Extracorporeal Life Support in Critical Care Medicine

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WITH THE INTRODUCTION of intensive care units in the 1960s, an environment was established for aggressive patient care. Current technologic achievements continue to improve the means by which this care is provided. Hemodialysis, ventilators, parenteral nutrition, and ventricular assist devices all offer temporary, or occasionally permanent, support for failing organ systems. Extracorporeal circulation devices, utilizing pumps and external oxygenators, represent one of the most powerful tools available to the intensivist, surgeon, or neonatologist. They can provide pulmonary or combined cardiopulmonary support. The technique of extracorporeal circulation has been available and in use for the past 20 years. It has become an accepted form of therapy in the management of neonates with respiratory failure, secondary to pulmonary hypertension, infection, or toxic aspiration. Its role in the management of pediatric and adult respiratory or cardiac failure is becoming more clearly defined. It is incumbent that the intensivist understand the potential benefits of extracorporeal life support (ECLS), its proper applications and inherent complications, to fully incorporate this therapeutic modality in patient management.

HISTORIC ASPECTS

Extracorporeal life support dates back to the development of the first heart-lung machine by Gibbon in 1936.[1] The ability to externally oxygenate and pump blood prompted the evolution of cardiac surgery in the 1950s. Technical considerations in the design of external oxygenators resulted in the "membrane lung" which permitted prolonged bypass without excessive protein denaturation or hemolysis.[2-4] Several studies in animals demonstrated its safety and efficacy.[5-7] Extracorporeal bypass in a nonoperative setting for the purpose of providing oxygenation to patients with severe respiratory failure was attempted in the late 1960s. The first successful case occurred in 1971 when a 24-year-old man, who sustained multiple injuries after being struck by a car, was managed for 75 hours with extracorporeal oxygenation during the acute phase of "shock lung syndrome."[8] Several other successful cases followed, and a potential role for extracorporeal membrane oxygenation (ECMO) in the management of patients with adult respiratory distress syndrome (ARDS) began to emerge.[9-11] In 1975, a prospective randomized study, funded by the National Institutes of Health (NIH) was initiated to assess the efficacy of ECMO in the management of ARDS.[12] Study results did not demonstrate a significant difference in survival rates between patients managed with ECMO (9.5%) or conventional ventilator therapy (8.3%).[13] Enthusiasm for ECMO subsided, except in a few centers throughout the world. In the United States, the application of ECMO was redirected from adults to neonates. Neonatal respiratory failure, which is usually a temporary consequence of prematurity or abnormal postnatal shunting of blood, provided an ideal clinical problem for ECMO management. The goal was to support the neonate until persistent fetal shunting of blood or pulmonary immaturity resolved, while preventing the barotrauma associated with mechanic ventilation. Several clinical trials using ECMO for neonatal respiratory failure occurred in the late 1960s and early 1970s, but no patient survived.[7,14,15] In 1975, Bartlett et al reported the first successful neonatal survivor in which ECMO was used.[16] Since that successful case, two studies have prospectively documented ECMO's therapeutic benefit in the management of neonatal respiratory failure.[17,18]

In Europe, several investigators continued to explore the role of ECLS in the management of adults with ARDS. Gattanoni et al has clearly improved on the results obtained in the 1975 NIH study. His clinical studies have been supported by extensive laboratory investigations by

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Supported in part by grants from the National Institute of Health and the W.R. Hearst Foundation.

Received June 22, 1990; accepted July 6, 1990.

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0883-9441/90/0504-0007$5.00/0

Kolobow at the NIH. These studies demonstrate the irreversible and permanent pulmonary parenchymal changes that mechanic ventilation may cause.

Emphasis on the specific function and role of ECLS in patient management has resulted in several acronyms which attempt to summarize its therapeutic goals. Extracorporeal membrane oxygenation is clearly the most commonly used descriptor in the United States. As implied, ECMO focuses on the oxygenating aspects of ECLS. Extracorporeal membrane oxygenation is a carry-over from operative bypass surgery, in which the primary goal is to provide oxygenation for the blood as it is bypassed around the heart and lungs. The device used to perform this task is a membrane lung. In Europe, the benefits of ECLS are not realized for its ability to provide oxygen, but for its ability to remove carbon dioxide. With this particular focus, extracorporeal carbon dioxide removal ($ECCO_2R$) became the appropriate acronym. Although the circuitry and devices used for ECMO and $ECCO_2R$ are nearly the same, the philosophy of their use and other management issues vary. In Japan, extracorporeal lung assist (ECLA) attempts to emphasize both the oxygenating and CO_2-removing functions of the lung. An older term, cardiopulmonary support (CPS), is occasionally used today. To be more generic and broad in our view of the role of external lungs (membrane or hollow fiber), roller pumps, heat exchangers, etc, we have adopted the term extracorporeal life support to describe the entire management process. These basic circuit components do not constitute the entire therapy provided. Hemofilters may be added to compensate for injured or failing kidneys. Mechanic ventilation, whether delivered by air jets, pressure limits, or tidal volumes, is, likewise, inseparable from patient therapy. Other support devices and medications including chest tubes, parenteral nutrition, cardiotonic drugs, antibiotics, and monitoring devices integrate with ECMO, ECCO2R, or ECLA in patient management of patients. This paper will introduce the theoretic indications, practical management issues, and therapeutic goals of ECLS, as it pertains to both the neonatal, pediatric, and adult populations.

METHODS OF BYPASS

Two forms of extracorporeal bypass are available; veno-arterial (V-A) and veno-venous (V-V). In V-A bypass, blood is siphoned from the central venous system and reinfused, after passing through the bypass circuit, into a major artery. This form of bypass has two functions. It exchanges gas in the membrane lung, and it provides hemodynamic support by delivering flow and a pressure head into the arterial system. It is ideally suited for the patient who experiences respiratory and cardiac failure simultaneously. The primary disadvantage of V-A bypass is that it can produce distal ischemic symptoms if insufficient collaterals are present about the arterial vessel used for cannulation. Emboli, either from the catheter tip or the circuit, can likewise lead to tissue loss and organ dysfunction.

Veno-venous bypass is suited for the patient who has isolated respiratory failure with adequate cardiac reserves. Blood is siphoned from the central venous system, as in V-A bypass, but it is reinfused into a major peripheral vein. The resulting effect is that the central venous blood becomes oxygenated and partially cleared of CO_2 before entering the lungs. Unlike V-A bypass, all blood will pass through the right heart and lungs and not be shunted around them. Some recirculation of blood through the bypass circuit occurs, but adequate gas exchange can still be accomplished. Veno-venous bypass avoids the sacrifice of a major artery and the consequent potential morbidity. Emboli released into the reinfusion line are trapped either in the membrane lung or native lungs, rather than in the arterial circulation. It provides no hemodynamic support.

CANNULATION

Cannulation for bypass occurs in the intensive care unit with full support from an operative team. The patient should have an indwelling arterial line, along with a transcutaneous oxygen saturation sensor for continuous monitoring during cannulation and initiation of bypass. After administering local anesthetic, an incision is made over the target vessels which are dissected free from the surrounding tissues. A loading dose of heparin (100 U/kg) is given for subsequent anticoagulation. The cannulas are placed into major vessels through extrathoracic dissections of the vascular branches. The largest sized can-

nula is inserted to permit maximum blood siphoning from the venous line, and to avoid overpressurizing the circuit on the arterial side. Venous drainage is usually accomplished by a catheter placed through the right internal jugular vein into the right atrium. Other drainage sites include the common femoral, and the external or common iliac veins. Reinfusion sites for V-A bypass include the right common carotid artery, and, less frequently, the axillary or superficial femoral arteries. Reinfusion sites for V-V bypass include the common femoral, saphenous, or internal jugular veins. A neonatal double lumen catheter, recently developed and tested at our institution, permits both siphoning and reinfusion of blood to occur into the right atrium with a single catheter.[19,20] The catheter has a 14 french outer diameter. Its inner lumen is disproportionately divided by septum. The larger channel primarily siphons blood through the tip of the catheter. Reinfusion occurs in the smaller lumen and out side holes in the catheter which preferentially direct blood into the right ventricle. An adult-sized double lumen catheter was described by Pesenti et al in 1982.[21]

EXTRACORPOREAL LIFE SUPPORT CIRCUIT

The circuits for all types of bypass support (ECMO, $ECCO_2R$, ECLA) consist of the same fundamental components. The circuit is built from polyvinyl chloride (PVC) tubing, 1/4 to 3/8 inch in diameter, and standard polycarbonate connectors. From the venous cannula, blood is removed at 100 cm of siphon drainage to a servoregulator with an expandable silicone rubber bladder and a microswitch which controls a double occlusion roller pump. When pump outflow exceeds venous drainage, the silicone bladder will collapse. This volume change is sensed by the microswitch which interrupts power to the roller pump. Pump flow stops, while venous drainage continues, replenishing the volume in the collapsed bladder. Once the bladder's volume is restored, the microswitch will return power to the roller pump and permit flow to resume in the bypass circuit. Without servoregulation of pump flow, excessive suction could be applied in the venous line and to the side holes in the venous catheter, causing cavitation of dissolved gasses, hemolysis, and damage to the vessel endothelium. From the roller pump, blood travels to a membrane or hollow fiber oxygenator which provides the gas exchange. The exposed tubing and large surface area of the membrane lungs cool the blood as it passes through the circuit. A heat exchanger is therefore incorporated into the circuit after the membrane lung to rewarm the blood before it is returned to the patient. Between the two patient-connecting lines is a bridge of PVC tubing. This bridge permits recirculation of blood through the bypass circuit during cannulation and trials off bypass. Fig 1 schematically illustrates the basic circuit components and additional monitoring devices frequently incorporated.

The size of the circuit and its components depend on the size of the patient and anticipated flow requirements. For V-A bypass, each circuit is designed to permit flows that will be comparable to the patient's cardiac output. Flows of 120 to 170 cc/kg/min are adequate for a neonate, 80 to 100 cc/kg/min for a young child, and 70 to 90 cc/kg/min for an adult. An appropriately-sized membrane lung must be selected to accommodate the anticipated flow rate through the circuit. Membrane lungs are characterized by their rated flow, which is the maximum flow rate at which blood, entering the oxygenator 75% saturated, will leave 95% saturated. Neonatal circuits typically incorporate membrane oxygenators with 0.4 to 0.8 m^2 of surface area, pediatric circuits with 1.5 to 2.5 m^2, and adult circuits with 3.5 to 4.5 m^2. For V-V bypass, the anticipated flow rates will differ, and depend on the type of gas exchange desired. If V-V bypass is to provide oxygenation in addition to CO_2 removal, anticipated flow rates should be approximately 20% higher than those for V-A bypass.[22] If the goal is strictly CO_2 removal, flow rates may be up to 75% less than the anticipated cardiac output.[23] For adequate CO_2 removal in the latter case, a much larger lung is used relative to the anticipated flow and patient size. In a low-flowing circuit, more than one lung is occasionally required to effect sufficient CO_2 clearance to produce eucapnia in arterial blood.

Several small variations in circuit design occur between different ECLS centers. The most important differences are the means of servoregulation and flow delivery. Instead of bladder reservoirs for servoregulation, some circuits employ in-line pressure transducers. When circuit pressure falls

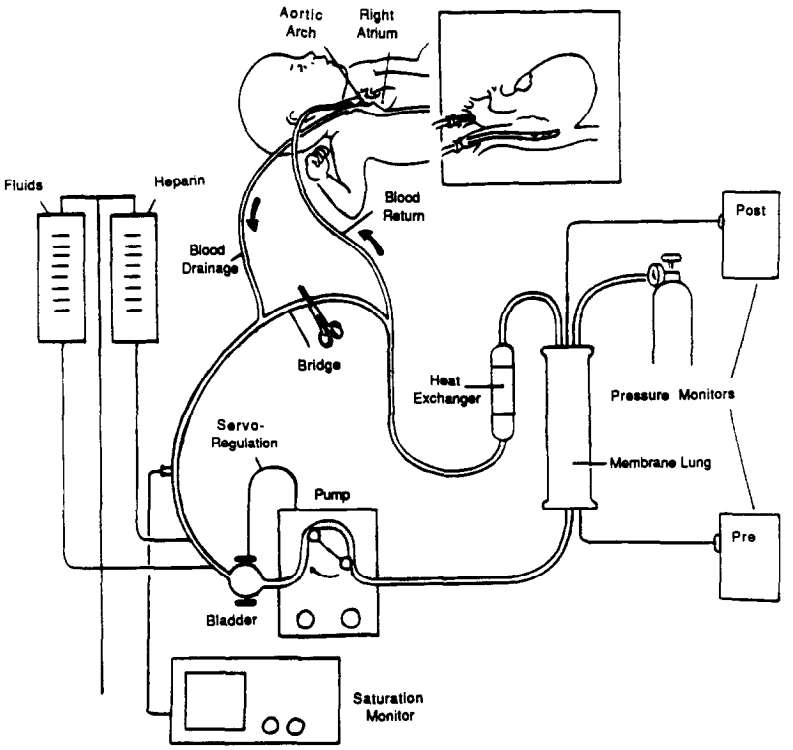

Fig 1. Basic circuit components and monitoring devices incorporated in ECLS.

below a preset value on the venous line or rises above a preset value on the arterial side, pump flow will progressively slow, thereby normalizing any changes. In France, nonocclusive double-stage rotor roller-pumps (Rhone-Poulenc, Paris, France) are used. Their rotating heads drive flow by pinching off segments of a collapsible piece of silicone raceway tubing that accepts the venous drainage. When venous drainage is insufficient, the amount of blood delivered will proportionately fall.[24] Other centers use centrifugal pumps to deliver flow. We have found that these pumps cause excessive hemolysis when compared with roller pumps.[25] Tidal flow bypass, where blood is siphoned and reinfused through the same single lumen catheter, has also been attempted.[26,27]

PHYSIOLOGY OF EXTRACORPOREAL LIFE SUPPORT

Extracorporeal circulation significantly alters the hemodynamic and pulmonary physiology of the treated patient. A goal of all forms of ECLS is the provision of adequate gas exchange, while reducing the barotrauma of conventional positive pressure ventilation. When a patient is placed on bypass, the amount of pressure support previously provided by a ventilator is reduced to "rest settings." These generally include a peak inspiratory pressure of 20 cm H_2O, with a positive end-expiratory pressure (PEEP) of 5 cm H_2O, at a rate of 10 to 20 breaths per minute, and an inspired oxygen concentration (FiO_2) of 21%. Other settings are possible, and depend on the patient's pulmonary disease process. High PEEP has been used to maintain alveolar expansion in neonates and may lead to a shorter course on bypass.[28] In patients with large air leaks from pneumothoracies or bronchopleural fistulas, low continuous positive airway pressure is often successful. Low frequency positive pressure ventilation (LFPPV), commonly used in adults, preserves functional residual capacity by maintaining inflation with 15 to 20 cm H_2O PEEP on a background ventilator rate of 4 to 6 breaths per minute.[29] Nearly any form of airway manipulation is possible, including extubation or frequent pulmonary lavages. The common denominator of all these options is the avoidance of high peak airway pressures.

With V-A bypass, manipulation of both cardiac output and gas exchange occurs simultaneously. Up to 80% of the venous return can be siphoned from the right atrium and diverted through an ECLS circuit. This blood, after being

oxygenated, is then returned into the patient's aortic arch, mixing with the blood pumped from the left ventricle. The total cardiac output will be the sum of the patient's own cardiac output and the bypass flow rate. The hemoglobin saturation will be determined by the rate of bypass flow and the function of the native lungs. Blood from an ECMO circuit will always be 100% saturated if a properly sized and functioning lung has been selected. The saturation of blood leaving the patient's native lungs will be considerably less and will depend on the amount of pulmonary dysfunction and the level of ventilator support provided. If at least 80% of the cardiac output can be captured by the bypass circuit, the patient's hemoglobin saturation will approach 95% to 100%. As a patient's own lungs recover, the amount of gas exchange provided by blood flow through a membrane lung can be reduced. In V-A bypass, this simply involves reducing the rate of bypass flow, which will permit more blood to pass from the right atrium into the pulmonary artery, rather than into the venous cannula.

Veno-arterial bypass also provides hemodynamic support and improves oxygen delivery to peripheral tissues. Our V-A bypass circuit incorporates an in-line blood saturation monitor which inserts into the circuit immediately before the bladder reservoir (Fig 1). A continuous display of the mixed venous saturation (SvO_2) is invaluable in selecting proper bypass flow rates. A low SvO_2 indicates either inadequate oxygen delivery or excessive oxygen consumption. Important components of oxygen delivery include cardiac output, hemoglobin concentration, and hemoglobin saturation. Management of patients on V-A bypass requires optimizing each of these variables. The hematocrit is maintained between 45% to 50%. Maximal saturation of hemoglobin is ensured by delivering more blood to an appropriately-sized membrane lung. Increasing circuit flow rates will enhance cardiac output in addition to improving oxygenation by shunting more blood away from the failing lungs. Tissue oxygen consumption can be minimized through the use of paralytics, sedatives, antibiotics, and modest hypothermia, when necessary. Each of these manipulations will result in an improvement in SvO_2 toward the desired level near 75%.

While V-A bypass controls both components of oxygen delivery, namely cardiac output and hemoglobin saturation, V-V bypass focuses only on gas exchange. Veno-venous bypass causes no direct improvement in cardiac output; all blood delivered to the tissues occurs from the pumping action of the left ventricle. Veno-venous bypass only alters the gas content of the central venous blood.

Gas exchange in blood consists of both oxygen delivery and CO_2 removal. The amount of gas exchange in patients on V-V bypass depends on the rate at which blood is siphoned to the membrane lung, the size of the lung, and the flow rate and composition of the gas ventilating the membrane lung. The two components of gas exchange are not inseparable. Oxygenation across a membrane lung is a function of the amount of unsaturated hemoglobin passing through it. In V-V bypass, desaturated blood returning to the central venous circulation is withdrawn into the circuit, oxygenated completely, and then reinfused to mix with more desaturated blood from the periphery. If no recirculation of blood existed (ie, only desaturated blood from the tissues was selectively siphoned into the circuit, and the oxygenated blood selectively returned to the right ventricle), blood entering the pulmonary artery would be 100% saturated. Escape of deoxygenated blood into the right ventricle and recirculation of oxygenated blood back into the circuit both contribute to inefficient oxygenation and cause the saturation of blood entering the pulmonary artery to be closer to 80% to 90%. To compensate for recirculation, the amount of blood actually needed to pass through a membrane lung to produce better oxygenation will frequently be in excess of normal venous return. The higher blood flow rates will require the use of a lung with a rated flow slightly greater than the patient's expected cardiac output.

Carbon dioxide clearance across a membrane lung depends on the surface area of the lung and on the CO_2 concentration gradient between the venous blood and the ventilating gas. If room air or oxygen ventilates a membrane lung, the gradient will be near 47 mm Hg when the gas flow rates are high. At lower sweep rates, CO_2 will not be cleared rapidly from the lung, and the gradient may decrease. The surface area of the membrane lung will determine the area over which the CO_2 gradient can dissipate. A larger surface area will permit greater CO_2 clearance. If the

goal of ECLS is CO_2 removal rather than oxygen delivery, high blood flow rates will not be required. Only a portion (usually 30%) of the cardiac output needs to be captured by the membrane lung to effectively clear all metabolically produced CO_2.[30] Hemoglobin does not serve as a sink for CO_2 as it does for oxygen; the pCO_2 of blood leaving the circuit will average with that of the blood returning from the periphery, after equilibrating with bicarbonate and water. A large lung with a relatively small amount of blood flowing through it can effectively eliminate enough CO_2 to produce eucapnia in mixed venous blood. Low-flow V-V bypass will not adequately oxygenate blood, since it is the amount of unsaturated hemoglobin, rather than the size of the membrane lung, that determines the extent of oxygenation possible.

Occasionally during V-A bypass or in high-flow V-V bypass where the goal is oxygenation, too much CO_2 will be removed across the membrane lung, and a marked respiratory alkalosis will ensue. This problem can initially be approached by decreasing the rate of gas flow ventilating the membrane lung to reduce the gradient for CO_2 diffusion. At very low-sweep flows, the efficiency of the membrane lung will fall, and oxygen transfer fails. In such circumstances, the lung can be ventilated with carbogen (95% O_2 and 5% CO_2) or a nonstandard mixture of O_2 and CO_2. The amount of carbogen added can be titrated to achieve a desired arterial pCO_2 of 40 mm Hg.

MANAGEMENT OF PATIENTS ON BYPASS

Caring for patients on ECLS typically requires a nurse and an ECMO specialist. Extracorporeal membrane oxygenation specialists are nurses, respiratory therapists, perfusionists, or physicians who have completed an extensive course in ECMO physiology and have received over 80 hours of bedside instruction and internship. They work with the nurse in providing total patient care. The ECMO specialist performs all circuit manipulations, administers blood products, adjusts the level of anticoagulation, and regulates pump blood flow in prespecified boundaries provided by a physician. The nurse tends to patient care needs, medication acquisition and dressing changes.

While on bypass, a patient remains anticoagulated by a continuous heparin infusion, ranging between 15 to 30 U/kg/h. The level of anticoagulation is monitored by the activated whole blood clotting time (ACT). Heparin is titrated to maintain an ACT between 180 to 200 seconds. Careful attention to urine output, plasma transfusions, and ACT levels permits a tight control. The infinite levels of anticoagulation used during operative bypass for cardiac surgery are excessive and lead to numerous bleeding complications during the relatively prolonged course on bedside bypass. Significant or unusual clotting within the components of the circuit have not occurred at this low level of anticoagulation.

Thrombocytopenia predictably occurs after the initiation of bypass, presumably by dilution in the circuit and platelet consumption in the membrane lung. Platelet transfusions are routinely administered at the initiation of bypass and periodically to maintain a level greater than $100{,}000/mm^3$. Platelets are transfused into the circuit at an infusion port downstream from the membrane lung. Thrombocytopenia may occur even after bypass has been discontinued, and, in light of this risk, platelet count should be monitored for an additional 4 days.[31] Oozing from operative sites and blood sampling require periodic blood transfusions to keep the hematocrit over 45%. A low level of hemolysis can be expected from surface interactions between blood cells and the artificial conduits, components, and occasional clots in the circuit. The rate of hemolysis is monitored with free serum hemoglobin levels. A level exceeding 30 mg/dL (normal < 5 mg/dL) may be the first indicator of significant clot formation or circuit damage.

An accurate record of fluid balance is essential for patient management. Frequently patients are edematous from prior fluid resuscitation and volume administration at the initiation of bypass. After 24 to 48 hours of stabilization, a diuresis towards dry weight is initiated with mannitol or furosemide. Hemofiltration can supplement urine output in patients that do not satisfactorily respond to diuretics.[32]

Patients on ECLS receive the same aggressive and supportive care other intensive care unit patients require. Nutrition is provided parenterally or by nasogastric or oral feedings. Prophylactic antibiotics are given to patients on bypass in the absence of specific infections. Stress ulcer

and decubeti prophylaxis are likewise provided. While a patient is on bypass and anticoagulated, care is taken with any invasive procedure. All blood sampling occurs through previously established access lines. Other procedures, such as chest tube insertions, are performed with electrocautery.

Management of flow rates has previously been described. Optimizing SvO_2 and blood pressure are of major importance in V-A bypass, while gas exchange is the goal in V-V bypass. As pulmonary or cardiac function improves, flow rates can be progressively decreased. When flow rates reach 20 to 30 cc/kg/min, a trial off bypass can be attempted. In V-A bypass, the patient connecting lines are clamped and the bridge opened to permit recirculation of blood within the circuit. In V-V bypass, the ventilating gas to the membrane lung is removed and the gas ports to the membrane lung capped. Blood is still siphoned from and returned to the patient, but no gas exchange occurs. During weaning attempts, the settings of the ventilator are increased to levels commensurate with physiologic support. A successful trial off for 45 to 60 minutes, as evidenced by adequate oxygenation, CO_2 removal, and hemodynamic stability, can be followed by decannulation.

NEONATAL EXPERIENCE

Neonatal pulmonary failure is distinctly different from its adult counterpart and usually results from pulmonary artery vasospasm. The high pulmonary vascular resistance causes blood to be shunted from the right to the left heart through a patent foramen ovale or ductus arteriosus. This prenatal blood flow pattern is known as persistent fetal circulation. The elevated pulmonary vascular resistance may result from toxic aspiration (meconium, blood, amnionic fluid), infection (bacterial, viral), immaturity (lack of surfactant), unknown causes (primary persistent pulmonary hypertension), or structural lesions (congenital diaphragmatic hernias). Medical measures to release the pulmonary vasospasm, including hyperventilation to induce alkalosis or tolazoline administration for vasodilation, are unsuccessful in 5% to 10% of patients. In these, one fourth develop persistent postductal hypoxemia, and ultimately die. Several predictors of mortality have been developed to quantitate degrees of respiratory failure while a patient is supported by a ventilator. At the University of Michigan Medical Center (UMMC; Ann Arbor, MI), the oxygenation index (OI) has been used. The OI is calculated as the product of the mean airway pressure $\times$ FiO_2 $\times$ 100/postductal partial arterial oxygen pressure (PaO_2).[33] Values greater than 40 are associated with an 80% to 90% mortality, while those greater than 25 are associated with a 50% mortality. Some centers use an alveolar to arterial oxygen gradient as an indicator of clinical dysfunction, with values greater than 600 to 620 indicative, of a 90% mortality.[34,35] Others have found that a ratio of arterial to alveolar oxygen partial pressures (PaO2/PAO2) less than 0.15 to be associated with an 80% predicted mortality.[18] A universally-accepted measure or index of respiratory failure has yet to be developed. The original pulmonary insufficiency index (PII), calculated on the basis of an effective alveolar to arterial gradient over time, is more cumbersome than the above methods and is no longer used.[36,37]

The goal of ECMO in the management of neonates is to provide oxygenation until the persistent fetal circulation reverses (usually 4 to 5 days), and avoid the barotrauma associated with mechanic ventilation. The complications of barotrauma caused by ventilators includes pneumomediastinum, pneumothoracies, diminished cardiac output, and the late development of bronchopulmonary dysplasia. In neonates, V-A bypass is more commonly used than V-V bypass. It has, up to now, been technically simpler than V-V. Only one surgical incision is required, and cannulation is more easily accomplished in the common carotid artery than in the femoral or external iliac veins. Persistent leg swelling occurs with ligation of these veins and poses a troublesome late complication. A new neonatal double lumen catheter obviates the technical concerns of V-V bypass previously performed with two separate cannulas. Only one incision is required, and one vessel is cannulated. Excellent oxygenation can be provided and, in recent experiences, very few patients require conversion to V-A bypass for hemodynamic support.[39] Neither V-A nor V-V bypass has been shown to be superior in its ability to reverse persistent fetal circulation.[38]

The indication for ECMO in neonates is relatively straight forward; failure of conventional

management. As noted, each center may vary in its measure of progressive respiratory failure. At UMMC, three out of five postductal arterial blood gasses, drawn 30 minutes apart, demonstrating an OI greater than 40 represents a clear indication, while OIs greater than 25 represent a relative indication. Other relative indications include severe barotrauma or rapid and acute deterioration in respiratory function.

Contraindications to ECMO seek to identify patients who are not likely to benefit from ECMO or who are likely to succumb to a complication of anticoagulation.[40] Prematurity and low birth weight are both associated with an increased incidence of intracranial hemorrhage.[41] Neonates with gestational age less than 35 weeks who have been placed on ECMO suffered a high incidence of intracranial hemorrhage and a 75% immediate mortality after ECMO was discontinued.[42] Previous intracranial hemorrhage, as demonstrated by a preoperative ultrasound, is likely to worsen with anticoagulation, and represents an additional contraindication. Postductal hypoxemia, due to congenital cardiac malformations, must also be ruled out with an echocardiogram before ECMO is initiated. Mechanical ventilation greater than 10 days is associated with a high incidence of bronchopulmonary dysplasia and irreversible parenchymal changes, prohibitively reducing the benefits of ECMO. Neonates with severe congenital anomalies or neurologic deficits incompatible with a meaningful existence are typically not considered as candidates for heroic and aggressive management.

Complications that occur in neonates on bypass fall into three broad categories: bleeding, circuit-related, and physiologic. Bleeding is common, and occurs in 20% to 40% of patients. Its severity ranges from minor oozing at the cannulation site to grade IV intracranial hemorrhage. Intracranial hemorrhage is most serious but occurs in only 14% of full term neonates (>35 wk gestational age).[42] There were, on average, 0.28 mechanic complications per case during the first 715 neonates placed on bypass.[43] These included oxygenator failure (7%), tubing rupture (3%), pump failure (2%), heat exchanger malfunction (1%), cannula-related problems (7%), and miscellaneous problems (7%). They created only temporary physiologic instability, and none were associated with a decreased patient survival rate compared with overall survival rate. Physiologic complications occurred 1.77 times per case, and included hematologic changes, seizures, electrolyte imbalances, arrhythmias, renal dysfunction, sepsis, etc. The incidence of physiologic complications decreased as the experience of an ECMO center increased. Circuit-related problems are likewise decreasing, as better parts and components are developed.

The efficacy of ECMO has been measured in terms of survival. Initial studies demonstrated an improved survival compared with historic controls.[44] The first prospective randomized controlled study, using a "randomized play-the-winner" statistical method, showed that ECMO improved survival when compared with conventional management.[45,17] Using identical entry criteria, the single patient assigned to conventional management for respiratory insufficiency died while all nine of the patients assigned to ECMO management survived. These findings were supported by a second prospective, randomized study which likewise demonstrated a significantly improved survival rate with ECMO.[18] Four of 10 patients assigned to conventional therapy died, while 28 of 29 assigned to ECMO survived. The study was terminated once a P value of .05 was reached.

Table 1 summarizes a recent compilation of data from neonates treated with ECMO.[46] The most frequent diagnosis is meconium aspiration syndrome, occurring 36.4% of the time. The best results occur in patients with meconium aspiration syndrome (survival rate, 92.5%). The average survival rate of all diagnoses is 82.9%. Current survival rates may actually be higher, since the values listed are from all patients,

Table 1. Extracorporeal Life Support for Neonatal Respiratory Failure

Diagnosis	Survival (%)	Mortality (%)	Total No. Patients
Meconium aspiration syndrome	92.5	7.5	1,313
Respiratory distress syndrome	83.2	16.8	517
Congenital diaphragmatic hernia	62.5	37.5	546
Pneumonia/sepsis	76.8	23.2	366
Persistent fetal circulation	86.8	13.2	456
Other	74.5	25.5	137
	82.9	17.1	3,335

Data from the Neonatal ECMO Registry of the Extracorporeal Life Support Organization as of January 1990.[46]

including the earliest cases. A learning curve is present at new ECMO centers, and the survival rate of the first 20 patients is less than that in the remainder.[43] The improved survival rate may be related to a decrease in physiologic complications from 2.26 per case for the first 10 cases to 1.6 per case for the remaining patients.[43]

Extracorporeal membrane oxygenation has been shown to improve survival rates in patients with congenital diaphragmatic hernias. In our institution, there has been a clear trend ($P = .06$) toward enhanced survival (76%) in patients with congenital diaphragmatic hernias after 1981, since ECMO has been available, compared with survival rates (50%) prior to the availability of ECMO.[47] This enhanced survival rate with ECMO is not universally present. A multicentered study involving 93 congenital diaphragmatic hernia patients demonstrated only a 58% survival rate in patients managed with ECMO, compared with the UMMC study where survival in similar patients was 87% (13 of 15).[48] Mortality was associated with intracranial bleeding, operative site bleeding, and renal failure. Extracorporeal membrane oxygenation has also been used in the neonatal population as a bridge to or support after cardiac surgery, including heart transplantation.[49,50]

Follow up of neonatal patients treated with ECMO has revealed excellent results. In one study, 63% of the patients (45 of 72) were normal or near normal. Major developmental delay occurred in 17% (12 of 72) and major pulmonary problems occurred in 8% (6 of 72) of neonates.[51] Similar success rates have been reported by other centers.[52,53] There are no control groups with whom to compare this complication rate, since the predicted mortality of the neonates placed on ECMO is 85%. Most neurologic sequelae result from perinatal hypoxemia and hypotension which occur in up to 50% of similar patients not managed with ECMO.[54] Carotid artery ligation may contribute to some of the neurologic changes in the ECMO-treated population, since a preponderance of unilateral right-sided brain lesions have been identified.[55]

PEDIATRIC AND ADULT EXPERIENCE

Enthusiasm for the role of ECLS in ARDS rapidly waned when the NIH-sponsored trial of 1979 did not demonstrate any improved survival with ECMO compared with conventional management.[13] A retrospective assessment of this study reveals several points which cloud or obviate the potential benefits of ECMO. In the NIH ECMO study, the amount of bleeding from the anticoagulation averaged between 1.5 to 2.0 liters per person per day. Ventilator support was often continued at near maximal levels, including high pressures with rapid rates, causing continued barotrauma. Many patients had been intubated for several days (average 9.6 days) prior to the initiation of ECMO, and probably had preexisting, irreversible pulmonary changes, caused either by the disease process or aggressive mechanic ventilation. Seven of the eight surviving patients had been intubated for less than 7 days. Additionally bacterial and viral pneumonia predominated as the main cause of respiratory insufficiency. Extracorporeal membrane oxygenation has been demonstrated to be more effective in patients with ARDS than with infections.[56]

Continued investigation into the pathophysiology of respiratory failure and the benefits of ECLS persisted, predominantly in Europe and at the NIH. The role of ECLS took on a new focus, that of the prevention of barotrauma induced by mechanic ventilation. Kolobow at the NIH, using sheep models for lung disease, demonstrated the consequences of high pressure ventilation and pure oxygen on normal lungs.[57] Ventilating healthy sheep with a peak inspiratory pressure of 30 cm H_2O, keeping $PaCO_2$ normal, caused a significant reduction in pulmonary function within 48 hours; with peak pressures of 50 cm H_2O, pulmonary deterioration occurred more rapidly over 12 to 36 hours.[58,59] Similar findings, along with a measured loss of surfactant activity, have also been demonstrated to occur in dogs ventilated for 1 to 2 hours with a PIP of 26 to 32 cm H_2O.[60]

In Milan, Italy, clinical trials continued in adults. To reduce the amount of pressure support required from a ventilator, Gattinoni et al used ECLS to separate the two components of gas exchange; O_2 delivery and CO_2 removal. A primary function of respiration, ie, the movement of gas into and out of lungs, was viewed to be CO_2 elimination. When CO_2 was cleared by other means (as through extracorporeal removal), alveolar ventilation in otherwise healthy animals was shown to significantly decrease or stop.[61] As

previously described, $ECCO_2R$ is accomplished at relatively low-flow bypass rates (20% to 30% cardiac output) through an oversized membrane lung. The bypass technique is usually V-V. Adequate oxygenation may occur by a continuous flow of oxygen into the alveoli, where it can then diffuse down its concentration gradient into the capillary blood. The continuous flowing of blood preserves this concentration gradient. Apneic oxygentation has been reported in the past, but its usefulness has been limited by CO_2 accumulation and the resultant respiratory acidosis.[62,63,64,65,66] The advent of external "oxygenators" or "CO_2 removers" obviates this limiting complication. Apneic oxygenation, after several hours, produces a loss of functional residual capacity and decreases total lung compliance.[67] This complication is avoided if a few (3 to 4) mechanic breaths are delivered every minute to simulate a sigh of normal ventilation. The process of delivering a continuous flow of oxygen to alveoli by maintaining PEEP or continuous positive airway pressure at 5 to 10 cm H_2O with a respiratory rate of 3 to 4 breaths per minute is referred to as LFPPV. Low frequency positive pressure ventilation works best when accompanied by V-V bypass, since no blood will be diverted from the pulmonary circulation. Combining LFPPV with $ECCO_2R$ theoretically produces an ideal environment to permit pulmonary recovery, providing adequate gas exchange, and preventing additional barotrauma from mechanic ventilation. $ECCO_2R$ will remove metabolically produced CO_2 to maintain eucapnia (in addition to providing a small amount of oxygenation), while LFPPV will provide adequate oxygen delivery (with a small amount of CO_2 clearance). The safety and efficacy of this theory was supported by experimental trials in sheep and other animals.[68,69]

Low frequency positive pressure ventilation with $ECCO_2R$ is one of several methods by which adults and children can be supported by ECLS. Veno-arterial or high-flow V-V bypass are also possible. Extracorporeal CO_2 removal requires lower blood flow rates; smaller sized catheters used for this bypass technique are easier to place and usually do not interrupt major peripheral vessels. The specific needs and technical issues related to individual patient needs will often dictate the form of bypass to be initiated.

The indications for ECLS in the pediatric and adult populations are similar to those in the neonate with a few modifications. At the UMMC, several criteria have been introduced, the most important of which is the presence of a reversible pulmonary disease process. A transpulmonary shunt greater than 30%, despite optimal therapy, should exist along with a static pulmonary compliance of less than 0.5 cc/kg/cm H_2O. Significant underlying pulmonary insufficiency or high pulmonary artery pressures imply poor pulmonary reserves, and detract from the benefits ECLS may provide. Patients should be intubated for less than 7 days. Periods of intubation greater than 10 days increase the incidence of barotrauma-induced pulmonary fibrosis. Patients should be younger than 65 years and have no underlying bleeding disorders or contraindications to anticoagulation. Additional contraindications include major brain injury, or conditions incompatible with a favorable long term prognosis. Relative contraindications include immunosuppression (because of a high rate of bacterial infection) and multisystem organ failure (because of uniformly poor results).

Tables 2 and 3 summarize the results of the pediatric cases entered into the international registry. Two broad categories have developed for pediatric ECLS support; cardiac and pulmonary. While intraaortic balloon pumps, intravascular pumps, implantable ventricular assist devices, and total artificial hearts can provide nonpharmacologic cardiac support in the adult population, no such devices exist for the pediatric population. Veno-arterial bypass presently is the only means by which mechanic cardiac support can be delivered to children. Veno-arterial bypass may serve as a bridge to transplantation, surgery, or recovery after cardiac surgery. The

Table 2. Extracorporeal Life Support for Pediatric Cardiac Failure

Diagnosis	Survival (%)	Mortality (%)	Total No. Patients
Cardiac surgery	43.1	56.7	123
Cardiac transplant	33.3	66.7	9
Myocardopathy	25.0	75.0	4
Other	50.0	50.0	2
	42.0	58.0	138

Data from the Pediatric Cardiac ECLS Registry of the Extracorporeal Life Support Organization as of January 1990.[46]

Table 3. Extracorporeal Life Support for Pediatric Pulmonary Failure

Diagnosis	Survival (%)	Mortality (%)	Total No. Patients
Respiratory distress syndrome	41.4	58.6	29
Viral pneumonia	45.8	54.2	24
Aspiration	60.0	40.0	10
Bacterial pneumonia	0	100	3
Other	46.7	53.3	15
	44.4	55.6	81

Data from the Pediatric Pulmonary ECLS Registry of the Extracorporeal Life Support Organization as of January 1990.[46]

Table 4. European Experience With Extracorporeal Life Support for Adult and Pediatric Respiratory Failure

Site	No. of Patients	No. of Survivors	Survival Rate (%)
Marburg, Germany	86	46	53
Berlin, Germany	8	6	75
Dusseldorf, Germany	4	1	25
Milan/Monza, Italy	73	35	48
Stockholm, Sweden	13	5	38
Lund	2	2	100
Paris, France	14	6	43
	200	101	51

Data presented at the 36th Annual Meeting of ASAIO and represent a cumulative summary as of April 1990.[73]

most common indication for V-A bypass is for perioperative cardiac support, occurring in 89.1% of the cases. The average survival rate is 42% for all diagnoses. The two most common reasons for initiating bypass are cardiogenic shock (18.8%) and cardiac arrest (15.9%), each with associated mortalities of 61.5% and 77.3%, respectively.

Pulmonary diagnoses account for 37% of the diagnoses for initiating ECLS in the pediatric population. The two most frequent diagnoses are aspiration and viral pneumonia. The overall survival rate is 44.4% for all diagnoses. Failure to respond to conventional management, the major reason for initiating bypass, occurs in 46.2% of the cases and has an attendant mortality of 59.5%. Barotrauma, as an indication, occurs second most frequently (28.7%), with an eventual mortality of 56.5%.[46]

Relatively few case summaries for adults treated with ECLS have been published in the last decade. Most of the recent adult experience has developed in Europe, predominantly in Italy and Germany. Pesenti et al have reported a survival rate of 47% in 55 patients treated with LFPPV-ECCO$_2$R.[70] The entry criteria to their study were essentially the same as that for the NIH ECMO study (PaO_2 < 50 mm Hg at FiO_2 of 0.60, PEEP of 5 cm H_2O or higher) with the addition of a total static lung compliance less than 30 mL/ccH_2O. The NIH ECMO criteria resulted in 90% mortality, so the Pesenti et al data represents a major improvement compared with these historic controls. However, many aspects of treatment have changed in the last decade, and this historic comparison has been questioned.[71] Knoch, in a review of 33 patients treated with LFPPV-ECCO$_2$R in Marburg, Germany, reported that 73% were weaned from mechanic ventilation and 55% survived.[72] Although no randomization was present, their results were compared with a 100% mortality in 11 of their patients, who also met ECCO$_2$R criteria for treatment but had contraindications. As of April 1990, a total of 200 adults and children have been treated with ECLS in Europe at seven separate centers. The overall survival rate is 51%.

Table 5. Centers in the United States With Major Extracorporeal Life Support Experience for Cardiorespiratory Failure in Children

Center	Location	Director
Ochsner Foundation Hospital	New Orleans, LA	Kenneth Falterman, MD
Boston Children's Hospital	Boston, MA	James Fackler, MD
Children's Hospital of Michigan	Detroit, MI	Michael Klein, MD
University of Michigan Medical Center	Ann Arbor, MI	Robert Bartlett, MD
Minnesota Regional ECMO Program	Minneapolis, MN	Thomas Green, MD
Cardinal Glennon Children's Hospital	St Louis, MO	Tom Weber, MD
St Louis Children's Hospital	St Louis, MO	Thomas Spray, MD
Babies Hospital	New York, NY	Charles Stolar, MD
Children's Hospital of Pittsburgh	Pittsburgh, PA	Ralph Siewers, MD
John Sealy Hospital	Galveston, TX	Jay Zwischenberger, MD

NOTE. This summary was composed in May 1990, and may not be inclusive of all centers. The centers listed have had experience with a significant number of pediatric cases.

Table 6. Adult Extracorporeal Life Support Centers in North America

Center	Location	Director
Sharp Hospital	San Diego, CA	Walter Dembitsky, MD
Pacific Medical Center	San Francisco, CA	J. Donnald Hill, MD
University of Michigan Medical Center	Ann Arbor, MI	Robert Bartlett, MD
University of Minnesota Medical Center	Minneapolis, MN	Jerome Abrams, MD
St Louis University Medical Center	St Louis, MO	Glenn Pennington, MD
Hershey Medical Center	Hershey, PA	Michael Snyder, MD
LDS Hospital	Salt Lake City, UT	Alan Morris, MD

NOTE. This summary was complied as of May 1990, and may not be inclusive of all centers performing adult ECLS. Centers listed have had major experience with adult ECLS.

Table 4 summarizes the results from these centers.[73] While convincing data in the adult population is not as apparent as in the neonatal population, a clear trend towards improved survival rates exists. These encouraging results have prompted the resumption of adult ECLS in our institution. Evolving experience continues to redefine our indications for bypass. Morris et al are carrying out a prospective randomized study to reassess the role for ECLS in the management of adult respiratory failure.[71] Tables 5 and 6 are lists of centers in the United States that are using ECLS for pediatric and adult respiratory failure.

The future of ECLS lies in the development of techniques and devices to make the bypass process less invasive, safer, and simpler in management. Several steps have already been taken toward this goal. Heparin-coated circuits, which have been in use in Europe, will soon be available in the United States. Bleeding complications, which affect the great majority of patients treated with ECLS, will markedly be reduced or eliminated. These circuits will also permit the treatment of a new population of patients: the premature neonates who are most susceptable to fatal intracranial hemorrhages. The low flows needed with $ECCO_2R$ permit the use of smaller catheters that can be inserted percutaneously without the need for surgical incisions. Double lumen catheters are entering the United States' market with promising initial results. The neonatal double lumen catheter has simplified the cannulation process for this age group with isolated respiratory failure. Smaller-sized catheters, designed for low birth weight or premature, infants are presently in the developmental process. Adult and pediatric double lumen catheters shall shortly be available for use in the United States. Computerized software that integrates patient and circuit monitors with the pumping device and ventilator is being developed to simplify patient management. New concepts of providing gas exchange have emerged. An intravenous gas exchange device, recently introduced, eliminates the need for external blood conduits and pumping mechanisms. The "IVOX" resides in the caval system in vivo to accomplish O_2 delivery and CO_2 removal.[74] The efficacy of this device remains to be demonstrated in humans.

As with all the other new or modified support devices, it is important for the physician who cares for intensive care patients to be familiar with the potential benefits of ECLS. Presently, over 50 centers in the United States are able to provide ECLS for neonates. Several centers can treat children and adults. Transport to one of these centers is difficult but widely practiced with neonates. Some centers are developing convenient means to transport children and adults for considerable distances while on bypass. The availability of ECLS technology is therefore readily apparent. Familiarity with the concept of ECLS breeds a better understanding as to its applications and, ultimately, to improved patient care.

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