Extracorporeal Life Support: History and New Directions

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This review recounts the development of extracorporeal life support (ECLS, ECMO) from the laboratory and early clinical trials to routine clinical application. Lessons from neonatal ECMO have led to better understanding of neonatal lung physiology, improved methods of treatment, and application of ECLS to other patient populations.

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The first neonatal extracorporeal membrane oxygenation (ECMO) survivor is 30 years old this year. In one medical generation, the use of prolonged extracorporeal circulation for life support in the intensive care unit has gone from a laboratory curiosity to clinical trials to routine practice. Every major Children's Hospital has an extracorporeal life support (ECLS) program to sustain the life of patients with severe heart or lung failure when other treatments fail. Although the technology was first developed for the care of neonatal respiratory failure, growth and innovation are now primarily in the pediatric and adult intensive care units. In fact, the use of ECLS for neonatal respiratory failure is steadily decreasing as we develop a better understanding of the pathophysiology and better methods of prevention and treatment in the neonatal population. After three decades of experience, it is worthwhile to review the current status and future directions of ECLS in neonatology, which is the subject of this issue of Seminars in Perinatology.

The heart/lung machine (a mechanical device to temporarily replace heart and lung function) was developed primarily by surgeon John Gibbon, beginning in 1939 and culminating in the first successful heart operation using a heart–lung machine in 1954. Dr. Gibbon's motivation was to develop a technique to treat massive pulmonary embolism, but what resulted instead was the entire field of intracardiac surgery. The artificial heart was simply a blood pump and the artificial lung was direct exposure of the flowing blood to oxygen gas. For cardiac surgery, all the venous return is diverted into the machine and pumped into the systemic circulation, leaving the heart empty long enough to repair intracardiac defects or operate on the coronary circulation. The opportunity to operate directly on the heart was miraculous, but the heart–lung machine itself caused damage to the fluid and solid elements of the blood. In fact, the heart–lung machine caused fatal complications if it was used for more than 2 or 3 hours. The major cause of blood damage was the direct exposure of blood to gas. Interposing a gas exchange membrane of plastic or cellulose between the flowing blood and the gas solved most of the blood-damage problems, but experimental devices required very large surface areas and were impractical for any clinical use.

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was itself considered a radical intervention of questionable value.) After Hill’s case, several other successful cases were reported in children and adults with severe pulmonary and cardiac failure. At the same time, there seemed to be an epidemic of “ARDS” and it looked like extracorporeal support would be the answer. A multi-center clinical trial of prolonged extracorporeal circulation for adults with ARDS was commissioned by the National Institutes of Health in 1975. This was the first prospective randomized trial of a life-support technique in acute fatal illness in which the endpoint was death. There were many problems with the design and execution of that clinical trial, but from it we learned that the mortality for all patients with ARDS was 66%, and the mortality for severe ARDS was 90%. We learned that extracorporeal support attempted by inexperienced teams in veno arterial mode for 1 week did not improve the ultimate survival in severe ARDS. We learned (the hard way) the mistakes to avoid when conducting a prospective trial in acute fatal illness. And we developed a name for the technology: extracorporeal membrane oxygenation (ECMO). The results of that study were published in 1979; laboratory and clinical trials. Clinical trials progressed through Phases I, II, and III with reporting and discussion at regular intervals but without sensational reports in the lay press. A registry of all cases in all centers was kept from the beginning of clinical application, which proved to be very valuable as the technology grew. The use of ECMO allowed study of respiratory failure secondary to meconium aspiration. The major cause of hypoxemia was pulmonary hypertension with right to left shunting through the ductus arteriosus and foramen ovale. This was mysterious at the time, but we soon recognized that persistence of the fetal circulation physiology (persistent pulmonary hypertension of the newborn, PPHN) is the underlying pathophysiology for most causes of respiratory failure in full-term newborn infants. Using techniques of vascular access, anticoagulation, ventilator management, and extracorporeal circulation which had been developed in the laboratory, we used extracorporeal support for infants with a variety of conditions. Forty newborn patients were treated over the next 5 years with 50% survival. Neonatologists and surgeons from other institutions joined us to learn the technology. By 1986, 18 neonatal centers had successful ECMO teams.

As with intubation and mechanical ventilation for newborn infants two decades before, the advent of this new technology met with skepticism among the relatively new field of neonatology. A prominent senior neonatologist announced at a national meeting that anyone pursuing research in ECMO was committing academic suicide. Pediatric journals declined to publish reports of the growing experience with ECMO, hence most of the reports from this early experience are in the artificial organs and surgical literature. We conducted the first prospective randomized trial of ECMO in neonatal respiratory failure, using an adaptive design to correct some of the mistakes we had made in the earlier adult trial. After lengthy discussions, the report of this trial was published in Pediatrics in 1985 along with invited commentaries criticizing the technology and the trial. This criticism and controversy lead to the second prospective randomized trial performed by O’Rourke and associates at the Boston Children’s Hospital. A similar adaptive trial design was used by the Boston group with similar results (94% survival in the ECMO group). The Michigan trial was criticized for exposing critically ill infants to the high risks of ECMO. Two years later, the Boston study was criticized for denying ECMO to the patients in the control group. Academic controversies aside, neonatologists realized that ECMO regularly resulted in high survival rates of healthy children and ECMO became standard treatment for neonatal respiratory failure unresponsive to other measures.

In 1990, the National Institutes of Health held a workshop on the diffusion of high-tech medicine from bench to bedside using neonatal ECMO as an example. Several factors were identified in the neonatal ECMO experience which facilitated the translation from concept to routine application. All aspects of the technology were thoroughly developed in the bench and animal laboratory before clinical trials. Clinical trials progressed through Phases I, II, and III with reporting and discussion at regular intervals but without sensational reports in the lay press. A registry of all cases in all centers was kept from the beginning of clinical application, which proved to be very valuable as the technology grew. The use of ECMO allowed study of patients who would have been dead without it. This unveiled many aspects of neonatal respiratory failure pathophysiology and treatment, which in turn resulted in better understanding and the implementation of other simpler techniques. As the technology developed, it was standardized, disseminated, studied, and improved in an organized fashion by the actual and potential users. This group of investigators and clinicians was formally organized as the Extracorporeal Life Support Organization (ELSO) in 1989. For the last 15 years, that group has developed guidelines and practices, published the standard textbook in the field, and maintained a registry of ECLS cases. ELSO has followed and documented the growth of ECLS in other populations and other diseases. As of January 2005, there were over 30,000 patients in the registry, half of whom are newborn infants. Two other prospective randomized trials have been reported. One of these is the large neonatal trial conducted in the United Kingdom. The design of this trial solved almost all of the problems of prospective randomized trials in acute fatal illness. Major advances in ECLS technology and application have occurred over the last decade. This volume is focused only on the use of ECLS for neonatal respiratory failure.
Current Status of Neonatal ECMO

ECMO is currently used for neonates with respiratory failure unresponsive to other treatment. Overall survival is 85%, ranging from 98% in meconium aspiration to 55% in diaphragmatic hernia. The use of ECLS in neonatal respiratory failure has allowed the identification of aspects of pathophysiology and treatment which should ultimately make ECMO obsolete, or more accurately, unnecessary for the treatment of neonatal respiratory failure. This is, in fact, happening as demonstrated by the number of neonatal ECMO cases reported by the Registry since the beginning of the technology. The use of ECLS peaked in 1992 and has been steadily decreasing since that time. The primary reasons are identification and avoidance of ventilator-induced lung injury and the use of inhaled nitric oxide as a pulmonary vasodilator. In our experience, 40% of the patients who would have required support with ECMO in 1992 are now successfully treated with pressure-controlled (low stretch) ventilation and inhaled nitric oxide using standard or oscillation ventilator techniques. Another factor is the successful use of surfactant for prematurity-related infant respiratory distress syndrome, obviating the need for extracorporeal support in most of the premature babies suffering from that condition. As other aspects of treatment improve, those patients who do not respond (and are therefore treated with ECMO) are the most difficult cases: bilateral hypoplasia secondary to congenital diaphragmatic hernia, fulminant neonatal sepsis, pulmonary failure complicating congenital heart disease, and the occasional patient who does not respond to gentle ventilation with nitric oxide inhalation. These problems are under study in the laboratory and in clinical trials, and the need for ECLS will decrease even further in the future. However, there will always be some newborn infants with respiratory failure who will not recover and survive without extracorporeal support.

Today almost all of our patients are managed with a specially designed double lumen right atrial catheter placed through the internal jugular vein. This simplifies the vascular access and avoids the complications of venoarterial access. Bleeding is rarely a problem, neurologic injury and developmental delay are rare, and the technique is simply a part of routine management in the neonatal ICU.

Lessons from the Neonatal Experience

Basic research studies of prolonged extracorporeal circulation which began in the 1960s continue today in many laboratories and in industry. Elimination of the direct blood gas interface solved most of the problems which limited prolonged use of extracorporeal circulation. The advantages of membrane oxygenators for prolonged use led to the routine use of membrane oxygenators for all of cardiac surgery. When microporous membranes became available, laboratory studies showed that those surfaces appeared as solid membranes to flowing blood, even though there is direct exposure to gas through the micropores. Microporous materials are much easier to handle and manufacture than solid silicone rubber membrane, so that today almost all of the membrane lungs used for cardiac surgery are made of microporous polypropylene, in hollow fiber configurations. This type of membrane lung has greatly reduced the air and particulate embolism complications of open-heart surgery. Paradoxically, microporous membrane lungs are not suitable for prolonged extracorporeal support because plasma will leak through the micropores in an unpredictable fashion after many hours of use. The cause of this plasma leakage is phospholipid accumulation on the blood side of the membrane with subsequent “wetting” of the membrane and plasma leakage.

Basic research today has focused on the development of membrane lungs, which use solid membrane in hollow fiber configurations. These membrane lungs have very low blood flow resistance and very high gas exchange efficiency. They are used for ECMO in Europe and in Japan with major improvements in clotting and anticoagulation, platelet function, and ease of use. These devices have not yet received FDA approval for use in the United States.

Identification of the problems of direct gas interface led to more intense study of gas interfaces which still exist in cardiac surgery (open blood reservoirs and direct suction of blood from the operative field). Eliminating these gas interfaces is another major step in improving the safety of extracorporeal circulation for cardiac surgery.

Simple bench studies of the characteristics of vascular access catheters have led to the development and use of double and single lumen catheters especially designed for prolonged extracorporeal support. The management of anticoagulation during clinical ECMO is based on laboratory studies in healthy animals. Heparin-bonded surfaces looked very attractive in the laboratory, but do not eliminate the need for systemic anticoagulation in patients. However, experience with heparinized surfaces identified platelet adhesion as the major problem in surface-induced thrombogenesis. Current basic research is focused on plastic surfaces which are modified to prevent platelet adhesion.

All of these developments in basic bioengineering research would be of minor importance if it were not for concomitant development of devices in biomedical industry. To be uniformly useful, devices must be standardized, manufactured, and generally available to practitioners at a reasonable cost. A sizable medical industry devoted to extracorporeal circulation has built up over the years, based on the much wider market of devices for cardiac surgery. In 1976, the Food, Drug, and Cosmetic Act was expanded to include FDA regulation of biomedical devices. Although very important for the standardization and safety of devices for prolonged support, the market is relatively small and the expense of FDA certification has slowed the development of such devices in the United States. The basic research continues everywhere, but the transition from clinical implementation is now seen primarily in Europe and Japan.

We have learned a lot about clinical research from the ECMO experience. Principles and practices which apply to simple interventions (such as a drug, an artificial joint, or a
cardiac pace maker) do not apply to complex life support systems like ECLS. Before beginning Phase I clinical trials, the entire hospital must learn and be prepared for the technology. In the case of ECLS this includes the operating room, the emergency room, the blood bank, the clinical laboratory, radiology, the patient transfer and referral system, the financial administrative system, and all the ICUs and the intensive care staff that would be involved with the trials. The technology has to be thoroughly learned before beginning clinical cases. Protocols covering the possible complications have to be developed and practiced before starting clinical cases. The clinical team may include perfusionists (who are very familiar with the technology but not with intensive care medicine), ICU nurses and respiratory therapists (who are very familiar with critical care but not with perfusion technology), and physicians who may need to learn both perfusion technology and ICU nursing regimens in addition to the complex physiology and pathophysiology of extracorporeal life support. A study of such a complex technology which includes inexperienced centers will give poor results (like the 1970s ECMO trial). Such poor results can inhibit laboratory and clinical research on a new technology for decades.

ECLS is the only life support technique which has ever been studied by prospective randomized trials. There has never been, and never will be, a prospective trial of intubation and mechanical ventilation, the use of antibiotics for sepsis, the use of vasoactive drugs for shock, or the use of mechanical renal replacement for acute renal failure. ECLS has been studied in four prospective randomized trials in neonatal respiratory failure and inhaled nitric oxide for treatment of neonatal pulmonary hypertension. Clinical trials of ECLS in neonates, and a decade later led to a change in treatment of respiratory failure in children and adults. Unlike children and adults, however, the underlying pathophysiology in most infants with neonatal respiratory failure is pulmonary vaso spasm with right to left shunting. This led to the study of various inhaled pulmonary vaso dilators, the most successful of which is nitric oxide gas. Similar studies identified pulmonary hypertension as the primary culprit in respiratory failure associated with congenital diaphragmatic hernia. Two decades ago, standard practice was immediate emergency repair of diaphragmatic hernia, assuming the cause of hypoxemia was the presence of the hernia itself. Now we know that the presence of the hernia causes lung hypoplasia, which in turn leads to pulmonary hypertension with pulmonary vasospasm. However, reduction of the hernia is now the last step in treatment rather than the first. This same line of investigation led to the observation that fetal tracheal occlusion in animal and clinical diaphragmatic hernia causes lung growth and avoids the hypoplasia and pulmonary hypertension following delivery. Unfortunately, the practice of fetal operations still leads to significant incidence of premature labor and fetal loss, so pressure-induced lung growth is no longer practiced clinically even in an experimental setting. However, pressure-induced lung growth in diaphragmatic hernia patients performed after birth while patients are on ECMO support is not only feasible, is likely to be successful in solving this last remaining high-mortality problem in neonatal respiratory failure. Clinical trials of fluoro carbon-induced lung distention in ECMO-supported CDH patients are currently underway.

The Future of ECLS in Neonatology

Steps in prevention and treatment of neonatal respiratory failure, discussed above, will decrease the need for and use of ECLS for respiratory failure in full-term newborn infants. However, there will always be infants with severe neonatal sepsis, hypoplasia, diaphragmatic hernia, and pulmonary hypertension unresponsive to other methods of treatment, who will survive and lead healthy lives after a period of extracorporeal support. The use of fluoro carbon-induced lung distention to cause lung growth in hypoplasia, as discussed above, has the potential to result in routine survival in this group of patients. There are some full-term infants with incurable lung disease, such as alveolo capillary dysplasia, profound hypoplasia, and alveolar proteinosis in the newborn. In time these conditions will be treated with lung transplantation. ECMO support will be needed from birth to the time...
of transplantation, and in some cases, after transplantation until the transplant is working successfully.

ECMO will always be needed for severe cardiac failure in the newborn. Whether bridging to recovery, bridging to an implanted device, or bridging to cardiac repair or transplantation, extracorporeal support will be required for some children with severe cardiac malformations which are symptomatic from birth. In addition, ECLS provides excellent support during shock caused by sepsis or hypovolemia in the newborn.

In the next decade, the most significant laboratory and clinical investigation will be in the area of ECLS for the very premature, very low birth weight infant. Even with the availability of surfactant as treatment, prolonged intubation and mechanical ventilation are still required for many premature infants. The mortality and the incidence of intracranial bleeding and neurodevelopmental delay are significant. It is obvious that a fetus living in utero is much simpler and much safer than a premature infant trying to live while breathing air and subject to the complications of intensive care. Because of this, we go to great extremes to try to prevent premature delivery. One approach being studied in the research laboratory is modification of the ECMO system to an artificial placenta, permitting simulation of in utero growth rather than trying to make a premature infant survive on extraterine conditions. An artificial placenta is simply a membrane oxygenator and hemofilter which is driven by arterial pressure through an arterial venous fistula, ideally via the umbilical vessels. Management of the extracorporeal gas exchange is modified to maintain fetal hypoxemia to encourage, rather than eliminate, the physiology of pulmonary vaso spasm and fetal circulation. Excretory and nutritional functions of the placenta are fairly easily duplicated with a microporous filter in the circuit. With such a system, growing fetuses would be maintained in a simulated artificial uterus (floating in artificial amniotic fluid and maintained in a small temperature-controlled, fluid-controlled, and electrolyte-controlled chamber). The goal of current research is to maintain premature fetal animals in such a system until they reach maturity, then “deliver” the fetus from the artificial uterus and the placenta directly to normal newborn conditions. The importance of this research related to neonatology includes the potential elimination of the complications of current management of low birth weight premature infants. This system would also greatly decrease the expense of managing premature infants who must survive outside the mother.

These improvements in ECLS rely on improvements in the technology which are under study in many laboratories. The development of plastic which is inherently nonthrombogenic will permit the use of extracorporeal support without any systemic anticoagulation and without the complications of thrombocytopenia, embolism, and bleeding. This would expand the potential applications of ECLS to newborn infants at risk for intracranial bleeding, newborns who require major operations, etc. New techniques of vascular access under study are the use of tidal blood flow through a single lumen catheter, modified double lumen catheters to allow single vein access, and techniques and devices to avoid spasm of the umbilical vessels, allowing umbilical vessel access for premature infants. Many of the potential complications of ECLS as currently practiced relate to the use of the high-blood flow resistance, relatively thrombogenic, solid-silicone rubber membrane lung as standard practice in the United States. Hollow fiber devices of various sizes using solid membranes are available in Europe and Japan and will some day be available in the United States, greatly simplifying the extracorporeal circuit. This simplification will allow routine use of ECLS without a specialized technical team as currently practiced. In the future, ECLS will be managed as a routine part of treatment, similar to the way that mechanical ventilators are used today.

In summary, the use of prolonged extracorporeal support has prolonged the life of many critically ill infants into healthy adulthood. In the process, we have identified many aspects of the technology of the devices and the pathophysiology of neonatal respiratory failure which have improved the care of many other patients. Current research is focused on simplifying the technology and applying it to other populations, such as the very premature infants.

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