TECHNIQUES & PROCEDURES

Nutrition Considerations in the Neonatal Extracorporeal Life Support Patient

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ABSTRACT: Extracorporeal life support (ECLS) is a type of heart-lung bypass commonly used to support neonates with life-threatening respiratory or cardiac failure. These patients are among the most critically ill patients in the neonatal intensive care unit and are at significant nutritional risk. Unfortunately, there is a paucity of literature regarding guidelines for nutrition support of the neonatal ECLS patient. The purpose of this article is to provide an overview of the indications, techniques, and complications of ECLS and to address the approach to nutrition support of these patients. Emphasis will be placed on issues unique to the neonatal ECLS patient.

Extracorporeal life support (ECLS) is a type of heart-lung bypass that provides short-term (days to weeks) support for the critically ill patient with acute life-threatening respiratory or cardiac failure. ECLS is a purely supportive, nontherapeutic intervention that maintains adequate gas exchange and circulatory support while "resting" the injured lungs or heart. Although the use of ECLS has been described in both pediatric and adult populations, the greatest experience has been reported in neonatal respiratory failure.[1] Discussion therefore will be limited to neonatal ECLS. Since 1975 when the first neonate survived ECLS,[2] it has become the standard of care for neonatal respiratory failure unresponsive to maximum conventional medical management. It is practiced in more than 80 centers worldwide with an overall survival rate of 83%.[3]

The major indications for initiation of neonatal ECLS include meconium aspiration, respiratory distress syndrome, persistent pulmonary hypertension, sepsis, and congenital diaphragmatic hernia. Occasionally, neonates with congenital cardiac anomalies may be supported with ECLS until surgical repair can be accomplished. Meconium aspiration syndrome is the most common indication for neonatal ECLS and is associated with the highest survival rate (>90%).[3]

Selection criteria for initiation of neonatal ECLS vary slightly from institution to institution. Generally, an infant must have at least an 80% predicted mortality with continued conventional medical management. The alveolar-arterial oxygen gradient ($AaDo_2$) may be used to predict mortality, where $AaDo_2$ = (atmospheric pressure − 47) − (Pao_2 + $Paco_2$). An $AaDo_2 > 620$ for 12 hours or an $AaDo_2 > 620$ for 6 hours associated with extensive barotrauma and/or severe hypotension requiring pressor support is associated with a mortality risk of >80% and is therefore considered an indication for ECLS support. The oxygen index (OI) likewise may be used to predict mortality, where OI = (fraction of inspired oxygen × mean airway pressure × 100) ÷ Pao_2. An OI > 25 predicts a mortality risk of 50%, and an OI > 40 is predictive of 80% mortality.[4] Additional inclusion criteria include gestational age ≥ 34 weeks, birth weight ≥ 2 kg, and a reversible pulmonary process. Exclusion criteria include the presence of cyanotic congenital heart disease or other major congenital anomalies that preclude survival, intractable coagulopathy or hemorrhage, sonographic evidence of a significant intracranial hemorrhage (> grade I intraventricular hemorrhage), and more than 10 to 14 days of high pressure mechanical ventilation.[5] Before initiation of ECLS, all infants must undergo a cardiac echocardiogram to rule out congenital heart disease and a cranial ultrasound to exclude the presence of significant intracranial hemorrhage.

The basic principle in ECLS is to drain venous blood, remove carbon dioxide and add oxygen via the artificial membrane lung, then return blood to the arterial (veno-arterial) or venous (veno-venous) circulation. Veno-arterial bypass provides both cardiac and respiratory support, whereas veno-venous bypass provides

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only respiratory support. Veno-arterial bypass is used most commonly, and the right internal jugular vein and common carotid artery are typically chosen for cannulation because of their large size, accessibility, and adequate collateral circulation.

The ECLS circuit (Fig 1) is composed of a silicone rubber collapsible bladder (which collapses if there is low venous return), a servoregulated roller pump, a membrane oxygenator, a heat exchanger, tubing, and connectors. Venous blood from the right atrium drains through the venous cannula to the bladder and is pumped to the membrane oxygenator where carbon dioxide is removed and oxygen is added. The oxygenated blood then passes through the heat exchanger and is returned to the patient through the arterial cannula.

To prevent clotting of the ECLS circuit, systemic anticoagulation is maintained. The heparin dosage is adjusted hourly to maintain the activated clotting time at roughly 1.5 to 2 times normal. The fully heparinized patient is at risk for serious bleeding complications. A complete blood cell count is obtained every 4 hours. Platelets and packed red blood cells are transfused as necessary to maintain the platelet count > 150,000 to 200,000/mm^3 and the hematocrit > 0.35 to 0.40, respectively. Fibrinogen levels are followed closely and cryoprecipitate is given as needed to maintain normal levels. Daily cranial ultrasonograms are obtained to rule out hemorrhage.

Extracorporeal flow is gradually weaned as native cardiac or pulmonary function improves. Indicators of lung recovery include an increasing PaO_2, improved lung compliance, and clearing of the chest x-ray. Once the extracorporeal flow rates are at minimal levels, the venous and arterial cannulas may be clamped to give the patient a trial off bypass. If the patient remains hemodynamically stable and is able to maintain adequate oxygenation and ventilation while the cannulas are clamped, the cannulas are surgically removed and conventional ventilatory support is continued. The mean duration of ECLS in neonates is 5.5 ± 2.5 days, with mean duration of support for meconium aspiration syndrome and persistent pulmonary hypertension 5 days, sepsis 5 to 7 days, and congenital diaphragmatic hernia 7 to 14 days.[6]

ECLS is associated with significant morbidity and mortality related to ligation and cannulation of the right common carotid artery and right internal jugular vein, systemic heparinization, exposure to multiple

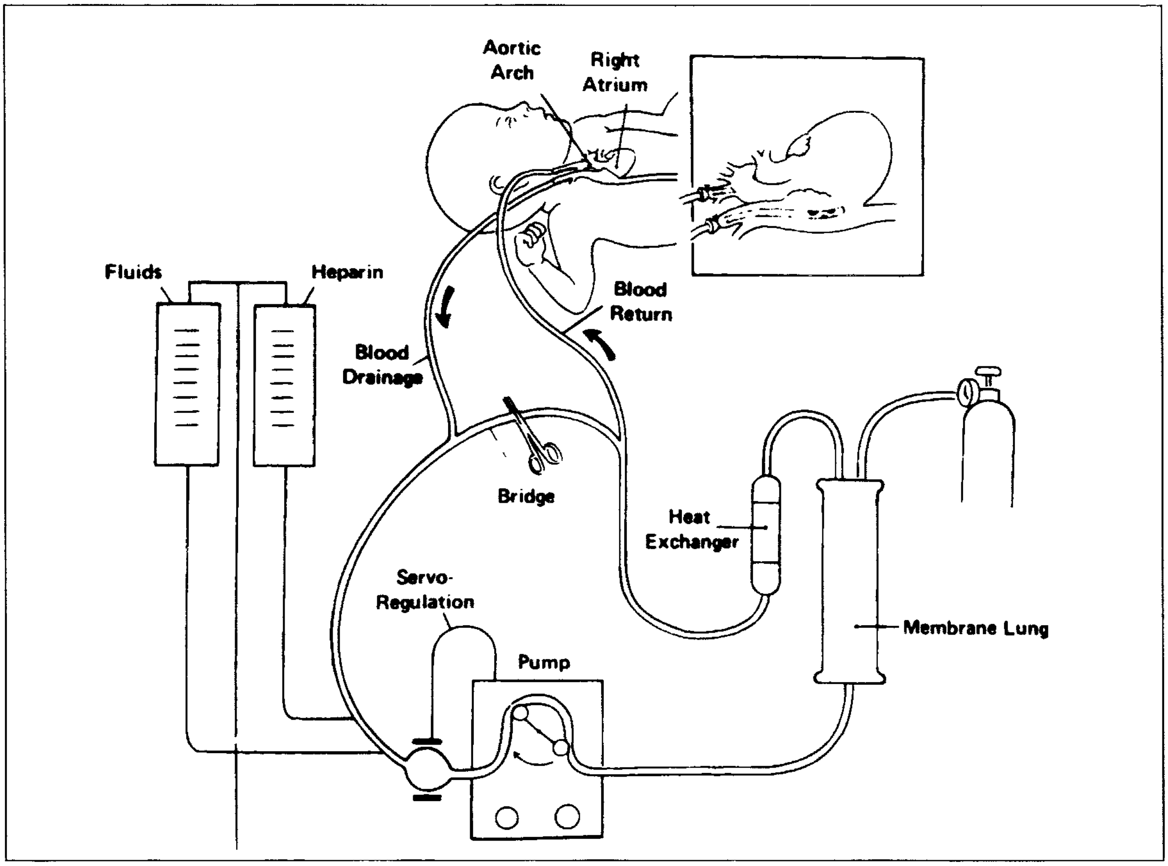

Figure 1. Diagrammatic representation of a veno-arterial ECLS circuit. (Reprinted with permission from Shanley CJ, Bartlett RH. Extracorporeal life support: techniques, indications, and results. In: Cameron JL, ed. Current surgical therapy, 4th ed. St. Louis: Mosby Year Book, 1992:1062-6.)

blood products, and potential for mechanical failure of the circuit. Bleeding is the most common complication and may be either medical (too few platelets, too much heparin, intracranial) or surgical (neck cannulation site, intrathoracic, gastrointestinal, etc). Birth weight and gestational age are the most significant correlates of intracranial hemorrhage on ECLS, with infants weighing < 2.2 kg and of < 35 weeks' gestational age at the highest risk.[7] Other significant complications associated with ECLS include seizures, neurologic impairment, renal failure requiring hemofiltration or hemodialysis, hypertension, infection, and mechanical malfunction (failure of the membrane oxygenator, pump, heat exchanger, etc).

PARENTERAL NUTRITION

Total parenteral nutrition (TPN) is generally begun as soon as possible after institution of ECLS. Early institution of nutrition support is critical to the newborn infant with limited endogenous nutrient stores and relatively high nutritional requirements. Parenteral nutrition traditionally has been preferred over enteral nutrition mainly because of concerns about necrotizing enterocolitis (NEC) and problems related to ileus. Most infants have never been enterally fed and have suffered a significant hypoxic insult. The ECLS circuit can be considered a large central line, and TPN and lipids can be delivered directly into the circuit.

Fluid and Electrolyte Management. Careful attention to fluid and electrolyte balance is essential to proper management of the neonatal ECLS patient. Before initiation of ECLS, most infants have received aggressive fluid resuscitation and are relatively volume overloaded. Increased vascular permeability caused by prolonged hypoxia and hypotension as well as the underlying disease process may result in significant "third-spacing" of fluid. Edema may worsen with ECLS because of several factors including the effect of nonpulsatile flow on the kidney, which results in activation of the renin-angiotensin system with sodium and water retention.[8,9] High plasma renin activity may also be caused by loss of feedback inhibition by angiotensin II, because at high levels of bypass, a significant proportion of cardiac output is not available to the pulmonary circulation and angiotensin-converting enzyme.[9] Additionally, because of unloading of the right atrium during ECLS, concentrations of circulating atrial natriuretic factor are increased.[10] Furthermore, a significant volume of blood products and colloid may be required during ECLS. Because of the propensity for significant fluid retention by neonates while on ECLS, fluids are typically restricted to 80 to 100 mL/kg per day, including TPN, lipids, antibiotics, and continuous drug infusions (eg, heparin, inotropic agents, and sedatives). Diuretics are used aggressively to improve pulmonary function and facilitate weaning. Hemofiltration or hemodialysis may be indicated in patients who become significantly oligonuric or anuric.

Hypernatremia is common and may be related to a combination of several factors including administration of large amounts of sodium (normal saline, sodium bicarbonate) during pre-ECLS resuscitation,[11] inadequate free water administration, and excessive free water loss during diuresis. Hypokalemia is common, and potassium requirements may be as high as 4 to 5 mEq/kg per day.[11] Hyperkalemia may occur with renal failure or hemolysis, in which case potassium should be decreased or deleted from fluids. The patient on ECLS who requires frequent transfusions of packed red blood cells may develop hypocalcemia because of binding of calcium by citrate. The usual calcium requirement is 2 to 3 mEq/kg per day. Infants on ECLS may have increased phosphorus needs as well. Replacement should be advanced or decreased as needed on the basis of serum phosphorus measurements. A 2:1 calcium to phosphorus ratio is recommended; however, if the serum phosphorus is low, the ratio may need to be altered to provide more phosphorus. It may be difficult to administer sufficient calcium and phosphorus in TPN if the volume of fluids to be administered is low, because precipitation may occur. The usual magnesium requirement is 0.5 to 0.6 mEq/kg per day and may be increased or decreased on the basis of serum magnesium measurements. Consideration must also be given to antacids, which may contain a significant amount of magnesium, used for ulcer prophylaxis. In our institution, a renal panel and serum calcium level are obtained every 4 hours. Serum phosphorus and magnesium levels are measured daily.

Energy Requirements. Several studies have measured energy expenditure in other critically ill[12] and postoperative patients[13] whose energy requirements may be similar to those of the neonatal ECLS patient. In 1988, Chwals et al[12] measured energy expenditure in 20 critically ill pediatric patients with a mean age of 14 months (range: 5 days to 46 months) by indirect calorimetry. The measured energy expenditure was significantly lower than the predicted energy expenditure (52.2 ± 16 vs 101.8 ± 16.2 kcal/kg per day). In 1991, Shanbhogue et al[13] measured energy expenditure in both preterm and term neonates after major abdominal or thoracic surgery. The mean measured postoperative resting energy expenditure (REE) (39.18 ± 6.44 kcal/kg per day) was not significantly different from the mean preoperative predicted REE (40.98 ± 8.83 kcal/kg per day). There were no significant differences in measured REE between preterm and term infants.

The critically ill neonatal ECLS patient is severely stressed and catabolic. Unfortunately, the energy requirements of this group of patients are not well defined. In the only known study of these patients, Cilley et al[14] used closed-circuit spirometry to measure gas exchange in 10 term neonates on ECLS. The summation of gas exchange measurements across the native lung and membrane lung were then used to calculate REE, which ranged from 38 to 80 kcal/kg per day (mean 57 ± 11 kcal/kg per day). Because caloric intake needed to promote growth may exceed REE by as much as 45%,[14] the estimated caloric requirements for this group of patients may be as high as 55 to 116 kcal/kg per day (mean: 83 kcal/kg per day).

These results demonstrate that energy expenditure in critically ill and postoperative neonatal and pediatric patients may be grossly overestimated when measured and predicted values are compared. Our current practice is to provide 80 to 100 kcal of a balanced nutrient solution per kilogram per day. This goal is often difficult to achieve given the imposed fluid restrictions.

Protein. Nitrogen balance studies in neonatal ECLS patients demonstrate that a slightly positive nitrogen balance may be achieved with delivery of nonprotein calories > 60 kcal/kg per day and nitrogen intake > 240 mg/kg per day.[15] To support growth in the healthy newborn, a positive nitrogen balance of 180 to 190 mg/kg per day is believed to be necessary.[16] To achieve this level of nitrogen balance in the neonatal ECLS patient, a daily nitrogen intake of approximately 400 mg/kg per day is required.[15]

For reference, the nitrogen intake required by parenterally fed infants to duplicate the accretion rates of healthy human milk–fed infants is 280 mg/kg per day, and 2.3 to 2.7 g of protein per kilogram per day is recommended.[16] In the neonatal ECLS patient, our nutritional goal is to provide 2.5 to 3.0 g of protein per kilogram per day, which should be sufficient to promote positive nitrogen balance. Protein is generally begun at 1 g/kg per day, then advanced by 0.5 to 1 g/kg per day until the goal of 2.5 to 3.0 g/kg per day is reached. Sufficient calories are provided to maintain the calorie:nitrogen ratio > 150:1.

Frequently, neonatal ECLS patients develop acute renal failure, often requiring hemofiltration or hemodialysis. With increasing blood urea nitrogen and creatinine levels, the protein in the TPN should be decreased to 1 to 2 g/kg per day. If hemodialysis is begun, then protein in the TPN is liberalized.

Carbohydrate. Because of the fluid restrictions on the neonatal ECLS patient, higher concentrations of dextrose may be necessary to deliver adequate nonprotein calories. Glucose infusion rates of 4 to 6 mg/kg per minute are the minimum required to prevent hypoglycemia. Glucose infusion rates are advanced by 1 to 2 mg/kg per minute daily until caloric goals are met or glucose intolerance occurs.

Sepsis may be heralded by the onset of hyperglycemia, which may persist until the source of sepsis is identified and appropriately treated. If unexplained refractory hyperglycemia occurs in the neonatal ECLS patient, underlying sepsis should be ruled out as a potential cause. Hyperglycemia may also occur in association with severe stress or catecholamine infusion. Hyperglycemia may have important implications in the neonatal ECLS patient because the resultant hyperosmolar state may precipitate intraventricular hemorrhage.[17,18] Appearance of a new intracranial hemorrhage or enlargement of a preexisting bleed are generally indications for discontinuing ECLS.[7] Hyperglycemia may also cause an osmotic diuresis[19] leading to volume depletion, hypotension, and electrolyte imbalance. Furthermore, hyperglycemia may limit the use of glucose as an energy source.

Hypoglycemia likewise poses a significant threat because it may precipitate seizure activity, which is associated with an increased risk of intracranial hemorrhage and permanent neurologic impairment.[20]

Fat. Because of the limited reserves of the neonate, essential fatty acid deficiency may develop rapidly (within days) if inadequate fat is provided. To prevent essential fatty acid deficiency, 2% to 4% of the total calories should be provided by fat, or a minimum of 0.5 to 1.0 g/kg per day.[21]

Lipids are a concentrated source of energy for the neonate and may be used to provide up to 40% of the total calories. Delivery of a highly concentrated energy source is important in the neonatal ECLS patient in whom fluids are restricted. Continuous 20% lipid infusions are generally begun at 0.5 to 1.0 g/kg per day and advanced by 0.5 to 1.0 g/kg per day to a maximum of 3 g/kg per day[22] in the nonseptic patient and 2 g/kg per day[23] in the septic patient. Lipid tolerance may be significantly impaired in sepsis, which is associated with decreased lipoprotein lipase activity, impaired triglyceride clearance, and fatty acid oxidation.[23] Triglycerides are monitored daily in ECLS patients, and lipid delivery is adjusted accordingly.

Heparin has been shown to release endothelium-bound lipoprotein lipase and hepatic lipase into the circulation, thus stimulating intravascular lipolysis, resulting in elevated free fatty acid levels.[24] Spear et al[25] demonstrated that a high heparin dosage (137 U/d) was associated with significantly elevated free fatty acid levels. A low heparin dosage (24 U/d) and a continuous 24-hour infusion of lipid resulted in less elevation of free fatty acids. Inasmuch as the ECLS patient typically receives 10 to 40 U of heparin per kilogram per hour, elevated free fatty acid levels would be expected. These data, however, are not presently known. We have not clinically observed differences in fat clearance in patients on ECLS vs other patients.

Unconjugated hyperbilirubinemia is a common problem, and lipids should be used cautiously because high circulating levels of free fatty acids may displace albumin-bound bilirubin[26,27] and place the infant at increased risk for kernicterus. Also, because of prior hypoxic insult, the permeability of the blood-brain barrier to unconjugated bilirubin may be increased. Spear et al[25] demonstrated no adverse effects on bilirubin binding to albumin with either 15-hour or 24-hour lipid infusions of 2 g/kg per day at either low or high heparin dosages. In vitro studies demonstrated that a free fatty acid/albumin molar ratio of 5, or a free fatty acid concentration of 2 mEq/dL, is required to displace bilirubin from albumin,[26] whereas in vivo studies revealed that a ratio > 6 is required.[28] As a general rule, lipid infusions ≥ 2 g/kg per day should be tolerated in the hyperbilirubinemic patient as long as the free fatty acid/albumin molar ratio is < 6 and/or the bilirubin is < 10 mg/dL.

The effect of lipid emulsions on pulmonary diffusion capacity remains controversial.[29] There are no data to support the concerns that lipid may interfere with membrane lung function or oxygen diffusion in the neonatal ECLS patient.[11]

Cholestasis. Cholestasis occurs commonly in the neonatal ECLS patient and is characterized by direct hyperbilirubinemia without enzymatic evidence of hepatocellular or canalicular injury.[30,31] Neonatal ECLS patients have usually had significant periods of hypoxia, acidosis, and hypotension, all of which may predispose to hepatic injury. Other factors that may contribute to cholestasis include immaturity of the biliary secretory system, loss of enteric stimulation, disturbed enterohepatic circulation, intestinal bacterial overgrowth, sepsis, major surgery, and TPN itself.[32]

Hemolysis due to mechanical stresses on red blood cells as they pass through the ECLS circuit may result in an increased bilirubin load presented to the liver. Hemolysis normally results in indirect hyperbilirubinemia; however, in the neonate, immature bile flow mechanisms may limit excretion of conjugated bilirubin, and direct hyperbilirubinemia may also occur.[30]

Di-2-ethylhexyl phthalate (DEHP), a plasticizer found in the polyvinyl chloride tubing of the ECLS circuit, has been postulated to contribute to ECLS-associated cholestasis.[30,31] Clinically significant levels of DEHP have been detected in infants requiring ECLS.[33] DEHP is extracted from tubing at a rate directly related to the duration and temperature of exposure.[34] During ECLS, warm blood may be circulated through DEHP plasticized tubing for days to weeks, resulting in significant DEHP accumulation, which is thought to predispose to cholestasis by direct inhibition of canalicular excretion of bilirubin or, alternatively, by increasing hemolysis.[30]

Because of many of the above factors, the neonatal ECLS patient may also be at increased risk for cholelithiasis.[35] Diuretic use, which is common in the ECLS patient, may predispose infants to a higher incidence of gallstones.[36] The natural history of gallstones and/or sludge that occurs in infancy is not known.

ENTERAL NUTRITION

Despite its obvious merits, enteral nutrition has not been used in the neonatal ECLS patient, mainly because of concerns about NEC and the commonly encountered ileus. The cause of NEC is probably multifactorial, but NEC may result from an ischemic insult to the intestine and impair the effectiveness of the mucosa as a barrier to bacteria or other toxins.[37] Enteral feeding has also been associated with the development of NEC, inasmuch as 90% to 95% of infants who develop the disease have been enterally fed.[37] Neonatal ECLS patients may be at increased risk for the development of NEC because of the significant hypoxia, hypotension, and acidosis incurred before the initiation of ECLS.

On the other hand, NEC is a disease of prematurity and occurs only rarely in term infants. Susceptibility to NEC appears to be inversely related to gestational age.[38] Ninety percent of patients who develop NEC are born at less than 36 weeks' gestation.[37]

Most neonatal ECLS patients, however, are term infants, and should therefore be at lower risk for development of NEC. The issue of the prior ischemic insult remains. Studies have shown that enteral feeding is both safe and effective during acute burn shock,[39] and, interestingly, four burn patients who required ECLS at our institution were fed enterally without adverse sequelae. Studies addressing the safety of enteral nutrition in the neonatal ECLS patient are warranted.

Technical problems may be associated with the use of enteral feedings. Transgastric feedings would be preferred to intragastric feedings because of ileus and concerns about aspiration. The placement of a transgastric feeding tube, however, requires fluoroscopy, which may be difficult at the bedside because of the large amount of equipment surrounding the infant. Moving the patient on ECLS to the radiology suite is a major task and is associated with significant risk.

SUMMARY

There is currently scant literature regarding nutrition guidelines for the neonatal ECLS patient, which is unfortunate because these patients are critically ill and at significant nutritional risk. Early institution of parenteral nutrition support with use of standard guidelines for neonates in general is critical. Because of imposed fluid restrictions, however, it is often difficult to meet nutrition goals. Although parenteral nutrition has traditionally been used in these patients, enteral nutrition may be preferred and therefore warrants further investigation.

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