CHAPTER 137 ■ EXTRACORPOREAL CIRCULATION FOR RESPIRATORY OR CARDIAC FAILURE

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You probably turned to this chapter because you are caring for a patient with acute heart or lung failure, and the patient is failing despite your best treatment. The risk of death for your patient is over 80% any way you measure it. The patient might be a woman with streptococcal pneumonia, a child who cannot come off cardiopulmonary bypass after a cardiac operation, a man with chest trauma, acute respiratory distress syndrome (ARDS), or massive pulmonary embolism, or an emergency room (ER) patient undergoing cardiopulmonary resuscitation (CPR). Your only option to improve survival is extracorporeal life support (ECLS) with mechanical artificial organs.

ECLS is the use of an artificial heart (pump) and lung (membrane oxygenator) to replace organ function for days or weeks, to allow time for diagnosis, treatment, and organ recovery or replacement. The indications for ECLS are acute, severe heart or lung failure, not improving on conventional management. In a patient with an 80% to 100% risk of dying, the healthy survival results with ECLS range from 40% in cardiac arrest with CPR to 95% in neonatal meconium aspiration. ECLS is routine treatment in every major neonatal ICU and pediatric cardiac surgery program. Why is ECLS not used routinely in every adult ICU and emergency room? The reasons are complexity, expense, the need for special equipment and experienced personnel, and education. Improvements in the technology for ECLS will solve some of these limitations. Intensivists in neonatology and pediatrics understand the principles of ECLS, so most of this discussion is devoted to adult patients.

BACKGROUND

The heart/lung machine was developed by John Gibbon, beginning in 1939 and culminating in the first successful heart operation using a heart–lung machine in 1954 (1). 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, causing fatal complications if it was used for more than 4 hours. The major cause of blood damage was the direct exposure of blood to gas (2,3). Interposing a gas exchange membrane of plastic (4) or cellulose (5) 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 (4–6). This changed when thin sheets of dimethyl polysiloxane polymer (commonly called silicone rubber) became available in the 1960s. Using silicone rubber membrane, artificial lungs with potential clinical application were designed and studied (7–10). By eliminating the gas interface it was possible to use a modified heart–lung machine for days at a time, and the physiology and pathophysiology of prolonged extracorporeal circulation was worked out in the laboratory (11–13).

The first successful use of prolonged life support with a heart–lung machine was conducted by J. Donald Hill et al. in 1971 (14). The patient was a young man suffering from ARDS, a newly recognized entity in those days and initially called "adult respiratory distress syndrome." The entire discipline we now call critical care was evolving at the same time. After Hill's case, several other successful cases were reported in children and adults with severe pulmonary and cardiac failure (15). At the same time there seemed to be an epidemic of ARDS, and it looked like extracorporeal support would be the answer. A multicenter 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 end point 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%, with or without ECLS. We learned that extracorporeal support attempted by inexperienced teams, in venoarterial mode for 1 week without protecting the lung from ventilator injury, 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 finally, we developed a name for the technology: extracorporeal membrane oxygenation (ECMO). The results of that study were published in 1979 (16). Laboratory and clinical research on ECLS in adults essentially stopped for a decade. However, the results in neonatal respiratory failure were very encouraging.

We reported the first successful case of ECLS for respiratory failure in a newborn infant in 1976 (17). Our laboratory had been studying membrane oxygenator development and prolonged extracorporeal circulation in animals for 10 years. We and others had used extracorporeal support for postoperative cardiopulmonary failure in children with the first successful

pediatric cardiac case in 1972 (18). White et al. (19) and Dorson et al. (20) had initiated clinical trials in neonatal respiratory failure without success. We treated 40 newborn patients over the next 5 years with 50% survival (21). Neonatologists and surgeons from other institutions joined us to learn the technology. By 1986 eighteen neonatal centers had successful ECMO teams (22).

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 (23). Another prospective randomized trial was carried out by O'Rourke et al. at the Boston Children's Hospital (24). ECMO became standard treatment for severe neonatal respiratory failure by 1986, and standard treatment for severe cardiac failure in children by 1990.

Kolobow (25) showed that high ventilator inspiratory pressure (lung stretch) and high FiO_2 caused severe lung injury. Gattinoni et al. (26) and Kolobow (25) separated respiration from oxygenation by removing CO_2 by extracorporeal circulation (making ventilation unnecessary) and oxygenating by insufflation. Using extracorporeal CO_2 removal, they prevented stretch injury, and reported 56% survival in severe ARDS. These observations led to renewed interest in ECLS for adult respiratory failure. By the 1990s several groups reported similar results (27–29). The value of avoiding lung stretch injury has been verified in many studies (30–32), decreasing the incidence of iatrogenic lung injury (and decreasing the need for ECLS). Even with these and other improvements, the mortality for ARDS in otherwise healthy patients was still 30% (32).

The use of ECMO allows study of patients who would otherwise have died. This unveiled many aspects of respiratory 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 20 years that group has developed guidelines and practices, published the standard textbook in the field (33), and maintained a registry of ECLS cases.

ECLS TECHNIQUE AND PHYSIOLOGY

Extracorporeal life support is simply the use of a modified heart/lung machine to provide gas exchange (and systemic perfusion if necessary) to prolong the life of a patient when native heart and lung function is not adequate to sustain life. The technique, indications, methods, and results are described in detail in the book *ECMO: Extracorporeal Cardiopulmonary Support in Critical Care* published by the Extracorporeal Life Support Organization (www.elso.med.umich.edu) (33). The heart–lung machine used for cardiac surgery is modified, both in devices and technology, to be used for days or weeks in the intensive care unit, but the purpose is the same: to keep the body alive during heart or lung failure. The technique is invasive and complex. A large (23–30 French catheter) is inserted into the inferior vena cava or right atrium; venous blood is drained, passed through an artificial lung, and pumped back into the patient, either into the aorta (venoarterial [VA] bypass) or into

the right atrium (venovenous [VV] bypass). VA bypass puts the artificial lung in parallel with the native lungs and substitutes for both heart and lung function. In VV bypass, the artificial lung is in series with the native lungs and the patient is reliant on his own hemodynamics for pulmonary and systemic perfusion. ECLS allows decreasing the ventilator to nondamaging "rest" settings (typically FiO_2 0.3, pressure 20/10, rate 4), decreasing vasoactive drugs, and optimizing other aspects of treatment.

Because the surfaces of the extracorporeal devices are plastic, it is necessary to anticoagulate the blood with a continuous infusion of heparin, titrated to a low but constant level of anticoagulation. This level of anticoagulation is measured by whole blood activated clotting time (ACT). The normal is 120 seconds, and during ECLS, ACT is maintained at approximately 180 seconds. Although this level of heparinization prevents thrombosis in the extracorporeal circuit, circulating platelets still adhere to the plastic surfaces, become activated which attracts more platelets, grow into platelet aggregates, and eventually break off and recirculate as effete platelets, which are removed by the reticuloendothelial system in the liver and spleen. Because heparinization and thrombocytopenia are necessary components of ECLS, the major risk of the procedure is bleeding. As currently practiced, significant bleeding is rarely a serious problem, but this requires the continuous bedside attendance of a specialist whose primary job is to measure the ACT and platelet count at very frequent intervals and titrate heparin dose and platelet infusions accordingly. Properly managed, ECLS can be used for weeks without hemolysis, device failure, clotting, or bleeding, but it is invasive and expensive. The technology not only must be learned and practiced by the intensive care unit team, but also must be endorsed by the entire hospital. Management of the patient during ECLS includes management of perfusion and gas exchange as above, but also attention to fluid balance, oxygen consumption and delivery, nutrition, position, and the monitoring and sustaining of function of other organs.

In *respiratory failure*, VV access is preferred. Gas exchange across the native lungs is usually minimal during the first several days of ECLS; therefore, the patient is totally dependent on the extracorporeal system. As native lung function returns, systemic blood oxygenation and CO_2 clearance improve, improved gas exchange can be measured at the airway, and the extracorporeal blood flow rate is gradually decreased, allowing the native lungs to assume a larger percentage of gas exchange. When the native lungs have improved, the patient is tried off ECLS at nondamaging ventilator settings. When this trial is successful, the cannulas are removed and recovery continues. Patients who are successfully weaned off ECLS have a 90% likelihood of complete recovery.

In *cardiac failure*, VA access is required (usually via the femoral vessels). Inotropes and pressors are weaned off, and systemic perfusion is maintained by extracorporeal flow. Lung function usually returns to normal in a day or two, and the patient can be awakened and extubated. When the patient is stable, and the function of other organs can be determined (especially the brain), a decision can be made regarding bridge to recovery or bridge to ventricular assist device (VAD) and transplantation. When ECLS is used for cardiac support, the pulmonary and left ventricular blood flow is decreased in proportion to the extracorporeal flow. This can lead to two problems. First, if the heart stops altogether, the left atrium and the left ventricle will gradually distend with bronchial

venous blood, leading to high left atrial pressure and pulmonary edema. This condition is diagnosed by the lack of pulsatility in the systemic arterial system. If left ventricular (LV) function is inadequate to maintain emptying of the left heart, the left side of the heart must be drained into the venous line, either by direct catheterization of the left atrium or by creation of an atrial septal defect. The second problem with VA bypass in the totally failing heart is thrombosis in the left atrium or left ventricle. This will occur even in the presence of systemic heparinization. Thrombosis is diagnosed by echocardiography. If a patient has left atrial or left ventricle thrombus, it is important to avoid spontaneous left ventricular function. Usually such patients are candidates for VAD or cardiac replacement, and the clot is removed before embolism could occur.

CLINICAL RESULTS

The most recent data from the ELSO registry are shown in Table 137.1. Participation in the Extracorporeal Life Support Organization is voluntary, but almost all cases treated with ECLS in established centers are included in the registry. There are currently over 30,000 patients who have been managed with ECLS. Although there are extensive data on gas exchange, perfusion, coagulation, and so on, the only important statistic is hospital discharge survival because the technique is a life-support technique and it is applied only to patients who are not expected to survive otherwise with a high (80%–100%) risk of dying with continuing conventional treatment. The mortality risk is measured differently in different age groups.

Neonatal Respiratory Failure

The largest group of patients treated with ECLS is newborn infants with respiratory failure. There are only a few causes of severe respiratory failure in newborn infants. Survival after

ECLS for meconium aspiration, infant respiratory distress syndrome (IRDS), primary pulmonary hypertension of the newborn (PPHN), and neonatal sepsis is 80% to 95%, and 60% for congenital diaphragmatic hernia. The reason for these excellent results is that the causes of respiratory failure in neonates do not destroy lung tissue. The primary pathophysiology is pulmonary hypertension with right-to-left shunting through the ductus arterious (persistent fetal circulation). During ECLS the pulmonary vasculature relaxes, the ductus closes, and lung recovery occurs promptly. The problem in congenital diaphragmatic hernia is that the hernia compresses the lungs and causes bilateral lung hypoplasia *in utero* in addition to pulmonary vasospasm. The hypoplastic lungs may be too small to support the infant.

The early neonatal ECMO patients are now adults with children of their own, and there is abundant information on long-term follow-up. About 10% of surviving patients have some neurologic disability; the most common is some degree of hearing loss. This is lower than the incidence of complications in critically ill infants not treated with ECLS, indicating that these are the complications of profound illness in the newborn. The use of ECLS in neonatal respiratory failure decreased after the initiation of nitric oxide inhalation to treat pulmonary hypertension. Approximately 1,000 per year are entered into the ELSO registry.

Pediatric Respiratory Failure

Severe respiratory failure in older children is relatively rare, compared to the incidence in newborn infants and adults. The most common cause is viral or bacterial pneumonia. Status asthmaticus is another life-threatening problem in children. ECLS is used when a patient is not responding to other methods of management. The survival rate is approximately 75%, varying to some extent with the primary condition. The effectiveness of ECLS in pediatric respiratory failure was

TABLE 137.1

OVERALL PATIENT OUTCOMES WITH ECLS FOR CARDIAC AND
RESPIRATORY FAILURE

	Total	Surv	ECLS	Surv to	DC
Neonatal					
Respiratory	20,993	17,889	85%	16,005	76%
Cardiac	2,898	1,684	58%	1,095	38%
ECPR	274	176	64%	109	40%
Pediatric					
Respiratory	3,390	2,173	64%	1,895	56%
Cardiac	3,658	2,199	60%	1,624	44%
ECPR	523	263	50%	200	38%
Adult					
Respiratory	1,255	740	59%	646	51%
Cardiac	671	300	45%	216	32%
ECPR	189	80	42%	59	31%
	33,851	25,504	75%	21,849	65%

ELSO registry data, December 2006. The data for 2006 are incomplete. ELSO, Extracorporeal Life Support Organization; Surv, survival; ECLS, extracorporeal life support; DC, discharge; ECPR, extracorporeal cardiopulmonary resuscitation.

demonstrated in a contemporary matched pairs study by Green et al. (34). Most children with respiratory failure can be managed successfully with venovenous access. In children who do not survive, the most common cause of death is progressive lung destruction from the primary infection, or brain damage from the period of hypoxia and ischemia that preceded ECLS. These children are all essentially normal in follow-up. Once the lung recovers, pulmonary function and exercise tolerance return to normal.

Adult Respiratory Failure

The cause of ARDS is a primary lung event in about half the cases (viral or bacterial pneumonia, aspiration, pulmonary vasculitis, etc.), and secondary to extrapulmonary causes in the others (shock, trauma, pancreatitis, sepsis). The overall mortality for ARDS is approximately 30% even with excellent management. ECLS is indicated for those patients who have a high mortality risk within the first week after intubation. These patients are relatively easy to identify. They have an alveolar-arterial (A-a) gradient for oxygen greater than 600 on day 2, 3, or 4 following initial intubation. The mortality risk for those patients is approximately 80%, and the recovery rate with ECLS in those patients is approximately 70% (35–38). Patients on the ventilator more than 5 days pre-ECLS have less chance of recovery; hence the overall survival rate for ECLS treatment of ARDS is approximately 55%. The University of Michigan has reported the largest experience with ECLS for ARDS. In that series, the overall survival rate was 52% and rose to 65% in 2002 (35). The series is large enough to characterize the patient population and identify the likelihood of recovery based on age and days on mechanical ventilation.

As technology for adult respiratory failure has evolved, ECLS is now practiced using primarily venovenous access, with high blood flow adequate to sustain oxygenation as well as CO_2 removal, lung rest, diuresis, and prone positioning. This approach leads to the 50% to 60% survival discussed above, but a new prospective randomized trial is clearly indicated, and is currently being conducted in the United Kingdom (UK), following the study design of the UK neonatal ECMO trial (39). This brilliant study design solves many of the logistic and ethical problems of prospective randomized trials of life support in which death is the end point. Patients who meet entry criteria in participating intensive care units throughout the country are randomized to continuing conventional care in that center or referral to an ECMO center. In the adult trial, there is one ECMO center in Leicester, England (40). With this approach, the best available care in the entire country will be compared to a specific algorithm in a specific center. The results of this study will be available in the fall of 2007, and preliminary results may be viewed at the Web site. (40) If ECLS is not used for adults in your intensive care unit, the answer to the question posed in the introduction is clear. Do the best you can with what you have, but do not try to set up an ECLS system on the spur of the moment.

Another important application for ECLS in children and adults is status asthmaticus. There are patients with acute asthmatic attacks unresponsive to bronchodilators, intubation, ventilation, sedation, heliox, general anesthesia, and the other extreme measures used to treat status asthmaticus. These patients have overexpansion, air trapping, normal oxygenation,

and profound CO_2 retention. Pneumothorax often occurs and is usually a fatal complication. Approximately 4,000 people die of acute asthma in the United States every year. This condition is ideally treated with ECLS. Simple VV cannulation and relatively low blood flow is all that is required to achieve normal CO_2 clearance and return to normal blood gases. Once this occurs, bronchospasm invariably clears within a day or two (41). Because the risk of pneumothorax and death is significant, and because the risk of ECLS is low, ECLS should be considered in any patient who has a severe asthma attack with PCO_2 >80 despite mechanical ventilation and other optimal treatment. When ECLS is used for status asthmaticus, the gas flow to the membrane lung is slowly increased over hours to avoid potential complications of sudden changes in PCO_2 and pH.

Cardiac Failure in Children

Venoarterial ECLS is currently the only mechanical support system available for children in the United States. Most of the children treated with ECLS have cardiac failure following a cardiac operation, usually for congenital heart disease. These patients cannot be weaned from cardiopulmonary bypass in the operating room, or are weaned but remain in profound cardiac failure despite full inotropic support following operation. Patients who cannot be weaned from cardiopulmonary bypass are attached to the ECLS machine using the same cannulas used for cardiopulmonary bypass (CPB), typically in the right atrium and aorta. If the patient has been weaned off bypass and the chest is closed, vascular access is gained by cannulation of the right internal jugular vein and right common carotid artery, as in newborn respiratory failure. This same vascular access is used for children with myocarditis or myocardiopathy. Because ECLS is commonly used directly after cardiopulmonary bypass, bleeding is a more common occurrence in cardiac patients than in respiratory patients. This is best managed by maintaining the chest open with a sterile plastic sheet over the open wound and blood drainage tubes placed in the chest. In this way the amount of bleeding can be observed directly, and it is easy to reexplore the chest, which is often required every 8 to 12 hours for the first day on ECLS. Bleeding is managed by maintaining the heparinization at very low levels (1.25 times the upper limit of normal ACT), maintaining platelet count over 100,000, and adding aprotinin to enhance platelet function and Amicar to minimize fibrinolysis. A combination of Amicar, aprotinin, and low-level heparinization can lead to thrombus formation in the extracorporeal circuit. In these cases it is important to keep a primed extracorporeal circuit available so that the circuit can be changed if clotting occurs. Aprotinin has been removed from the market due to a higher incidence of renal failure, and further studies are being done.

Generalized fluid overload is a common problem associated with cardiac failure in children. Diuresis is begun immediately with ECLS. If satisfactory negative fluid balance cannot be achieved with continuous infusion of diuretics, continuous hemofiltration is instituted. Survival with ECLS in pediatric cardiac failure is 40% to 50% (42).

Cardiac Failure in Adults

The experience with ECLS for cardiac failure in adults is shown in Table 139.1. The most common indication for ECLS for

cardiac support in adults is acute myocardial failure following myocardial infarction or heart failure following cardiac operation. Vascular access is usually achieved by cannulation of the right atrium via the right internal jugular or femoral vein with arterial return retrograde via the femoral artery. Intraaortic balloon pumping is possible in adults and will support approximately 40% of the cardiac output. Most of the patients treated with ECLS have failed balloon pumping, as well as full inotropic support. If a balloon pump is in place through one of the femoral arteries, it is best left in place because of the risk of bleeding once the pump has been removed. The opposite femoral artery is used for arterial access.

Adult patients in acute cardiac failure are candidates for left ventricular assist device (LVAD) placement as a bridge to recovery or a bridge to transplantation. However, in the acute failure situation it is best to institute ECLS first, to stabilize the circulation and gas exchange, and to determine if other organs are functioning, specifically the brain. If severe brain injury has occurred during the period of acute cardiac failure, ECLS is discontinued, avoiding the futile thoracotomy and expense of LVAD placement. The survival for ECLS in adult cardiac failure is 40% to 50% (43–45).

EXTRACORPOREAL LIFE SUPPORT FOR CARDIOPULMONARY RESUSCITATION

ECLS can be used in association with resuscitation to support cardiac and pulmonary function in cardiac arrest or profound shock. In this application the ECLS circuit must be primed and available within minutes. Therefore, the extracorporeal life support for cardiopulmonary resuscitation (ECPR) cases are done primarily in established ECLS centers, which have both the equipment and the team to institute ECLS on a moment's notice. The limiting factor in establishing ECLS in these cases is vascular access. It is difficult to get rapid arterial and venous access in a patient in full cardiac arrest. Most successful ECPR cases have been in patients who arrested, then briefly resuscitated, with simple vascular access gained following initial resuscitation. Then ECLS cannulas can be placed over a wire through smaller catheters if and when the patient arrests again or proceeds to cardiogenic shock or intractable arrhythmias. In our institution we consider ECPR for patients who have been in cardiac arrest for less than 5 minutes. A few patients who have been arrested with full and well-documented resuscitation for over an hour have been treated successfully, but if the arrest has been prolonged and if profound metabolic acidosis exists, then establishing extracorporeal support is often futile. The overall results for successful, healthy survival after ECPR is approximately 40%, much better than the 5% successful results of external message only (46,47).

OTHER APPLICATIONS OF ECLS

The ability to totally control perfusion and gas exchange with an extracorporeal system offers unique opportunities in other aspects of acute medical care. Profound hypothermia can be treated by extracorporeal support. This is particularly important because patients who are hypothermic may develop ventricular fibrillation during external warming. Hypothermia associated with exsanguinating hemorrhage in the operating room can be treated successfully with ECLS. Perfusion is maintained during the period of bleeding, and hypothermia can be maintained to protect organ function. After bleeding is controlled, blood is returned to the patient associated with warming to avoid the coagulopathy caused by low temperature. Hyperthermic perfusion can be established, either for total body warming or for regional warming, as an adjunct to cancer chemotherapy.

Septic shock was once considered a contraindication to ECLS. However, sepsis often clears during ECLS, and this has become a standard indication in our institution. It is common for patients in septic shock to regain normal vascular tone and to come off all vasopressors within a day or two of instituting ECLS (48). This is partly related to establishing healthy perfusion and gas exchange, and partly related to adsorption of inflammatory mediators by the plastic in the circuit.

ECLS has also been used to support perfusion in potential organ donors, particularly in situations in which death prior to organ donation occurs because of cardiac arrest following elective withdrawal of ventilator support (49).

SUMMARY

Extracorporeal life support sustains cardiac and pulmonary function by mechanical means for patients with profound cardiac or respiratory failure. The technology includes extracorporeal vascular access, perfusion devices, and management of anticoagulation. ECLS does not treat cardiac or pulmonary failure, but offers hours or days of time to establish a diagnosis and allow time for organ recovery or replacement. Overall success is measured in survival because ECLS is used only in patients at a high risk of dying from acute heart or lung failure. Healthy survival ranges from 95% in some cases of newborn respiratory failure to 40% when ECLS is used as adjunct to cardiac resuscitation.

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