
Extracorporeal Membrane Oxygenation in Acute Respiratory Insufficiency in Neonates: A Review of the Literature

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Abbreviations

ECMO—extracorporeal membrane oxygenation

ARI—acute respiratory insufficiency

AV—arteriovenous

VV—venovenous

VA—venoarterial

VVA—venovenous arterial

RDS—respiratory distress syndrome

CDH—congenital diaphragmatic hernia

MAS—meconium aspiration syndrome

PFC—persistent fetal circulation

IVH—intraventricular hemorrhage

Introduction

Extracorporeal gas exchange was primarily developed for the intraoperative support of patients requiring open heart surgery. A second application has been attempted, the prolonged support of patients with severe pulmonary disease who fail to respond to conventional mechanical ventilation. The purpose of this paper is to review the use of prolonged extracorporeal gas exchange for patients with acute respiratory failure and the application of this technique to the care of sick newborns.

History

Early study of extracorporeal gas exchange involved cross-circulation in animals, heterologous lung preparations and human cross-circulation. Andreasen and Watson reviewed the experience through 1953 with cross-circulation of animals and concluded that this technique could support an animal whose heart and lungs have

been excluded from its own circulation.¹ Mustard reported that his group had used lungs excised from rhesus monkeys to oxygenate the blood of 13 babies during operations for transposition of the great vessels.² Although the operations were technically unsuccessful, oxygenation was provided; subsequently, a patient with tetralogy of Fallot was successfully operated using blood perfused through an excised rhesus monkey lung. In 1955, Lillehei et al reported a series of eight children who underwent open ventriculoseptal defect repair while supported by “controlled cross-circulation” with volunteer adult donors.³ The patients were bypassed for up to 26-1/2 minutes using this technique. Two patients died in the postoperative period, but none of the patients or donors experienced morbidity or mortality attributable to cross-circulation.

Cross-circulation and the use of heterologous excised lungs for operative support of cardiac surgical patients were relatively crude and limiting techniques. Artificial extracorporeal gas exchangers replaced these techniques. As the mechanical devices were refined for surgical application, their use in patients with respiratory diseases was explored. In 1965, Rashkind et al maintained asphyxiated puppies for prolonged periods using extracorporeal oxygenators then attempted unsuccessfully to support several infants and children with cystic fibrosis, RDS, and congenital heart disease.⁴

In the controlled experimental environment, other investigators confirmed that fetal lambs, newborn lambs and puppies could be supported for hours using extracorporeal oxygenators.⁵ Zapol and Kolobow developed a technique which they called “artificial placentation” in 1969.⁶ Fetal lambs delivered prematurely by Cesarean section were supported with extracorporeal membrane oxygenators through circuits connected to the umbilical cord while the animal was placed in a tank of “artificial amniotic fluid”. Although gas exchange was possible, these animals frequently became infected from the “amniotic fluid bath.” In 1969, Dorson et al re-

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ported their experience perfusing a 1.16 kg. premature baby with severe RDS.⁷ This child was able to be supported for a period of 20 hours prior to death. The patient died with an intracranial hemorrhage, but the experience demonstrated that prolonged support of a sick infant was possible.

The early studies in animal and human newborns frequently employed arteriovenous circuits using the umbilical vessels. Subsequent work has concentrated on other circuit designs, primarily venoarterial, and to a lesser extent, venovenous or mixed venovenous-arterial. The distinction of these various flow patterns to the extracorporeal circuits is an important consideration and will be discussed later in this review.

In 1971, a group from Baltimore reported that they had supported three newborns with severe lung disease using venovenous bypass.⁸ Although all three babies died, one child had been supported from 12 hours of age until he died on the ninth day. Interest in prolonged extracorporeal support for acute respiratory insufficiency was further stimulated by Hill and co-workers when they successfully maintained a 24-year-old woman with shock-lung syndrome using the extracorporeal oxygenator for 75 hours.⁹ The patient's lung disease resolved and she recovered. Another early long-term survivor was reported; an 11-year-old boy with leukemia who developed progressive respiratory failure was supported for ten days on bypass and he survived without residual lung disease.¹⁰

Clinical Research

During the 1970s, interest flourished in the clinical application of prolonged extracorporeal circulatory support for patients with severe respiratory failure, then it faded as discouraging results were obtained. Experimental evidence from animal studies indicated that membrane oxygenators were superior to bubble oxygenators for long-term support.^{11,12} The major emphases of the studies in the 1970s were the mode of application of ECMO (that is, the design of the circuits—VA, AV, VV or mixed VVA) and ways of selecting patients who would benefit from ECMO.

Pioneering work by Bartlett's group (first at the University of California at Irvine and now at the University of Michigan) demonstrated that patient selection is crucial to successful application.¹³ In a report of six patients who were supported from 1-1/2 to 12-1/2 days, there was only one survivor. This report was one of the first to

suggest that irreversible pulmonary fibrosis was as much a limiting factor for success as were technical problems with the ECMO itself. Zapol and co-workers reviewed the literature as of 1977 and found that there had been only 15 survivors (excluding the neonatal patients) of prolonged ECMO for respiratory failure.¹⁴

In the mid-1970s, the National Institutes of Health sponsored a randomized clinical trial of extracorporeal support for respiratory failure.¹⁵ The NIH study was prompted by the fact that over 60,000 Americans were estimated to die each year from acute respiratory insufficiency. As of April 1976, nine centers had enrolled 73 patients with ARI and there were only six survivors (three in a control group and three in the ECMO treated group). Despite these discouraging preliminary results in adults, the authors suggested that the application of prolonged ECMO might be appropriate in selected sick newborns. The authors concluded that "wide-spread clinical application of ECMO for the treatment of severe ARI as defined in this study is not appropriate or justified at this time." In the final report of the NIH collaborative project, 90 adult patients had been randomized to either a control or ECMO treated group, and there were only four survivors in each group. The collaborators concluded that "ECMO can support respiratory gas exchange, but did not increase the probability of long-term survival in patients with severe acute respiratory failure."¹⁶

In further review of the world-wide experience of 1970 to 1977, only 37 of 230 patients treated with prolonged ECMO for ARI survived; eight of these were among 38 newborns treated with ECMO.¹⁷ Wetmore et al concluded that defining the reversibility of the underlying lung disease was the critical factor for successful ECMO therapy for children and adults (but not newborn infants).¹⁸ Lung lesions were usually found to be irreversible if the duration of ARI had been greater than five days, if the primary lung disease was infection or aspiration, or if pulmonary fibrosis was noted on lung biopsy. Their findings confirmed earlier reports that pulmonary fibrosis was a frequent factor preventing reversibility of acute lung disease. They noted that newborn infants are a special group; reversibility of the underlying lung disease is much more likely in babies than in older patients.

Subsequent work with prolonged ECMO for respiratory support has been focused on the newborn with PFC alone or in association with MAS or CDH and, to a lesser extent, with severe RDS complicated by air leak (pneumothoraces or pulmonary interstitial emphysema).^{19,20} Many of the early survivors of ECMO support were young patients. In 1977, Bartlett's group re-

ported their growing experience; 28 patients had been treated and five survived, three of them were among the nine newborns, one was a two-month-old child and the other was a 17-year-old patient.²⁰

Results of ECMO studies in neonates have been more promising than have studies in older patients. The major limitations of ECMO in neonates have been related to assuring adequate blood flow to and from the membrane oxygenator and the need to anticoagulate these babies who already are at great risk for IVH. Rashkind's early report of attempted ECMO in children involved AV perfusion circuits.⁴ Dorson et al perfused five terminally ill neonates, again using AV circuits via the umbilical or femoral artery catheters; all five died, but these investigators demonstrated that some of the babies could be supported for periods between five and 21 hours.²¹

Bartlett et al developed the VA technique using the jugular vein for flow to the membrane oxygenator and return via the common carotid artery to the aorta.²² This technique has become "the standard" for neonatal ECMO. Four of the first 13 patients treated with the VA technique survived. One major concern about this technique is that the common carotid artery must be ligated for cannula placement. Flows of 80-100 cc/kg/min were found to provide adequate gas exchange. As of 1978 Bartlett's group had treated 16 babies with a variety of underlying lung diseases and six survived.²³

More recent reports from Bartlett's group reviewed their cumulative eight year experience with 45 moribund newborns supported with ECMO.²⁴ Twenty of the twenty-five survivors were reported to be normal at the time of follow-up despite common carotid artery ligation. These survivors required ECMO for an average of 90 hours and patients in the entire series were supported from one to nine days on ECMO. By 1982, it appeared that some babies who would have otherwise died could be supported with prolonged ECMO. The causes of ARI in these patients were MAS, CDH or PFC.^{25,26}

Other investigators confirmed the findings of Bartlett's group that ECMO can be used to support neonates who are terminally ill with ARI. Six of eight neonates treated at the Medical College of Virginia using ECMO for 77 to 313 hours survived.^{27,28} All of these patients weighed over 2.5 kg. and had either MAS, PFC, or CDH. Hardesty's group at the University of Pittsburgh successfully supported three of four infants who had PFC following CDH surgery.²⁹ Both of these latter groups used Bartlett's jugular vein—common carotid VA technique.

At a conference at the University of Michigan in April 1984, representatives of seven American centers per-

forming ECMO for newborns with ARI discussed their experiences. A cumulative experience of 96 patients had been developed. The majority (55) were treated by Bartlett's group; the other centers have treated between 1 to 14 patients. The overall survival rate for neonatal ECMO is approximately 57 percent. Most centers have selected patients based on criteria that would predict a 90 percent mortality risk. The presenters agreed that the best candidates for ECMO are babies who have PFC alone or with MAS or CDH who weigh over 2.0 kg. Because of the occurrence of massive IVH when anticoagulated for ECMO, smaller, less mature neonates do not appear to respond better to ECMO than they respond to conventional mechanical ventilation. The leading cause of death in ECMO treated patients was intracranial hemorrhage.

Other Considerations

A number of considerations have evolved as experience grows in the application of ECMO for neonates with ARI. Some of these are: 1) circuit design for blood flow (the distinction between AV VV, mixed VVA and VA techniques), 2) partial versus full ECMO support (the concept of "carbon dioxide membrane lung/apneic oxygenation"), and, 3) anticoagulant therapy and bleeding problems.

Despite the emphasis in recent clinical work on the development of VA circuits using the jugular vein and carotid artery, early experimental work revealed that AV perfusion could be used to support newborn animals.^{6,30} Dorson and co-workers used umbilical artery and venous catheters to provide AV perfusion in their early attempts to apply ECMO to neonates.^{7,31} Bartlett's group's advances using VA techniques have led most investigators to abandon the study of AV perfusion.

There has been limited experience in venovenous perfusion in the neonate.³² Three patients who were supported using VV technique survived; but the design of the circuitry required the sacrifice of the femoral vein, was associated with lower pO₂s and required higher flow rates through the membrane oxygenator when compared to the previously reported VA perfusion techniques.

Some authors suggested that arteriovenous perfusion in adults and older children would lead to elevated cardiac output secondary to increased venous return with the potential risk of right and left ventricular overload.³³ Limited experience in dogs has not confirmed this con-

cern.³⁴ These are reasonable theoretical considerations in adult and older children, but the fetal circulation accommodates the large venous return from an "extracorporeal oxygenator," the placenta, which is supplied by the arterial circulation.³⁵ In the fetus, 65 to 70 percent of the total return in the inferior vena cava comes from the placenta of which one-third crosses the patent foramen ovale to the left ventricle. Thirty-six to forty-two percent of the combined ventricular output of the fetus goes to the placenta. The placental circulation supports the fetus at PO₂ levels which would be considered marginal (at best) in the extrauterine environment. Oxygenated venous return from the placenta has a PO₂ of 28 to 30 torr, blood in the descending aorta has a PO₂ of only 22 to 25 torr. Arteriovenous circuits may provide a more "physiologic" means of ECMO perfusion than the "standard" VA (jugular vein/carotid artery) technique. The development of an AV technique using umbilical vessels would obviate the need to sacrifice the common carotid artery. The sick newborn's circulation is similar to the fetal circulation with persisted pulmonary hypertension and right to left shunting present in most babies with severe lung disease.

An additional conceptual advance in the consideration of ECMO is the idea of the "carbon dioxide membrane lung."³⁶⁻³⁹ Investigators have noted that CO₂ exchange exceeds oxygen exchange in membrane lung.^{36,37} They further note that pulmonary oxygenation has depended on oxygen diffusion and can be accomplished without the bulk flow of gas in the respiratory system "apneic oxygenation;" in comparison, CO₂ exchange usually requires the bulk flow of gas in the respiratory tree. Using these concepts, the "carbon dioxide membrane lung" technique of ECMO was developed experimentally in which the membrane lung is perfused at lower rates. These lower perfusion rates afford adequate CO₂ exchange but are not adequate for oxygenation. In order to effect adequate oxygenation during apnea, a constant respiratory source of oxygen is provided. These investigators noted that extracorporeal blood flow at low rates ("not much higher than required for routine hemodialysis") provided adequate gas exchange for the experimental animals.³⁷ Two of three adult patients have survived with this technique.³⁸

Bleeding problems and anticoagulation remain major areas of ECMO research. Anticoagulation is required during ECMO to assure adequate blood flow through the extracorporeal circuits and to prevent thrombosis-induced diffusion problems in the membrane lung. Preterm neonates are particularly prone to IVH.⁴⁰ These babies tolerate anticoagulation poorly; they frequently

extend preexisting bleeds or develop massive IVH when heparinized. For this reason, the preterm baby has been excluded from ECMO studies in most centers. The development of a "heparinless system" may allow the application of ECMO to low birth weight premature babies. A precise method for monitoring anticoagulation during ECMO is required. Heparinization guided by the activated coagulation time has become the standard method of anticoagulation.⁴¹⁻⁴⁴ This technique has been successfully employed in most clinical studies.^{24,27,28} Thrombocytopenia may be seen with ECMO (although less commonly than with bubble oxygenators) and may herald sepsis rather than a technical problem with a membrane oxygenator.⁴³ Thrombosis of the membrane may impair gas exchange. Impaired carbon dioxide exchange appears to be a more sensitive indicator of this phenomenon⁴⁴ than impairment of oxygen exchange.

Conclusion

Extracorporeal circulation for respiratory gas exchange was developed for open heart surgery. To a lesser extent, prolonged ECMO has been attempted to support patients with severe respiratory failure. Studies of prolonged ECMO in adults with ARI have been discouraging; the collaborative NIH randomized study of the mid-1970s revealed that ECMO did not improve survival when compared to conventional intensive support.¹⁵ The limiting factor was found to be the rapid development of irreversible pulmonary fibrosis in most adult patients with acute respiratory failure.¹⁸

Experience with ECMO in term newborns with respiratory failure has been more encouraging primarily due to the fact that their lung disease is usually reversible. Newborn patients selected for ECMO have usually had either PFC alone or with CDH or MAS. Preterm babies with severe RDS usually develop massive IVH when heparinized for ECMO and have been excluded from most clinical studies at this time. Major considerations in the application of ECMO for neonatal patients is the flow through the membrane oxygenator circuits and vascular access. Although early studies employed arteriovenous flow,^{4,8} recent investigators have used venoarterial circuits which provide adequate flow through the membrane oxygenator but require the sacrifice of the right common carotid artery.^{24,27-29} Current VA techniques have led to a 57 percent survival rate in babies who were predicted to have a 90 percent mortality risk in seven American centers providing neonatal ECMO. Venovenous circuits have been used in a very limited

number of patients and provide less efficient gas exchange than VA technique.³²

Conventional intensive mechanical ventilation for neonatal respiratory failure may be approaching the limits of its effectiveness. New modifications such as high frequency ventilation have yet to find wide clinical application or acceptance.^{45,46} The development of a clinically applicable ECMO technique may be an alternative to further modifications of conventional mechanical ventilation for the care of newborn patients with severe neonatal respiratory failure. Potential major advances may include the development of a "heparinless system" which would allow the application of ECMO to the IVH—prone low birth weight prematures with RDS.

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