

Refinements in Prolonged Extracorporeal Membrane Oxygenation in Children and Neonates

John M. Toomasian, B.S.; Nick J. Haiduc, C.C.P.; Nancy E. Wetmore, R.N., B.S.;
H. Vernon Roohk, Ph.D.; Alan B. Gazzaniga, M.D.; and Robert H. Bartlett, M.D.

Department of Surgery
University of California, Irvine
Irvine, California 92717

INTRODUCTION

Prolonged extracorporeal circulation using membrane oxygenation (ECMO) has been used successfully in patients suffering from acute cardiac or respiratory insufficiency. Although the technique has been evaluated in adults, we have previously integrated successful application in newborn respiratory failure. The major causes of newborn respiratory failure are meconium aspiration syndrome (MAS), infant respiratory distress syndrome (IRDS), persistent fetal circulation syndrome (PFC), streptococcal pneumonia, and diaphragmatic hernia with lung hypoplasia.

Initial clinical results with neonatal and pediatric ECMO were encouraging. Twenty patients were supported and nine ultimately survived.^(1,2) Further refinements have been made in patient selection, the perfusion circuit, and pulmonary management, which have resulted in an increased survival rate during the past few years. This report outlines current neonatal and pediatric case selection and simplified ECMO perfusion techniques.

CLINICAL METHODS AND RESULTS

The overall 8 year UCI ECMO experience is shown in Table 1. Patients have been supported from one hour up to 17 days on venoarterial bypass with an average perfusion time of 80 hours. Neonatal results for the year 1978 are shown in Table 2. The best results were obtained from neonates with MAS.

Address correspondence to: Robert H. Bartlett, M.D., Department of Surgery, University of California, Irvine Medical Center, 101 City Drive South, Orange, California 92668.

TABLE 1

TOTAL PATIENT EXPERIENCE

	<u>NO.</u>	<u>IMPROVED</u>	<u>SURVIVED</u>
ADULTS	20	5	1
PEDIATRIC	9	3	3
NEONATAL	<u>28</u>	<u>16</u>	<u>13</u>
	<u>57</u>	<u>24</u>	<u>17</u>
NEONATES	<u>NO.</u>	<u>IMPROVED</u>	<u>SURVIVED</u>
MAS	17	9	9
PFC	4	3	2
RDS	5	4	2
STREP	<u>2</u>	<u>0</u>	<u>0</u>
	<u>28</u>	<u>16</u>	<u>13</u>

TABLE 2

1978 NEONATE EXPERIENCE

	<u>NO.</u>	<u>IMPROVED</u>	<u>SURVIVED</u>
MAS	6	6	6
PFC	1	1	0
RDS	<u>1</u>	<u>0</u>	<u>0</u>
	<u>8</u>	<u>7</u>	<u>6</u>

Patient Selection

Indications for ECMO in pediatric and neonatal patients are acute, severe reversible cardiac or pulmonary disease with a reasonable chance of recovery during one week of ECMO support. Severe is defined as less than a 10% chance of survival with maximal therapy. Contraindications are gross congenital anomalies, intracranial hemorrhage, neurologic dysfunction, and irreversible lung damage.

ECMO support is considered only when the chance of survival with maximal ventilator and pharmacologic therapy is very small. There are no perfect indices of mortality prediction for children; currently a number of methods are used to evaluate prognosis in respiratory insufficiency. In our experience quantitation of pulmonary insufficiency in the pediatric patients is best evaluated by the pulmonary insufficiency index (PII).⁽³⁾ The PII is an expression of effective alveolar-arterial gradient integrated with time as described by Bartlett, et al⁽⁴⁾ that establishes patient groupings based on mortality prediction. Reversibility is determined by lung biopsy.

Methods of scoring pulmonary insufficiency in the neonate have previously been based on subjective evaluations such as the Apgar test and the Silverman score.^(5,6) While these tests are useful, the Neonatal Pulmonary Insufficiency Index (NPII) quantitates the degree of pulmonary insufficiency from objective data within the first 24 hours of life.⁽⁷⁾ The NPII is calculated by integrating the fraction of inspired oxygen (FiO_2) and arterial pH with respect to time (Figure 1). As respiratory insufficiency develops the pH decreases and the FiO_2 increases. Index values are computed as the pH and FiO_2 converge

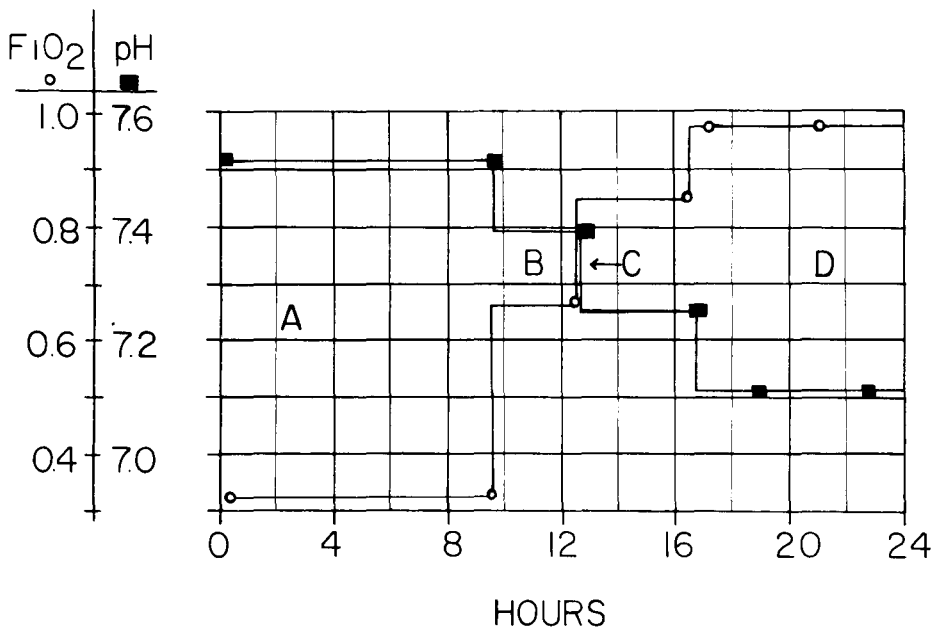


Figure 1. Neonatal Pulmonary Insufficiency Index (NPII) as judged by changes in FiO_2 and pH with time after birth (point A). The patient's course is normal until point B where increasing pulmonary insufficiency develops at 13 hours of life (point C). The lines cross and an insufficiency index is quantitated by counting between the lines (point D).

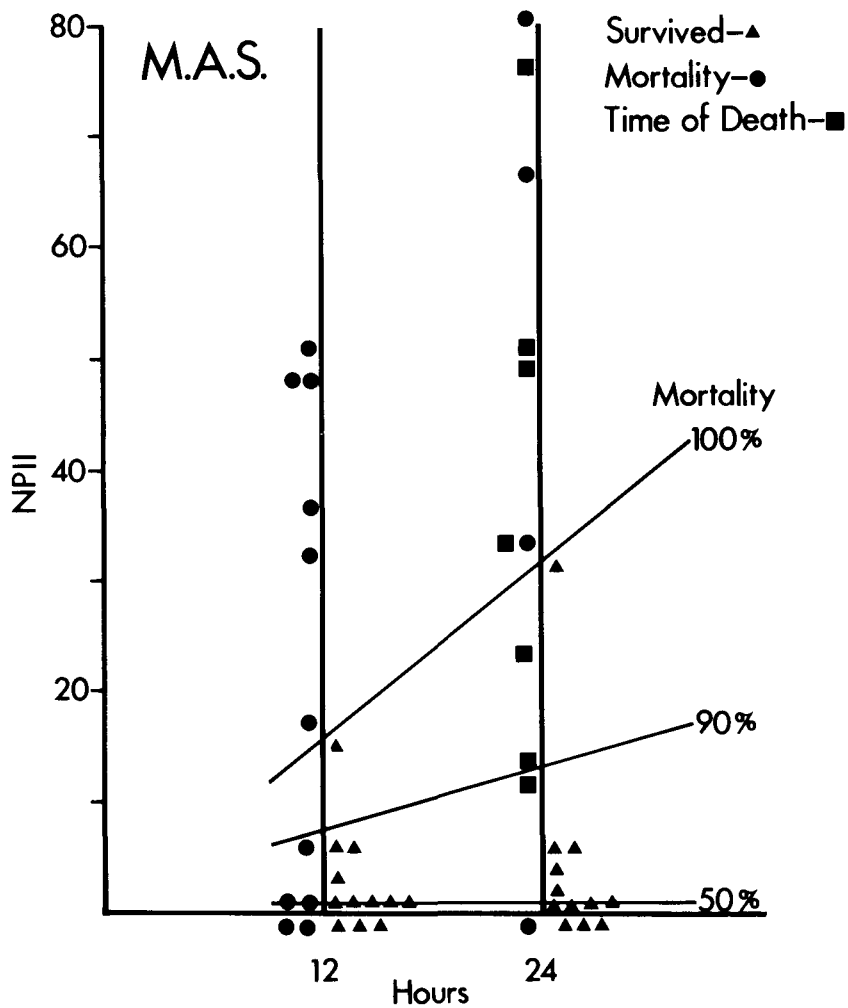


Figure 2. Mortality prediction for meconium aspiration syndrome NPII (as determined in Figure 1) and time. Patients with a lower index fall into lower mortality groups. Higher index number relate to a higher mortality. Time of death is also noted. Patients considered for ECMO support are taken from a 90% or greater mortality risk.

and cross and the space between the crossed lines are integrated. Patients are categorized according to the disease and index value. Over 300 neonates have been retrospectively and prospectively evaluated with the NPII. Figure 2 shows changes in NPII with time and shows the mortality range in neonates suffering from MAS. Clinical signs in conjunction with the NPII are principal factors in determining the indication for ECMO.

ECMO Circuit

The ECMO circuit has been described previously.⁽⁸⁾ The perfusion circuit consists

of PVC tubing (3/16" × 1/16" for neonates, 1/4" × 1/16" for infants, 3/8" × 3/32" for children) and polycarbonate connectors. Components of the circuit include a multiple sampling and infusion manifold located in the venous line, a collapsible silastic bladder which serves as a venous reservoir, and a bladder box with microswitch. An American Optical modular pump (5" pump head for neonates and infants, 7" pump head for children), membrane oxygenator, and Travenol pediatric miniprime disposable heat exchanger are the principal components of the remainder of the circuit. A shunt is incorporated between the venous and arterial line for recirculation. A holer pump is used for constant infusion of diluted heparin into the venous line. We currently use the Sci-Med Kolobow membrane lung. The Sci-Med lung is designed to transfer approximately 60–70 cc of O₂ and CO₂/M²/min at the rated blood flow. The lung size is selected by the patient's size and oxygen requirements. Generally the 0.8 M² membrane is used for neonates and infants and either the 1.5 M² or 2.5 M² membrane for children. Argyle chest tubes (10-16F) are used as cannulas in the neonate. Larger sized catheters are used in pediatric patients.

Platelet preservation, a major concern during bypass when using the narrow channeled Sci-Med Kolobow membrane lung has been significantly improved by partial vacuum priming technique recommended by Kolobow as shown by Roohk, et al.⁽⁹⁾ In this technique, the gas phase of the lung is exposed to a partial vacuum while flushing the blood phase initially with 1 atm CO₂ followed by crystalloid solution. This approach has been shown by Ward and colleagues^(10,11) to remove potentially thrombogenic microscopic gas nuclei from rough surfaces such as silicone rubber membrane. Subsequent flushing of the circuit with concentrated serum albumin and the use of freshly drawn heparinized blood (1 unit) for the final extracorporeal volume also contribute to higher blood platelet counts during the first day of perfusion.

Conduct of ECMO

The pathophysiology and conduct of ECMO has been described in detail by Bartlett and Gazzaniga.⁽¹²⁾ Venoarterial bypass involves siphoning blood from the right atrium as it returns to the heart from the right internal jugular vein, oxygenating and warming it and returning it to the systemic circulation via the right common carotid artery in the newborn, and either the right axillary artery or the right common carotid in children. ECMO flow rates are begun at 70–80% of the cardiac output. This is adequate for total gas exchange, and allows some blood to continue to flow through the patient's cardiopulmonary circulation and mix with oxygenated blood from the ECMO circuit in the aortic root. The systemic arterial pressure is maintained pulsatile by left ventricular ejection.

Once established, ECMO support permits the inspiratory inflation pressure of the ventilator to be decreased, reducing the risk of barotrauma to the lungs. The FiO₂ can be reduced to a less toxic level such as 0.4 or less. Patient blood gas measurements are made with samples taken from the umbilical artery in the newborn and the left radial artery in children. PaO₂ is maintained around 60 mm Hg (90% saturation). The PACO₂ and pH can in part be controlled by mixing 100% oxygen and carbogen ventilating the artificial membrane lung. When the patient's lungs improve the PaO₂ rises allowing the ECMO flow rate to be lowered, increasing blood flow through the pulmonary circulation.

Anticoagulation with heparin is required to prevent clotting within the extracorporeal circuit. After a loading dose of 100–200 units of heparin per kilogram of body weight, activated clotting time (ACT) is maintained 2–3 times the baseline ACT. This is accomplished by a continuous infusion of heparin into the circuit. Generally neonates require 30–50 units of heparin/kg/hr and children 20–40 units/kg/hr. Heparin requirement may vary during bypass due to platelet transfusion, urine output or bleeding.

Thrombocytopenia develops during ECMO and platelet transfusions are almost always necessary. Platelet concentrate is given when the platelet count drops below 50,000/mm³. Heparin requirement increases following platelet transfusion and ACT's are closely monitored.

Once hemodynamic equilibrium occurs (usually well within the first 24 hours), volume replacement should not exceed losses from blood sampling, incisional drainage, urine output, and water vapor loss across the oxygenator membrane. Total intake, including fluid to maintain nutritional requirements and electrolyte balance, and output should be closely monitored. Daily weighings help to assess fluid balance. When blood volume replacement is required, packed red blood cells are given if the hematocrit is less than 45%. Fresh frozen plasma or 5% albumin are given if the hematocrit is greater than 45%. Plasma is preferable to albumin due to the presence of clotting factors to augment hemostasis.

To evaluate the patient's progress, a trial period off ECMO is done daily. In the newborn, ventilatory pressures are increased to approximately 24/2 cm H₂O, FiO₂ set at 1.0 and the ventilatory rate is adjusted to approximately 24 breaths/minute. The lines are clamped and the blood pumped slowly through the A-V bridge. If the patient tolerates the test period off ECMO, arterial blood gases can be drawn after 10–15 minutes. As long as blood gases are adequate, the patient can remain off ECMO, perhaps with a decreased FiO₂ and another blood gas sample can be evaluated.

With improving PaO₂ the patient is eventually weaned off ECMO. Once flow rates of 30–50 cc/minute are reached in neonates, blood gases are evaluated for 8–12 hours to insure lung improvement. The circuit is clamped and the PaO₂ evaluated at FiO₂ values of 1.0–0.5. The cannulas are removed if the PaO₂ is 50 mm Hg or greater on FiO₂ of 0.4 and at a low inspiratory pressure (18 cm H₂O or lower). The cannulation vessels are ligated after ECMO and not repaired. The risk of thrombus formation and cerebral embolization from a reconstructed vascular surface is greater than the risk arising later from functional lack of these vessels.

Complications resulting from ECMO are few and are usually controlled. Abnormal bleeding occurs in virtually all ECMO-treated patients secondary to heparinization and thrombocytopenia. Bleeding complications range from cannulation site oozing to fatal gastrointestinal, nasopharyngeal or intracranial hemorrhage. Intracranial bleeding is associated with newborn respiratory failure.^(13,14) Hypoxia, acidosis, poor perfusion and consumption coagulopathy are all improved by ECMO and decrease the overall incidence of intracranial bleeding. In our entire ECMO experience only one adult perfusion was discontinued due to uncontrollable bleeding.

Incidence of infection during ECMO is low. Daily Betadine washing of cannulation sites and administration of broad-spectrum antibiotics have reduced the incidence of infection. Septicemia is almost always related to invasive sepsis within the lung or other tissue rather than contamination through the perfusion circuit.

Patient Care During ECMO

Lung improvement is greatly facilitated by diligent chest physical therapy. Postural drainage and percussion are done hourly, followed by turning the patient side to side. During ECMO support vigorous lavage and suctioning of the airway can be performed to clear obstructive secretions. The endotracheal tube may be changed if necessary and bronchoscopy performed without compromising the patient.

Patent ductus arteriosus (PDA) is a common anomaly in infant respiratory distress. Arteriographic studies are undertaken if congenital heart lesions or a PDA is suspected. While on ECMO, a murmur may not be audible if the left to right shunt is large. Acidosis, edema, and oliguria when ECMO flow rates are in excess of the predicted cardiac output are symptomatic of a PDA.

Twelve cineangiograms have been performed during ECMO to date. Renografin-60 (1 cc/kg) is injected through a stopcock placed near the arterial cannula while the patient is temporarily taken off ECMO. Seven PDA's have been documented and all have been surgically ligated without complications. Following ligation distal perfusion improves, acidosis can be reversed, and renal function improves. Ligation of PDA has been shown to be beneficial in newborn infants with respiratory failure.⁽¹⁵⁾

Representative Case Report

M.N. a 7 year old female weighing 16 kg was referred for ECMO support due to acute respiratory insufficiency. Her initial symptoms were general malaise, fatigue, and a dry cough. Progressive deterioration required intubation and mechanical ventilation with an FiO_2 of 100% on the sixth hospital day. Following transfer to UCIMC an open lung biopsy was performed which showed diffuse alveolar damage with a desquamative interstitial pneumonitis pattern and a mild to moderate degree of interstitial fibrosis. There was no evidence of viral pneumonia. Solumedrol (80 mg q 6 hr) and penicillamine were started along with aggressive colloid loading and diuresis. Penicillamine has been reported to inhibit collagen cross-linking in the lung, and may inhibit pulmonary fibrosis.⁽¹⁶⁾ No significant improvement resulted and ECMO was instituted on the eighth hospital day. The course is illustrated in Figure 3. Initial ECMO flows of 2L/min were obtained. Following initial pulmonary improvement, flows were reduced to 1.0 L/min by the third day of ECMO. Lung function did not improve appreciably over the first week of ECMO as shown by the high AaDO_2 when measured during a test period off ECMO with the patient breathing 100% oxygen. Subcutaneous emphysema with a pneumomediastinum were diagnosed and corrected by replacing the tracheostomy tube. Minor bleeding from the tracheotomy site was controlled by electrocautery. Due to the developing complications of increased bleeding due to thrombocytopenia, and the risk of sepsis, the decision was made to wean the patient from ECMO as soon as possible. After 10 days, with the flow rate weaned to 600 ml/min, ECMO was discontinued. The patient was then maintained on mechanical ventilation with an FiO_2 of 60% and a PaO_2 of 60 mm Hg. Pulmonary function slowly improved over the next two weeks, with the ventilator support decreased to intermittent mandatory ventilation (IMV) with an FiO_2 of 40%. The patient was weaned to a T-tube, with gradual improvement. The patient was discharged from the hospital six weeks after ECMO was started. This case is representative of the application of ECMO to provide long-term support to allow for therapeutic reversal of pulmonary damage.

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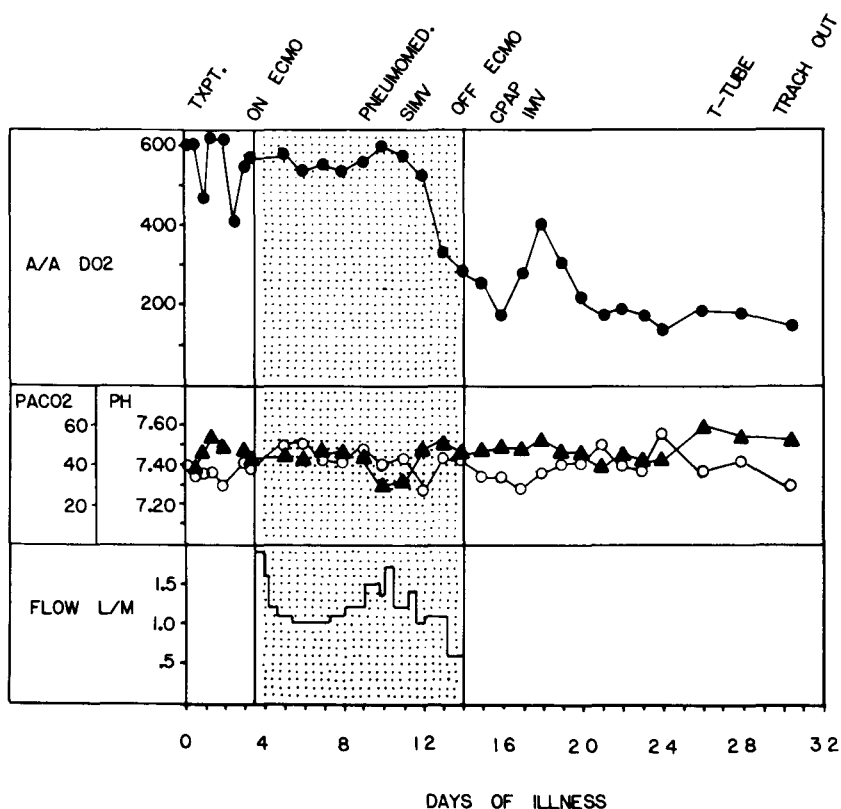


Figure 3. Changes in lung function, arterial blood gases, and ECMO flow before, during, and after cardiopulmonary bypass in pediatric patient with diffuse interstitial pneumonitis (DIP). No significant lung improvement occurred during the first week of bypass shown by the high alveolar-arterial (AaDO₂) gradient. Arterial pH (○) and PaCO₂ (▲) were normal as flows between 1.0–1.5 L/min were gradually weaned down which correlated with lung improvement by 10 days of ECMO.

DISCUSSION

Extracorporeal circulation in neonates was first attempted by Rashkind, et al, who used a femoral arteriovenous shunt and a bubble oxygenator to provide gas exchange.⁽¹⁷⁾ Dorson explored the techniques of neonatal ECMO using a capillary membrane oxygenator and umbilical vascular access.⁽¹⁸⁾ White and associates evaluated different modes of bypass in three neonates suffering from IRDS for 2.3 and 10 days.⁽¹⁹⁾ These early trials were unsuccessful, but important observations regarding cannulation sites, heparin management and the clinical course on bypass were made and the feasibility of neonatal ECMO was demonstrated.

With the advent of improved perinatal and ventilator management techniques in the early 1970's, attention shifted away from neonates to adult respiratory insufficiency.

Adult respiratory failure (ARF) is primarily caused by pneumonitis, capillary leak syndromes, fluid overload or thromboembolism. A large number of patients were supported on ECMO, subjects of the 1974–1977 NIH controlled-randomized study on ARF.⁽²⁰⁾ The mortality rate in the study was 91%, but the cause of death in both the control-ventilation and ECMO groups was end stage pulmonary fibrosis and not complications of ECMO.⁽²¹⁾ Patients with severe fibrosis indicated by lung biopsy demonstrated high fixed pulmonary vascular resistance and poor compliance. Zapol and Snider measured pulmonary vascular resistance and right ventricular function in 30 patients in acute respiratory failure. Increased pulmonary vascular resistance was associated with fibrosis and death, while a decrease in pulmonary vascular resistance was associated with reversibility of the lesion. Adult patients appear to benefit from ECMO support only if instituted early in the course of the disease. In all cases of adult ECMO survivors the pulmonary lesion was self limiting.

ECMO has also been used successfully in post-operative cardiac support in children with congenital heart lesions. Soeter and McNamara successfully used ECMO for combined cardiac and pulmonary support in a 4 year old child following correction of Tetralogy of Fallot.⁽²²⁾ Our group has successfully used ECMO to support a 2 year old child for 34 hours following Mustards' procedure for the repair of great vessel transposition.⁽¹²⁾ ECMO support can be useful in right ventricular or biventricular failure if myocardial damage is transient and reversible.

In addition to our own experience with pulmonary failure in children, Kolobow has successfully used veno-venous ECMO for 10 days in a 9 year old suffering from pneumocystis carinii pneumonia.⁽²³⁾ Successful 48 hour ECMO support in a 4 year old child with cystic fibrosis and pneumonia was reported by Awad.⁽²⁴⁾ In both cases the disease was defined early in the clinical course and treated aggressively.

Several factors lead to successful clinical application of ECMO. The use of the NPII and other physiologic data have defined reversible lung lesions which are treatable with ECMO support. Rigorous pulmonary management and the ability to correctly diagnose a patent ductus arteriosus lead to shorter overall bypass duration. The use of freshly drawn heparinized blood in an extracorporeal volume often twice that of the patient eliminates the need to render physiologic parameters such as glucose concentration which may be greater than 1000 mg/dl for several hours with ACD or CPD donor blood. The ECMO circuit has been scaled down and streamlined to reduce overall extracorporeal volume and set up time. Other technological improvements such as continual heparin infusion, infusion-withdrawal manifold ports, and smaller more efficient membrane oxygenators simplify the conduct of ECMO. Finally, the importance of refining the technique in the research laboratory and training a skilled team is essential to successful clinical performance of ECMO.

SUMMARY

We have used prolonged extracorporeal membrane oxygenation (ECMO) in the treatment of acute cardiopulmonary failure in neonates and children. In 1978 six of eight newborns judged clinically and by the NPII prediction index to have little chance for survival were successfully supported on ECMO. An additional pediatric patient successfully recovered from diffuse alveolar damage. Pediatric and neonatal ECMO is

proving to be a safe, routine procedure due largely to a highly skilled team and improved technology.

Our results also suggest that early detection and aggressive cardiopulmonary management during ECMO increase survival in severe, acute, reversible cardiopulmonary failure in neonates and children.

REFERENCES

1. Bartlett, R. H., Gazzaniga, A. B., Jefferies, M. R., Huxtable, R. F., Haiduc, N. J., Fong, S. W.: Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. *Trans. Am. Soc. Artif. Int. Organs* 22:80, 1976.
2. Bartlett, R. H., Gazzaniga, A. B., Huxtable, R. F., Schippers, H., O'Connor, M. J., Jefferies, M. R.: Extracorporeal Circulation (ECMO) in Neonatal Respiratory Failure. *J. Thorac. Cardiovasc. Surg.* 74(6):826, 1977.
3. Bartlett, R. H., Gazzaniga, A. B., Wilson, A. F., Geraghty, T., Wetmore, N.: Mortality prediction in adult respiratory insufficiency. *Chest* 67:680, 1975.
4. Bartlett, R. H., Drinker, P. A., Hill, J. D., Hill, R. N., Wetmore, N. E.: Indications for extracorporeal membrane oxygenation support: Quantitating pulmonary insufficiency. In Zapol, W. M. and Qvist, J. (editors) *Artificial Lungs for Acute Respiratory Failure* New York, Academic Press, 1976.
5. Apgar, V.: A proposal for a new method of evaluation of the newborn infant. *Anesth. Analg.* 32:260, 1953.
6. Silverman, W. A., Anderson, D. A.: A controlled clinical trial of effects of water mist on obstructive respiratory signs, death rate and necropsy findings among premature infants. *Ped.* 17(1): 1-9, 1956.
7. O'Connor, M. J., Huxtable, R. F., Bartlett, R. H., Amlie, R., Wetmore, N.: Neonatal Pulmonary Insufficiency Index (NPILI): A Method of Newborn Mortality Prediction. In preparation.
8. Haiduc, N. J., Wetmore, N. E., Roohk, H. V., Mullin, P. J., Bartlett, R. H.: Prolonged extracorporeal circulation with membrane oxygenator in infants. *AmSect Proc.* 4:93, 1976.
9. Roohk, H. V., Nakamura, M. K., Hung, E. K., Bartlett, R. H.: Blood compatibility and membrane oxygenation. *J. Extracorp. Tech.* 10(3):142, 1978.
10. Ward, C. A., Ruegsegger, B., Stanga, D., Zingg, W.: Reduction in platelet adhesion to biomaterials by removal of gas nuclei. *Trans. Am. Soc. Int. Organs* 20:77, 1974.
11. Ward, C. A., Ruegsegger, B., Stanga, D., Zingg, W., Herbert, M. A.: Relation of proteins, platelets, and gas nuclei in adhesion to a synthetic material. *Am. J. Physiol.* 233(1):H100, 1977.
12. Bartlett, R. H. and Gazzaniga, A. B.: Extracorporeal circulation for cardiopulmonary failure: Current Problems in Surgery Yearbook Medical Publishers, May 1978.
13. Hambleton, G. and Wigglesworth, J. S.: Origin of Intraventricular Hemorrhage in the Preterm Infant. *Arch. Dis. Child.* 51:65, 1976.
14. Volpe, J.: Editorial: Neonatal Intracranial Hemorrhage: Iatrogenic Etiology? *N. Eng. J. Med.* 291:43, 1974.
15. Coran, A. G., Cabal, L., Siassi, B., Rosenkrantz, J. G.: Surgical closure of patent ductus arteriosus in the premature infant with respiratory distress. *J. Ped. Surg.* 10:399, 1975.
16. Grob, K., and Unholtz, K.: Therapeutische beeinflussung der Bindegewebswucherung bei Lungenfibrosen. *Pneumologie* 148:201, 1973 (Engl. Abstr.).
17. Rashkind, W. J., Freeman, A., Klein, D., Toft, R. W.: Evaluation of a disposable plastic low volume, pumpless oxygenator as a lung substitute. *J. Ped.* 66:94, 1965.
18. Dorson, W. J., Baker, E., Cohen, M. L., Meyer, B., Molthan, M., Trump, D., and Ekas, R.: A perfusion system for infants. *Trans. Am. Soc. Artif. Int. Organs* 15:155, 1969.
19. White, J. J., Andrews, H. G., Resenberg, H., Mazur, D. and Haller, J. A.: Prolonged respiratory support in newborn infants with a membrane oxygenator. *Surgery* 70(2):288, 1971
20. NHLI Extracorporeal Support for Respiratory Insufficiency-Collaborative Program. Division of Lung Diseases, National Heart and Lung Institute, 1974.
21. Hill, J. D., Rodvien, R., Snider, M. T., Bartlett, R. H.: Clinical extracorporeal membrane oxygenation for acute respiratory insufficiency. *Trans Am. Soc. Artif. Int. Organs* 24:753, 1978.
22. Soeter, J. R., Mamiya, R. T., Sprague, A. V., McNamara, J. J.: Prolonged extracorporeal oxygenation for cardiorespiratory failure after tetralogy correction. *J. Thorac. Cardiovasc. Surg.* 66:214, 1973.
23. Kolobow, T., Stool, E., Sacks, K., Venk, G.: Acute respiratory failure-survival following ten days support with a membrane lung. *J. Thorac. Cardiovasc. Surg* 69(6):947, 1975.
24. Awad, J. A., Matte, J., Brassard, A.: Prolonged extracorporeal respiration with a membrane gas exchanger. *J. Thorac. Cardiovas. Surg.* 66(1):40, 1973.