9	5.36
5 min Apgar	289	1-10	7.21
10 min Apgar	34	2-10	6.76

ments, it was noted by clinic staff if there were any major handicaps with which the child had been diagnosed (e.g., mental retardation, cerebral palsy, hearing loss) and if there were any developmental concerns. Of the 322 children in the study, only 41 (12.74%) were identified in clinic records as having any form of major handicap. Mental retardation was the most frequent major handicap identified in children in the sample. 25 children (7.8% of the subjects) were identified in clinic records as having a form of mental retardation. Cerebral palsy was the second most commonly identified major handicap. Twenty children (6.2% of the subjects) were identified in clinic records as having some type of cerebral palsy. Other diagnoses included hearing loss (5 children, 1.6%), failure to thrive (4 children, 1.2%), and blindness (1 child, 0.3%). General developmental concerns (e.g., attention problems) were identified in 57 (17.70%) children (see Figure 3).

Children were identified as having had VV ECMO, VA ECMO, or both (in these cases, at some point during the procedure a switch was made from venovenous to venoarterial). In the present study, the specific type of ECMO received was recorded for 285 children (of the total sample of 322). Of these 285, 91 were treated with venovenous,

183 were treated with venoarterial, and 11 began with venovenous and switched to venoarterial (see Figure 4).

Records were also kept as to the age (in hours) of the children when ECMO was initiated. Of the 262 children for whom this information was available, mean age (in hours) of ECMO initiation was 67.18 (range = 4-458 hr). Of the 264 children for whom information regarding duration of ECMO was available, mean length of time on ECMO was 179.53 hr (range = 16-830 hr).

Main Analyses

Databases were collected from two different sources: The Children's Hospital of Alabama Neonatal Intensive Care Unit and the Newborn Follow Up Clinic. The two databases were merged for a total of 322 potential subjects.

Subjects were divided into groups based on their initial diagnosis (e.g., PPHN, MAS, CDH, Sepsis, PFC, or Other). In order to facilitate comparisons, groups were condensed by theoretical and medical considerations. Initially, the groups were combined as follows: PPHN and PFC (group one); MAS, Sepsis, and Other (group two); and CDH (group three). Given that PFC as a diagnosis has been changed in the medical literature to PPHN, these two groups were combined.

Further, as stated above, children with CDH are often the most physically affected by their diagnoses (and have the lowest survival rates) and therefore would appear to be most at risk for serious problems due to related outcomes. Therefore, subjects with this diagnosis were placed in a separate category. The original and resulting categories are displayed in Table 4.

Table 4
Original and Resulting Diagnostic Categories for Analyses

Original categories		New categories	
Diagnosis	*N*	Group	*n*
PPHN	67	PPHN/PFC	92
MAS	113	MAS/Sepsis/Other	180
CDH	36	CDH	36
Sepsis	50		
PFC	25		
Other	17		

Note. PPHN = Persistent Pulmonary Hypertension of the Newborn; MAS = Meconium Aspiration Syndrome; CDH = Congenital Diaphragmatic Hernia; PFC = Persistent Fetal Circulation.

Within the dataset, a large number of data points were missing. Missing data within analyses often result in decreased statistical power and increased error rates. Several options exist for dealing with missing data, including listwise deletion, plugging in means for each variable, or treating the fact that the data are missing as one aspect of the research findings (Chen & Astebro, 2003; Cohen & Cohen, 1983). However, a relatively new technique has been proposed and used with some success–Expectation Maximization. This procedure has been described as comparable to other missing data techniques and is relatively simple to implement in many standard computer statistical packages. Expectation Maximization defines a model for missing data and bases inferences on the likelihood under that model. The process is iterative and uses cases with data to estimate the missing values. These values are then used to calculate new parameters for the dataset, and the process is repeated until the parameters converge (Chen & Astebro, 2003; Schafer & Graham, 2002; Rovine & Delaney, 1990). The Expectation Maximization procedure was used in order to estimate missing values for the 1-year-old group. The 1-year dataset started out with 11.93% missing values. Of the 322 potential subjects (at 1

year of age), only 163 had no missing values on the variables of interest. Using LISREL (Version 8.54, Student Edition), the following variables were imputed: Age at start of ECMO, Duration of ECMO, Birth weight, Gestational Age, Mother's Age, Race, Sex, Type of ECMO, Diagnosis, Income, BSID Mental score, BSID Motor score, and Apgar scores at 1 and 5 min. The number of different missing patterns calculated prior to data imputation was 62. The Expectation Maximization algorithm converged in two iterations [-2 Ln(L) = 21605.40286].

Given the small number of children who returned for a two-year visit to receive the BSID or the 6-year visit to receive the WISC-III, these subjects were not included in any further analyses. Two of the variables, Age at start of ECMO and Duration of ECMO, were observed to be negatively skewed. Therefore, these variables were transformed using a log function. Although at 2½ years a language score is not typically calculated for the DAS, prior research had suggested the possibility of language delays for children who receive ECMO (e.g., Wilden et al., 1994). Therefore, a Verbal score was calculated for this age group, using norms created for the 3½-year-old children in the standardization sample. This score provided evaluators with a rough estimate of the child's language abilities at age 2½ years.

For each of the remaining age ranges (1 year, 2½ years, and 4 years), correlations were calculated among the predictor and the outcome variables; significant correlations are presented in Table 5.

For all age groups, race was used as a covariate. For the 1-year age group (BSID Mental and Motor scales), mother's age and birthweight were both used as covariates, as was type of ECMO for the Motor scale. For the 2½- and 4-year age groups, income was

Table 5

Significant Correlations of Predictor Variables with Outcome Variables

Age	Outcome variable	Predictor variable	Correlation
1 year	BSID Mental	Age at Start (log)	-0.127*
		Duration (log)	-0.163**
		Birth weight	0.114*
		Gestational age	0.155**
		Mother's age	-0.133*
	BSID Motor	Duration (log)	-0.298**
		Birth weight	0.295**
		Gestational age	0.304**
		Type of ECMO	-0.236**
2½ year	DAS GCA	Race	0.376**
		Income	0.299**
	DAS Verbal (est)	Race	0.260**
	DAS Nonverbal	Race	0.332**
		Income	0.315**
		Age at start (log)	0.212*
4 year	DAS GCA	Race	0.256*
		Income	0.353**
	DAS Verbal	Race	0.367**
		Income	0.246*
	DAS Nonverbal	Birth weight	0.228*
		Income	0.270**

Note. BSID = Bayley Scales of Infant Development; DAS = Differential Ability Scales; GCA = General Conceptual Ability standard score; ECMO = Extracorporeal Membrane Oxygenation.
* $p < 0.05$, two-tailed. ** $p < 0.01$, two-tailed.

also used as a covariate. A table presenting the covariates used for each age range is shown in Table 6. Using SPSS GLM (Version 11.5), outcome variables for each age range were analyzed using ANCOVA.

Table 6

Covariates Used for Each Age Group, by Outcome Variable

Age	Outcome variable	Covariates
1 year	BSID Mental	Race
		Birthweight
		Mother's age
	BSID Motor	Race
		Mother's age
		Birthweight
		Type of ECMO
2½ year	DAS GCA	Race
		Income
	DAS Verbal (est)	Race
		Income
	DAS Nonverbal	Race
		Income
4 year	DAS GCA	Race
		Income
	DAS Verbal	Race
		Income
	DAS Nonverbal	Race
		Income

Note. BSID = Bayley Scales of Infant Development; DAS = Differential Ability Scales; GCA = General Conceptual Ability standard score; ECMO = Extracorporeal Membrane Oxygenation.

In addition to the aforementioned analyses, the database was also examined to determine exactly how many children had true longitudinal information available. There were a total of 11 children who had evaluations at each of the four potential time periods: 1 year (BSID), 2½ years (DAS), 4 years (DAS), and 6 years (WISC). Of these children, nine were Caucasian and two were African American. There were 7 males and 4 females. One child had received VV ECMO and the other 10 had received VA. Diagnoses of the children were as follows: PPHN (n = 1), MAS (n = 6), CDH (n = 1), Sepsis (n = 2),

and PFC (n = 1). There were no children in this subsample who had an original diagnosis that fell into the "Other" category.

Given that so few children returned to the clinic for their 6-year follow-up visit, a second longitudinal analysis was conducted by only including children who had scores on the first three of the four assessment times: 1 year, 2½ years, and 4 years. This resulted in a total of 66 children. Of this subsample, 40 were Caucasian and 25 were African American (1 was identified as "Other"). The male-female ratio was even at 33 each. Information regarding which type of ECMO the children had received was available for 59 of the 66 children. Eighteen had received VV ECMO, and forty-one had received VA (7 children did not have a type of ECMO identified). Diagnoses were as follows: PPHN (n = 9), MAS (n = 24), CDH (n = 10), Sepsis (n = 12), PFC (n = 5), and Other (n = 6).

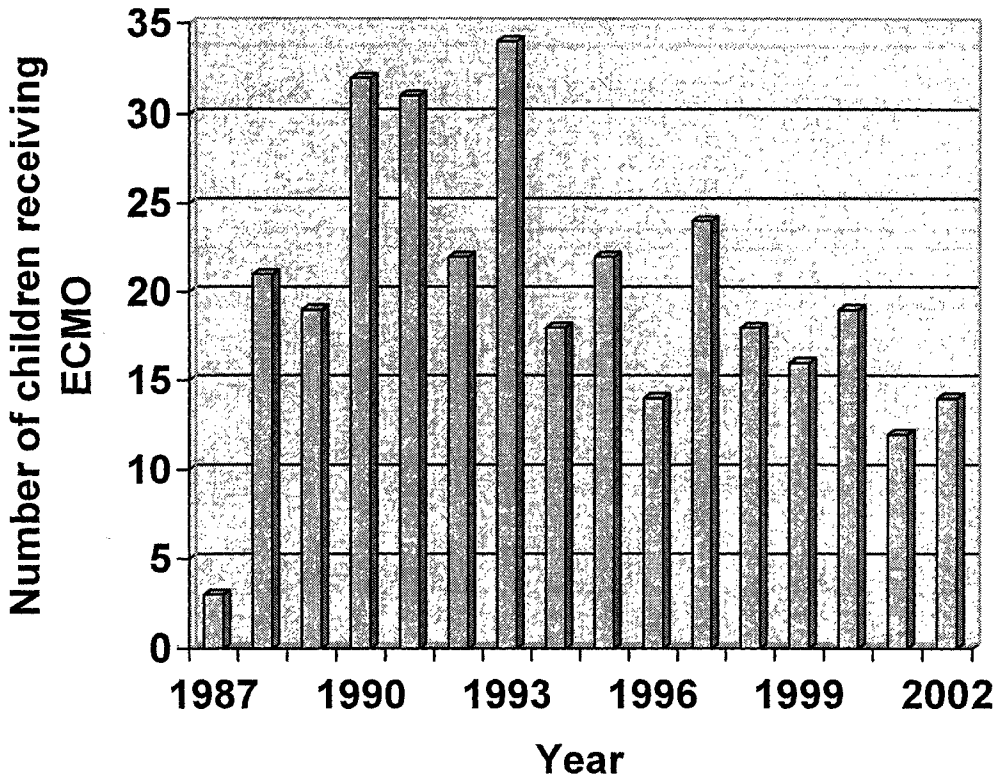

Figure 2. Frequency of Extracoporeal Membrane Oxygenation (ECMO) by year, 1987 through 2002.

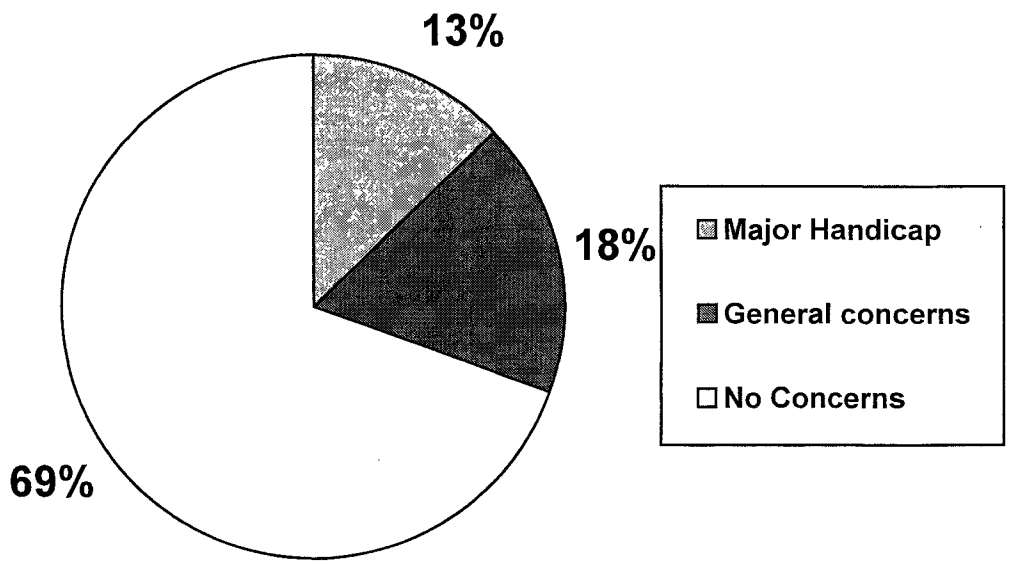

Figure 3. Rates of developmental concerns and major handicap, as identified by Newborn Follow Up clinic personnel.

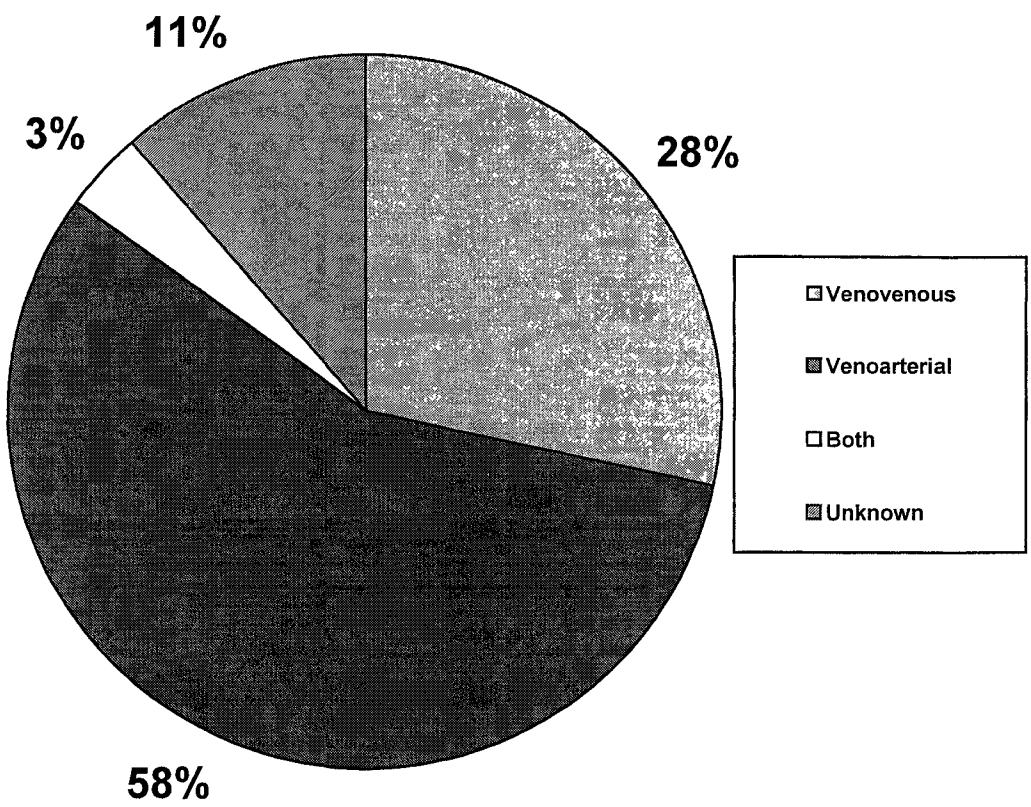

Figure 4. Type of Extracorporeal Membrane Oxygenation (ECMO) received.

RESULTS

Results are presented for each age group individually. Table 10 shows the overall significant findings for all ages. For ease of presentation, all figures are presented together at the end of this section.

One Year Olds

ANCOVA on the BSID Mental Scale yielded significance for Diagnosis, F (2,316) = 3.901, p = 0.021, and the covariates of Race, F (1,316) = 4.423, p = 0.036, and Mother's Age, F (1,316) = 7.802, p = 0.006. Birth weight did not reach significance.

ANCOVA performed on the BSID Motor Scale yielded significance for Diagnosis, F(2,315) = 3.804, p = 0.023. In addition, the following covariates reached significance: Type of ECMO, F (1,315) = 19.048, p = 0.000, Mother's Age, F (1,315) = 4.808, p = 0.029, and Birth weight, F (1,315) = 17.078, p = 0.000. Race was not significant in this analysis.

Means and standard deviations from the BSID Mental and Motor Scales for the 1-year-old analyses, by diagnosis group, are presented in Table 7, and overall mean scores for each scale of the BSID are presented in Figure 5.

Two-and-a-Half Year Olds

ANCOVA performed on the estimated Verbal score for the DAS using Race and Income as covariates yielded significance: Diagnosis, F (2,105) = 4.615, p = 0.012; Race,

Table 7

One-Year-Olds: Means and Standard Deviations of Assessments, by Diagnosis Group

Assessment	Diagnosis group	*n*	Mean	Adjusted means	SD
BSID Mental Scale	PPHN/PFC	92	95.196	95.037	17.506
	MAS/Sepsis/other	186	100.527	100.614	17.464
	CDH	44	95.409	95.372	16.929
	Total	322	98.304		17.545
BSID Motor Scale	PPHN/PFC	92	94.207	92.734	22.202
	MAS/Sepsis/other	186	97.737	97.511	20.567
	CDH	44	85.318	89.350	17.226
	Total	322	95.031		20.992

Note. PPHN = Persistent Pulmonary Hypertension of the Newborn; PFC = Persistent Fetal Circulation; MAS = Meconium Aspiration Syndrome; CDH = Congenital Diaphragmatic Hernia; BSID = Bayley Scales of Infant Development.

F (1,105) = 6.506, p = 0.012. Income was not significant.

ANCOVA performed on the overall GCA score for the DAS yielded significance for the covariates of Race, F (1,105) = 12.455, p = 0.001, and Income, F (1,105) = 4.958, p = 0.028. Diagnosis was not significant.

ANCOVA performed on the DAS Special Nonverbal Composite score yielded significance for the covariates of Race, F (1,105) = 8.486, p = 0.004, and Income, F (1,84) = 5.291, p = 0.023. Again, Diagnosis was not significant.

Means and standard deviations from the DAS for the 2½ -year-old analyses, by diagnosis group, are presented in Table 8, and overall means for the groups are presented graphically in Figure 6.

Table 8

2½-Year-Olds: Means and Standard Deviations of Assessments, by Diagnosis Group

Assessment	Diagnosis Group	*n*	Mean	Adjusted Means	SD
DAS GCA	PPHN/PFC	34	88.471	87.847	15.060
	MAS/Sepsis/other	65	91.600	92.713	11.313
	CDH	17	89.412	87.445	13.888
	Total	116	90.362		12.853
DAS Verbal (est)	PPHN/PFC	33	84.788	84.364	17.137
	MAS/Sepsis/other	67	91.582	92.327	10.853
	CDH	17	86.941	85.322	13.377
	Total	117	88.992		13.499
DAS Nonverbal	PPHN/PFC	34	94.382	93.524	17.286
	MAS/Sepsis/other	65	93.431	94.465	13.435
	CDH	17	93.941	91.994	15.586
	Total	116	93.784		14.838

Note. PPHN = Persistent Pulmonary Hypertension of the Newborn; PFC = Persistent Fetal Circulation; MAS = Meconium Aspiration Syndrome; CDH = Congenital Diaphragmatic Hernia; DAS = Differential Ability Scales; GCA = General Conceptual Ability standard score.

Four Year Olds

ANCOVA performed on the DAS overall GCA score using Race and Income as covariates yielded significance for Income, $F(1,87) = 9.817, p = 0.002$, and Diagnosis, $F(2,87) = 5.077, p = 0.008$, but race failed to reach significance.

ANCOVA performed on the DAS Verbal score using Race and Income as covariates yielded significance for Race, $F(1,84) = 12.515, p = 0.001$, and Diagnosis, $F(2,84) = 5.495, p = 0.006$. In this analysis, Income was not significant.

ANCOVA performed on the DAS Nonverbal score using Race and Income as covariates yielded significance for Income, $F(1,86) = 5.832, p = 0.018$. Diagnosis and Race were not significant.

Means and standard deviations from the DAS for the 4-year-old analyses, by diagnosis group, are presented in Table 9, and overall means for the groups are presented graphically in Figure 7.

Table 9

4-Year-Olds: Means and Standard Deviations of Assessments, By Diagnosis Group

Assessment	Diagnosis group	*n*	Mean	Adjusted Means	SD
DAS GCA	PPHN/PFC	23	79.870	79.426	19.330
	MAS/Sepsis/other	57	89.211	89.793	12.661
	CDH	13	83.923	83.905	13.744
	Total	93	86.161		15.098
DAS Verbal	PPHN/PFC	22	85.136	84.784	16.034
	MAS/Sepsis/other	55	92.182	92.975	12.520
	CDH	13	84.462	83.238	11.983
	Total	90	89.344		13.710
DAS Nonverbal	PPHN/PFC	22	84.955	84.280	18.464
	MAS/Sepsis/other	56	89.786	90.307	13.615
	CDH	14	84.714	85.069	16.448
	Total	92	87.859		15.336

Note. PPHN = Persistent Pulmonary Hypertension of the Newborn; PFC = Persistent Fetal Circulation; MAS = Meconium Aspiration Syndrome; CDH = Congenital Diaphragmatic Hernia; DAS = Differential Ability Scales; GCA = General Conceptual Ability standard score.

Table 10.
ANCOVA Significant Findings

Assessment (Age)	Source	Type III Sum of Squares	df	Mean square	*F*	Significance	Eta squared
BSID Mental (1year)	Diagnosis	2291.242	2	1145.621	3.901	0.021	0.024
	Race	1298.838	1	1298.838	4.423	0.036	0.014
	Mother's age	2290.942	1	2290.942	7.802	0.006	0.024
BSID Motor (2year)	Diagnosis	2922.982	2	1461.491	3.804	0.023	0.024
	Birth weight	6561.929	1	6561.929	17.078	0.000	0.051
	Mother's Age	1847.454	1	1847.454	4.808	0.029	0.015
	Type of ECMO	7318.977	1	7318.977	19.048	0.000	0.057
DAS GCA (2½year)	Race	1728.360	1	1728.360	12.455	0.001	0.106
	Income	687.959	1	687.959	4.958	0.028	0.045
DAS Verbal (2½year)	Race	1071.907	1	1071.907	6.506	0.012	0.058
	Diagnosis	1520.739	2	760.369	4.615	0.012	0.081
DAS Nonverbal (2½year)	Race	1629.326	1	1629.326	8.486	0.004	0.075
	Income	1015.855	1	1015.855	5.291	0.023	0.048

Note. ANCOVA = Analysis of Covariance; BSID = Bayley Scales of Infant Development; DAS = Differential Ability Scales; GCA = General Conceptual Ability standard score; ECMO = Extracorporeal Membrane Oxygenation; df = degrees of freedom; F =Fisher's F ratio.

Table 10 (continued).
ANCOVA Significant Findings

Assessment (Age)	Source	Type III Sum of Squares	df	Mean square	*F*	Significance	Eta squared
DAS GCA (4year)	Income	1777.195	1	1777.195	9.817	0.002	0.101
	Diagnosis	1838.016	2	919.008	5.077	0.008	0.105
DAS Verbal (4year)	Race	1844.794	1	1844.794	12.515	0.001	0.130
	Diagnosis	1620.011	2	810.006	5.495	0.006	0.116
DAS Nonverbal (4year)	Income	1276.580	1	1276.580	5.832	0.018	0.064

Note. ANCOVA = Analysis of Covariance; DAS = Differential Ability Scales; GCA = General Conceptual Ability standard score; ECMO = Extracorporeal Membrane Oxygenation; df = degrees of freedom; F =Fisher's F ratio.

Longitudinal Examination of Scores

For the first longitudinal examination, consisting of 11 children who had scores for each of the four assessment points, means for each of the measures are presented below in table 11. Overall scores for this first longitudinal group for each of the measures are presented graphically in Figure 8.

Table 11
Means of Assessment for 11 Children With Longitudinal Data (Ages 1-6)

Measure	Mean	SD	Minimum	Maximum
Bayley Mental	114.73	17.52	86	137
Bayley Motor	93.45	20.78	55	115
DAS GCA	93.82	12.89	70	112
DAS est. Verbal	92.73	12.51	70	106
DAS Nonverbal	95.91	16.03	76	122
DAS GCA	90.64	13.44	70	109
DAS Verbal	93.82	12.82	73	114
DAS Nonverbal	91.27	12.85	73	115
WISC FSIQ	85.09	9.82	65	101
WISC VIQ	85.91	10.23	69	106
WISC PIQ	86.82	10.36	64	100

Note. DAS = Differential Ability Scales; GCA = General Conceptual Ability standard score; WISC = Wechsler Intelligence Scale for Children; FSIQ = Full Scale IQ standard score; VIQ = Verbal IQ standard score; PIQ = Performance IQ standard score.

The second longitudinal evaluation consisted of 66 children who had data for each of the first three assessment points. Means for this group are presented in table format and graphically (Table 12 and Figure 9).

Table 12
Means of Assessment for 66 Children With Longitudinal Data (Ages 1-4)

Measure	Mean	SD	Minimum	Maximum
Bayley Mental	101.80	18.25	54	142
Bayley Motor	96.30	21.41	49	145
DAS GCA	91.80	12.70	67	125
DAS Nonverbal	94.36	14.45	71	131
DAS GCA	88.44	14.06	53	120
DAS Verbal	90.44	13.77	60	122
DAS Nonverbal	89.20	15.45	50	129

Note. DAS = Differential Ability Scales; GCA = General Conceptual Ability standard score.

Post-Hoc Analyses

In order to determine if an idiosyncrasy related to the combining of the different diagnoses (i.e., PPHN/PFC, MAS/Sepsis/Other, and CDH) was differentially responsible for the effects found, the groups were recombined. Groups were recombined as follows: PPHN/PFC/MAS, Sepsis/Other, and CDH, given medical considerations that children with Sepsis and CDH may have many more health problems and be more ill overall than children with PPHN, PFC, and MAS. Analyses were run with the new groupings. For the estimated Verbal score for the 2½-year DAS, the Verbal score for the 4-year DAS, and the overall GCA for the 4-year DAS, diagnosis was no longer significant.

An ANOVA was done examining the demographic information to look for differences between children who did return for follow-up appointments and those who did not. Of the 322 children who received ECMO, 71 did not return for follow-up appointments. Four of these children were reported as having passed away before hospital discharge (three were diagnosed with CDH, one was diagnosed with MAS). Two hundred and fifty-one children returned for at least one follow-up visit. Of these children, one (di-

agnosis of MAS) was reported as having passed away (after the 1-year follow-up visit). The only significant difference noted when comparing the demographic information between the two groups was for diagnosis of major handicap, $F(1,307) = 6.007$, $p = 0.015$. Of the children who did not return for follow-up visits, 3 of the 71 (4.41%) were reported as having a major handicap by clinic personnel. Of the children who did return for follow-up visits, 38 of the 251 were reported as having a major handicap by clinic personnel; this number is largely comparable with previous reports in the literature, indicating that the sample for this study is similar to other ECMO populations.

Finally, in order to determine if apgar scores would be a more effective predictor than the covariates used, analyses were rerun using these scores. Apgar scores were not found to be related to the findings described above.

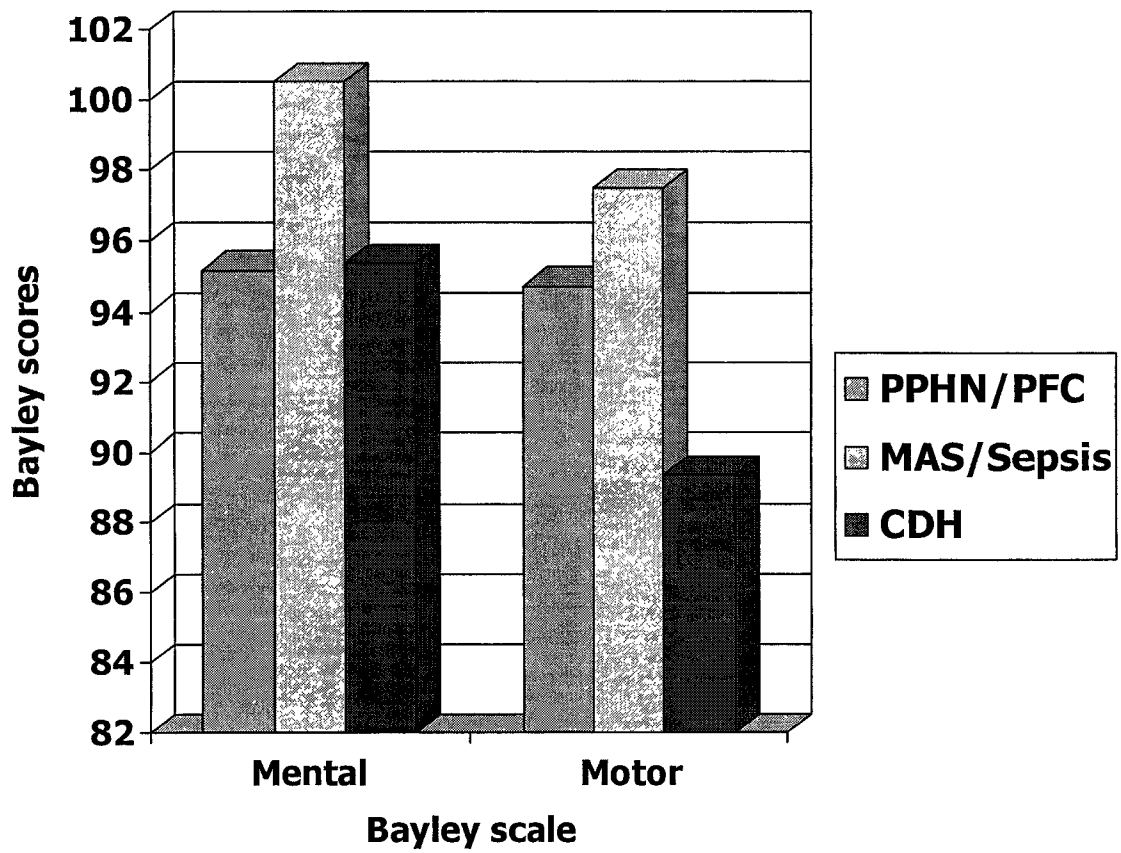

Figure 5. One-year-olds: Overall means of assessments, by diagnosis group. PPHN = Persistent Pulmonary Hypertension of the Newborn; PFC = Persistent Fetal Circulation; MAS = Meconium Aspiration Syndrome; CDH = Congenital Diaphragmatic Hernia.

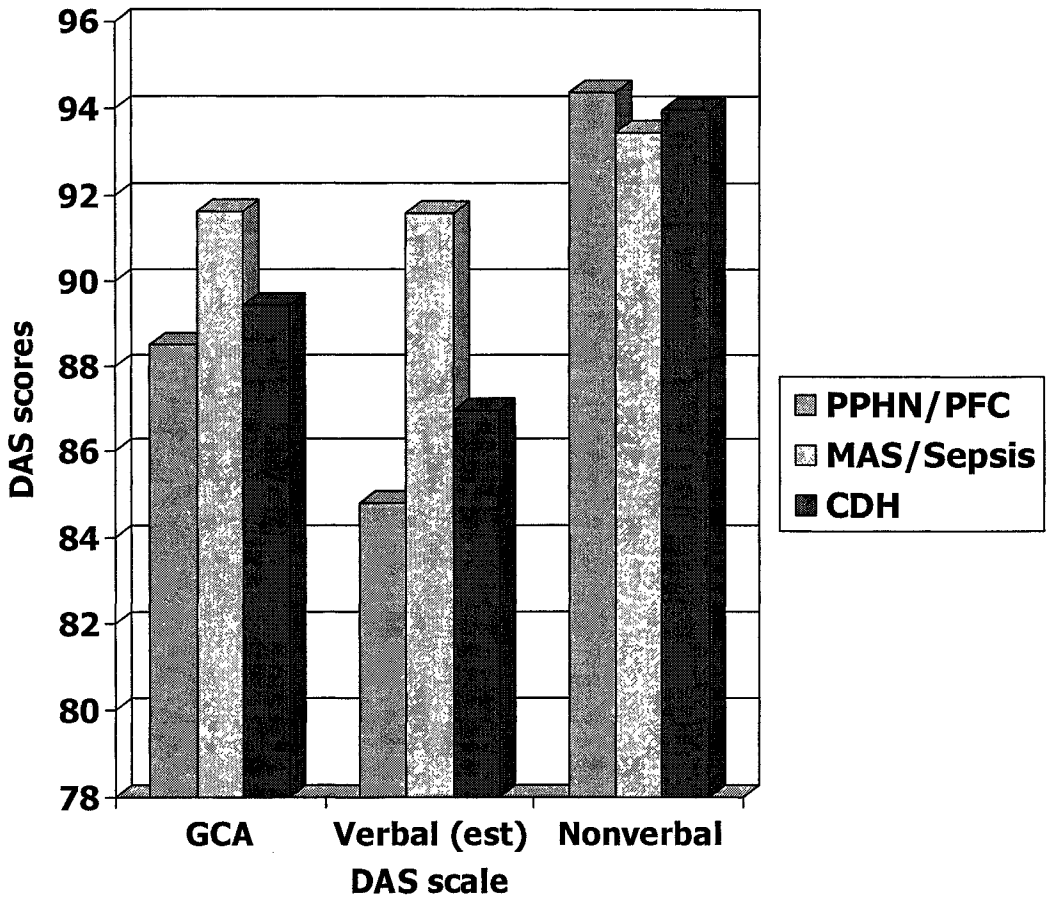

Figure 6. Two-and-a-half-year-olds : Overall means of assessments, by diagnosis group. PPHN = Persistent Pulmonary Hypertension of the Newborn; PFC = Persistent Fetal Circulation; MAS = Meconium Aspiration Syndrome; CDH = Congenital Diaphragmatic Hernia.

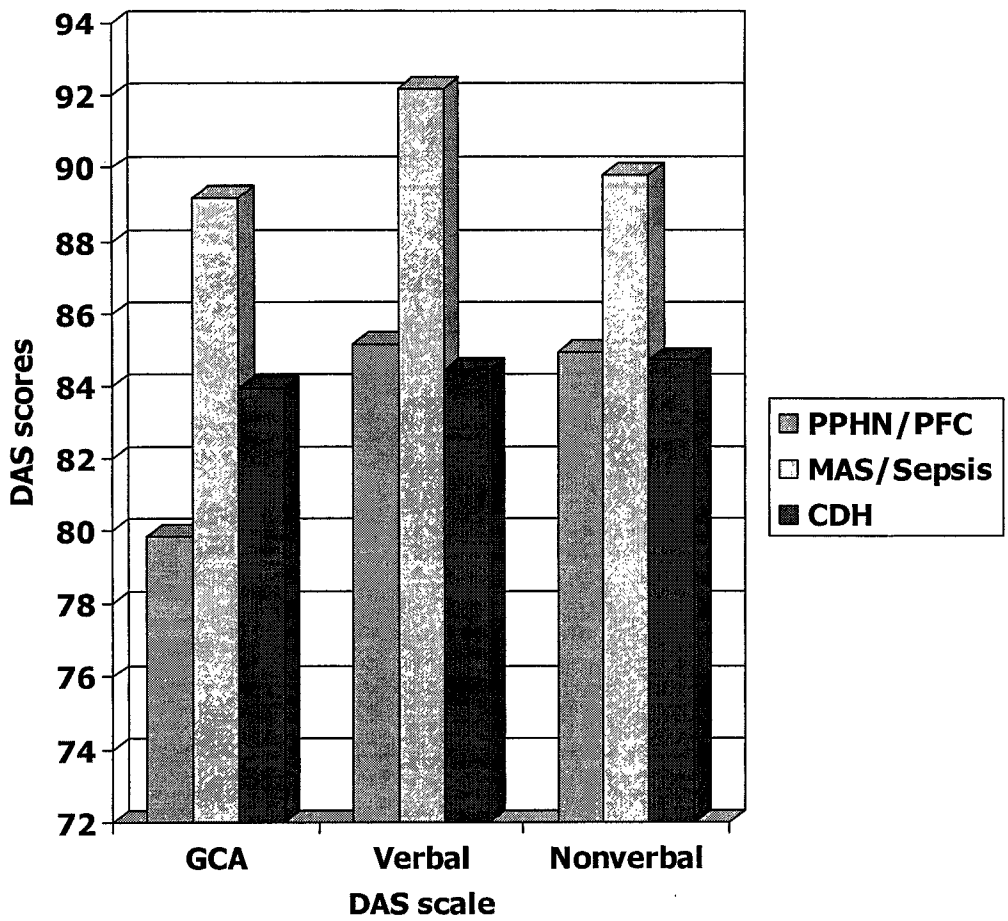

Figure 7. Four-year-olds : Overall means of assessments, by diagnosis group. PPHN = Persistent Pulmonary Hypertension of the Newborn; PFC = Persistent Fetal Circulation; MAS = Meconium Aspiration Syndrome; CDH = Congenital Diaphragmatic Hernia. DAS = Differential Ability Scales; GCA = General Conceptual Ability standard score.

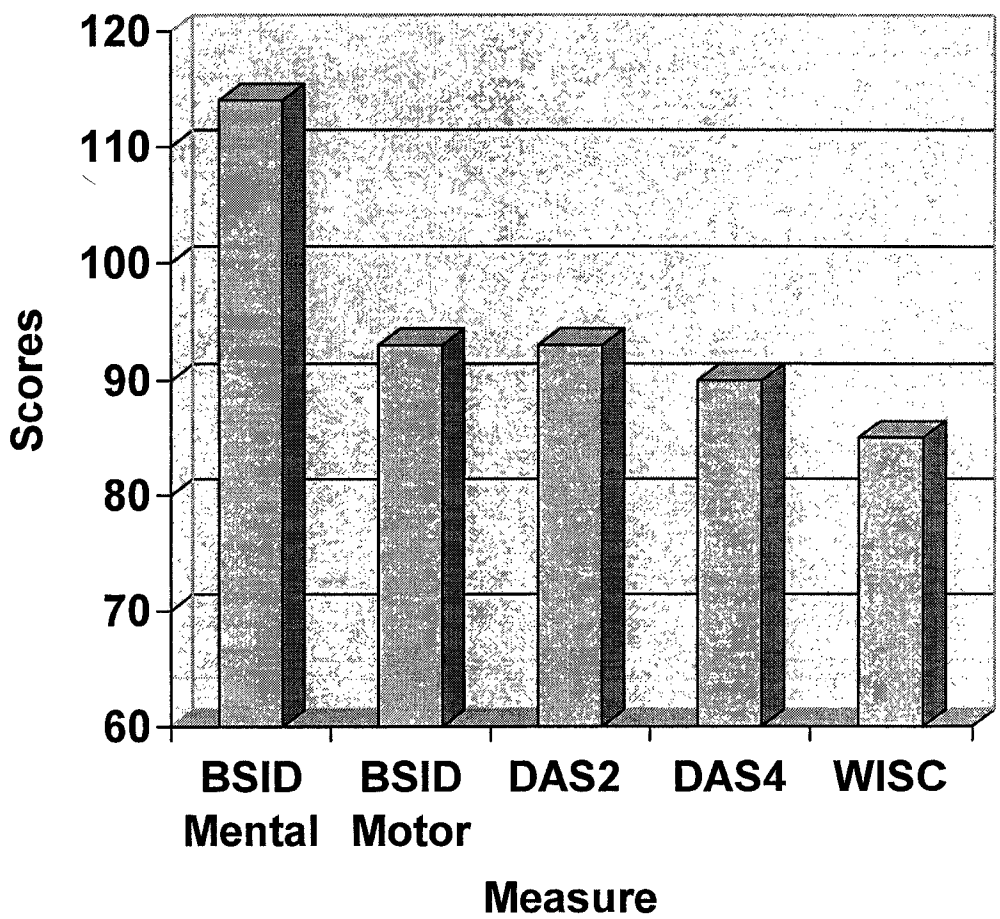

Figure 8. Overall mean scores for 11 children with longitudinal information, ages 1-6. BSID = Bayley Scales of Infant Development; DAS = Differential Ability Scales; WISC = Wechsler Intelligence Scale for Children.

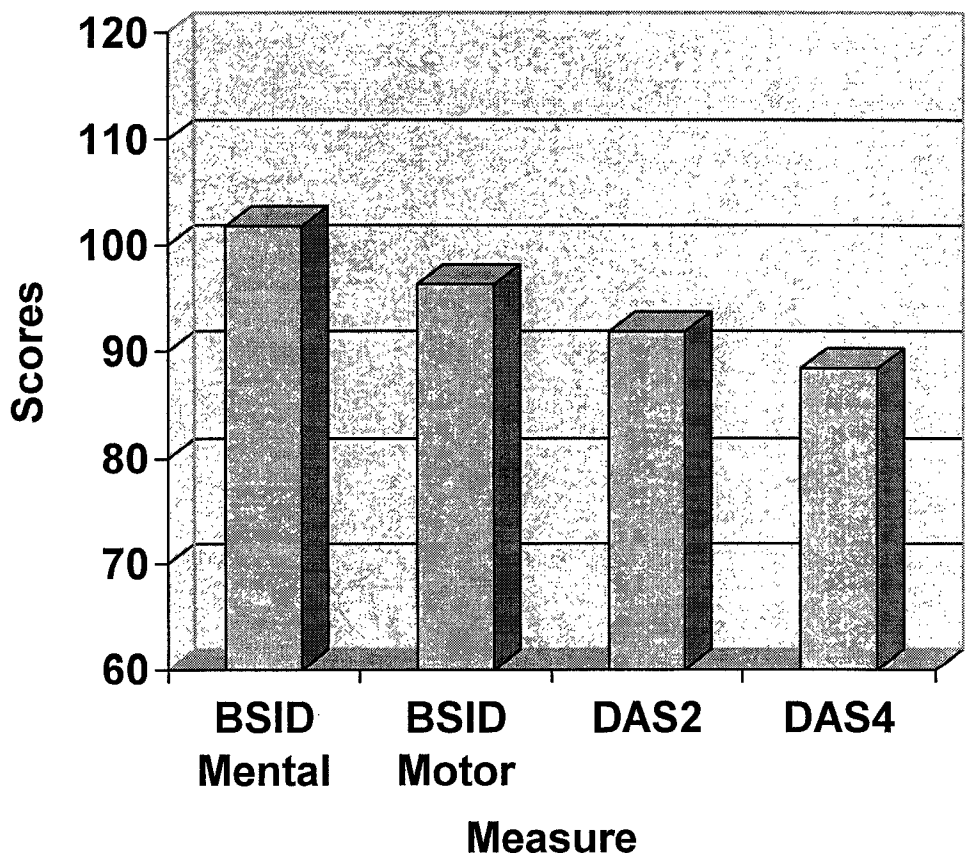

Figure 9. Overall mean scores for 66 children with longitudinal information, ages 1-4. BSID = Bayley Scales of Infant Development; DAS = Differential Ability Scales; WISC = Wechsler Intelligence Scale for Children.

DISCUSSION

ECMO is a medical procedure that has been used successfully since the 1970s in order to treat severe respiratory distress problems in adults and children. Although the effectiveness of the procedure in treatment of respiratory problems and reduction of mortality has been clearly demonstrated (Bartlett, 1989; Braden, 2002; Dorson, 1969; Hill et al., 1972; Ortiz et al., 1987; Rashkind, Freeman, Klein, & Toft, 1965; White et al., 1971), large-scale, long-term follow up studies of infants who have received ECMO have been severely lacking. Studies that have evaluated cognitive abilities have generally found a trend for children who received neonatal ECMO to obtain scores within the average range, although these scores are usually lower than scores received by healthy controls. In addition, some studies have indicated a possibility of difficulties with language abilities (e.g., Wilden et al., 1994), behavioral problems and/or risk of school failure (Glass et al., 1995), potential learning disabilities and significant scatter among subtest scores on typical intelligence tests (Ilke, Ilke, Moreland, Fashaw, Waas & Rosenberg, 1999; Langenbacher, Nield, & Kanne Poulson, 2001; Rais-Bahrami et al., 2000).

Although the general trend is for children who receive ECMO to score within the average range, there are likely to be differences in scores based on differences in the children's diagnoses at birth. Different diagnoses having different predicted outcomes and affecting areas of the brain differentially would certainly have an impact on cognitive measures. However, most studies to date have used the approach of combining all children who receive ECMO into one group, regardless of initial diagnosis. Although this approach was

adequate for initial studies in this area and is most certainly due to limited sample sizes overall, it is likely not sufficient for future, more detailed research.

Given the current trend of limited funds available to assist children who are at risk for delays, the ability to determine with some degree of certainty which children who received ECMO will likely be in need of additional services is of the utmost importance. Studies like the current one, examining in detail the differences children show on cognitive measures, are needed in order to assist service providers in making these determinations.

The current study evaluated some of the potential effects of ECMO on the cognitive development of infants who received the procedure in the neonatal period. The sample for the current study was similar to other previous reports of ECMO survivors. Variables such as pre-ECMO diagnosis, birth weight, race, and income were found to be significantly related to cognitive outcomes following ECMO. Specifically, at 1 year of age variable such as mother's age and diagnosis were found to be significantly related to subjects' scores on the BSID Mental and Motor scales. Scores on the Motor scale were further impacted by variables such as birth weight and type of ECMO. This is consistent with the hypothesis that one type of ECMO may differentially affect scores on cognitive measures and will need to be investigated further. Children at 1 year of age may be particularly sensitive to the effects of respiratory problems in the neonatal period, especially on motor tasks, given that many of them may have only recently started ambulating independently.

At ages 2½ and 4 years, diagnosis and race appear to be strongly related to scores on measures of verbal ability (the estimated Verbal score on the 2½-year DAS and the

Verbal Composite score on the 4-year DAS). Income was related to the overall scores (GCA standard score) at ages 2½ and 4 years as well as the nonverbal scores of the DAS at both ages. The effects of race on nonverbal abilities appear to diminish in significance with age for this sample, because this variable was related to both the overall score (GCA) and nonverbal score (Special Nonverbal Composite) at age 2½ but was no longer significant for the 4-year-olds. Although the effects of race and income on cognitive measures are not entirely unexpected, the effect of diagnosis on verbal ability, particularly at 4 years of age, is somewhat surprising.

The finding that children who suffered significant respiratory problems early in life experience physical problems and do not perform as well on the Motor Scale of the BSID as do their typically developing peers is not entirely surprising. However, a general trend suggested by the findings of this study appears to be that these survivors of ECMO are also experiencing language difficulties. Consistently, children who received ECMO scored lower on the verbal sections of the DAS at 2½ and 4 years of age and scored lower on the Mental Scale of the BSID. When the diagnostic groups were recombined based on different medical interpretations, the verbal scores for the 2½ and 4 year old measures were no longer significant. The implication, therefore, is that the diagnosis (or perhaps the underlying illness) is somehow related to a child's language skills. Further research will be needed to investigate this possibility.

Examination of the means on the assessments indicated that children who were diagnosed with CDH scored lower than the other groups, followed by children with idiopathic PPHN and PFC. That children with CDH have the most long-term difficulties is consistent with findings in previous literature.

There are several limitations to the current study, including the attrition rate. A number of children who would have been followed failed to return to the clinic for scheduled appointments. Given the attrition rate, a true longitudinal follow-up study was impossible to conduct. Instead, each assessment period had to be examined independently. The use of what is, in effect, a cross-sectional design limits the ability to generalize from these findings to the larger population of children who received ECMO in the neonatal period. Small longitudinal analyses ($n = 11$ and $n = 66$) were able to be conducted; however, given the extremely small sample sizes, only limited descriptive information is able to be presented.

In addition to the above concerns, these children represent a small subsample of the general population of ECMO recipients from one Southeastern hospital. There may be factors that are intrinsic to the medical staff, ECMO protocol, or population in general which cannot be examined with the sample used for this study. The limited information regarding income of the families and early intervention services received (if any) prohibits any statements about the effect these variables may have had (if any) on outcomes. Finally, because it was not possible to use a true experimental design, we cannot state with certainty that any or all of the delays some of the children in this study are experiencing are due to ECMO, environmental conditions, their pre-ECMO diagnosis, or some combination of the three.

Additional large scale long-term follow-up studies are necessary, given that ECMO has become more widely used as a method of last resort for children with severe respiratory problems. Despite the rise of newer, less invasive techniques, ECMO does continue to be used for children who fail to respond to these treatments. Studies examin-

ing cord blood gases collected at birth would also provide a better picture of the infant's oxygenation levels at that time. Other variables which would be beneficial to examine include the length of time to transport to an ECMO center from the hospital at which the infant was born, condition during transport, and the type of facility at which infants are born.

Research has been conducted on health-related quality of life in ECMO survivors and has indicated that these children appear to fall somewhere between typically developing controls and children with chronic health disorders (Rector, 2003). Future research should attempt to more carefully follow children longitudinally after receiving ECMO in the neonatal period. In addition to cognitive evaluations, it may benefit researchers to consider other variables that have been suggested to have an association with ECMO in the past, such as behavioral concerns, more specific tests of executive functioning, and language-specific evaluations. Studies looking at specific brain functions (e.g., measuring blood flow to certain areas of the brain such as the language centers) may also prove to be beneficial, because ECMO by its very nature interrupts blood flow. Finally, examination of a true longitudinal sample through the middle school years would be beneficial to determine if these children, as previous literature suggests, are at greater risk for learning disabilities and behavioral issues.

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APPENDIX

UAB INSTITUTIONAL REVIEW BOARD EXPEDITED APPROVALS

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

The Institutional Review Board for Human Use (IRB) has an approved Multiple Project Assurance with the Department of Health and Human Services and is in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines. The Assurance became effective on January 1, 1999 and the approval period is for five years. The Assurance number is M-1149.

Principal Investigator: CHOPKO, STEPHANIE

Co-Investigator(s):

Protocol Number: **X021220019**

Protocol Title: *Comparative Cognitive Development of Children who Received Extracorporeal Membrane Oxygenation (ECMO)*

The IRB reviewed and approved the above named project on 01-03-03. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 01-03-03

Date IRB Approval Issued: 01-03-03

Marilyn Doss

Marilyn Doss, M.A.
Vice Chair of the Institutional Review
Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office of Human Research Protections (OHRP). The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines. The Assurance became effective on November 24, 2003 and the approval period is for three years. The Assurance number is FWA00005960.

Principal Investigator:	CHOPKO, STEPHANIE
Co-Investigator(s):	
Protocol Number:	**X021220019**
Protocol Title:	*Comparative Cognitive Development of Children who Received Extracorporeal Membrane Oxygenation (ECMO)*

The IRB reviewed and approved the above named project on 3-15-04. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 3-15-04

Date IRB Approval Issued: 3-15-04

HIPAA Waiver Approved?: Yes

Marilyn Doss

Marilyn Doss, M.A.
Vice Chair of the Institutional Review Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

470 Administration Building
701 20th Street South
205.934.3789
Fax 205.934.1301
irb@uab.edu

The University of
Alabama at Birmingham
Mailing Address:
AB 470
1530 3RD AVE S
BIRMINGHAM AL 35294-0104

3/15/04

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Pt: CHOPKO, STEPHANIE
Protocol # X021220019

UAB IRB Approval of Waiver of Authorization/Waiver of Informed Consent

✓ **Approval of Waiver of Informed Consent to Participate in Research.** The IRB reviewed the proposed research and granted the request for waiver of informed consent to participate in research, based on the following findings:

1. The research involves no more than minimal risk to the subjects.
2. The research cannot practicably be carried out without the waiver.
3. The waiver will not adversely affect the rights and welfare of the subjects.
4. When appropriate, the subjects will be provided with additional pertinent information after participation.

Check one:
- ☑ **and** Waiver of Authorization (below)
- ☐ or Waiver of Authorization (below)
- ☐ Waiver of Authorization not applicable

☐ **Approval of Waiver of Patient Authorization to Use PHI in Research.** The IRB reviewed the proposed research and granted the request for waiver of patient authorization to use PHI in research, based on the following findings:

1. The use/disclosure of PHI involves no more than minimal risk to the privacy of individuals
   - i. There is an adequate plan to protect the identifiers from improper use and disclosure.
   - ii. There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention that is otherwise required by law.
   - iii. There is an assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted.
2. The research cannot practicably be conducted without the waiver or alteration.
3. The research cannot practicably be conducted without access to and use of the PHI.

_____The IRB reviewed the proposed research at a **convened meeting** at which a majority of the IRB was present, including one member who is not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities. The Alteration or waiver of authorization or waiver of consent (please circle) was approved by the majority of the IRB members present at the meeting.

Date of Meeting _____ Signature of Chair, Vice-Chair or Designee _____ Date _____

—OR—

✓ The IRB used an **expedited review procedure** since the research involves no more than minimal risk to the privacy of the individuals who are the subject of the protected health information for which use or disclosure is being sought. The review and approval of the alteration, waiver of authorization, or waiver of consent (please circle) was carried out by the Chair of the IRB, and by one of the Vice Chairs of the IRB as designated by the Chairman of the IRB.

3-15-04 Date of Expedited Review — Marilyn Davis Signature of Chair, Vice-Chair or Designee — 3-15-04 Date

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GRADUATE SCHOOL
UNIVERSITY OF ALABAMA AT BIRMINGHAM
DISSERTATION APPROVAL FORM
DOCTOR OF PHILOSOPHY

Name of Candidate Stephanie Chopko

Graduate Program Developmental Psychology

Title of Dissertation Cognitive Abilities of Survivors of Neonatal Extracorporeal Membrane Oxygenation

I certify that I have read this document and examined the student regarding its content. In my opinion, this dissertation conforms to acceptable standards of scholarly presentation and is adequate in scope and quality, and the attainments of this student are such that she may be recommended for the degree of Doctor of Philosophy.

Dissertation Committee:

Name	Signature
Fred J. Biasini, **Chair**	Fred J. B
Margaret P. Findlay	Margaret P. Findlay
Kathleen G. Nelson	
Eun-Young Mun	Eun-Young Mun
Amanda C. Walley	Amanda C. Walley

Director of Graduate Program Karlene Ball

Dean, UAB Graduate School

Date

UAB SCHOOL OF MEDICINE

Medical Student Services

March 3, 2005

UAB Graduate School
Attention: Janice Baird

Dear UAB Graduate School:

I have served as a member of Stephanie Chopko's thesis committee for her study entitled "Cognitive abilities of survivors of neonatal extracorporeal membrane oxygenation". Unfortunately, as I am not a Graduate School faculty member, I was unaware of the turn around time for final signoff. When she presented her dissertation initially, I had raised some concerns about the way the data was presented in her thesis. I continue to have these concerns, however, I feel quite confident that Stephanie understands my concerns and has dealt with them but has still not made the corrections in her final presentation sufficient enough for me to approve the dissertation.

Thus, I abstain from approval. It is my understanding that these changes will ultimately be incorporated in to any further publications that result from this data.

Please contact me if I can offer any additional information.

Sincerely,

Kathleen G. Nelson, MD
Sr. Associate Dean for Students
Professor of Pediatrics

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