Alternatives to ECMO

Nothing epitomises the technological advances in neonatal medicine more than extracorporeal membrane oxygenation (ECMO) treatment. This technique has dramatically improved the survival of infants with presumed intractable respiratory failure. Data from the Extracorporeal Life Support Organization Registry as of July 1993 show an overall survival rate of 81% for 8020 treated newborns.

ECMO has been embraced as a standard treatment in much of the world despite a paucity of controlled clinical trials. Two studies performed in the United States, using an adaptive randomisation design, achieved statistical significance and were terminated without many control patients and left many questions unanswered. In the ensuing years, use of neonatal ECMO has proliferated in spite of the fact that other respiratory treatment modalities and clinical strategies are now available which are less technical, less expensive, less invasive, and less labour intense. Most of these ‘alternative’ strategies are routinely available to neonatal intensive care units and have demonstrated the potential to relegate ECMO to its most effective role as a rescue treatment when more conventional therapy fails.

ECMO candidates
Patients considered for ECMO treatment are generally ≥2000 g and 34 weeks’ gestation and have intractable - but reversible - respiratory failure within the first 10 days of life. The causes of respiratory failure are diverse and include meconium aspiration syndrome, respiratory distress syndrome, sepsis/pneumonia, congenital diaphragmatic hernia, and others. Virtually all of these conditions involve secondary persistent pulmonary hypertension of the newborn (PPHN), and although management strategies differ from one condition to the next, alleviation of pulmonary hypertension and establishment of pulmonary blood flow is something they share as a common therapeutic goal.

Basic supportive measure
No matter what criteria are utilised to constitute indications for ECMO, they all presuppose that the infant has received ‘optimal medical management’. This includes the appropriate ventilatory modality and strategy, which is disease specific (see below). Support of systemic blood pressure is of the utmost importance in assuring tissue perfusion and decreasing right-to-left shunting of blood. Initial management consists of cautious expansion of blood volume (colloid, blood, or crystalloid) by up to 20 ml/kg. Central venous pressure monitoring is a useful adjunct and helps to determine the need for additional volume or inotropic support (dopamine, 2-5-15 μg/kg/min; dobutamine, 5-20 μg/kg/min; or isoprenaline, 0-1-0-4 μg/kg/min). Oxygen carrying capacity should be maximised by transfusion to maintain a packed cell volume above 0-4. Detection of impaired oxygen delivery, tissue oxygen extraction, or both may be made by monitoring mixed venous blood gases or oximetry. Surfactant deficiency should be corrected by exogenous surfactant administration. Antimicrobials should be given in cases where infection is presumed or proved. Vasodilator treatment (tolazoline 1-2 mg/kg/hour) may be beneficial in reducing pulmonary vascular resistance but must be used with great caution because of its non-selective nature and tendency to provoke systemic hypotension.

Alternative modalities
Infants unresponsive to conventional ventilatory techniques and basic supportive treatment may benefit from alternative treatment modalities. Unfortunately, there have been no controlled clinical trials which compare these modalities to each other or to ECMO. Utilisation has generally occurred as a rescue intervention or on the basis of clinical empiricism. Nevertheless, these treatments do suggest potential benefits and avoidance of ECMO.

Hyperventilation
Long the standard approach to PPHN in the United States, hyperventilation attempts to achieve significant alkalosis and hypocapnia through both metabolic and respiratory means. Target pH is usually 7-50-7-70 and arterial carbon dioxide tension (Paco₂) 2-0-4-0 kPa during the acute phase. Sedatives and paralytics are used liberally.
The physiological basis for this approach is the observation that alkalosis and hypocapnia exert independent effects on reducing pulmonary arterial pressure and improving pulmonary perfusion. This approach is modified at 72–96 hours when the infant reaches the 'transition stage' and exhibits less vascular responsiveness.

**Conservative ventilation**

This technique is almost diametrically opposed to hyperventilation. Developed by Wung et al, this approach is aimed at using the least possible ventilator support to achieve satisfactory gas exchange, thus limiting the adverse effects of barotrauma and hyperinflation. Target blood gases reflect these goals, where pH is kept from 7.25–7.40, PaCO₂ 5–3–8.0 kPa and arterial oxygen tension (PaO₂) from 6–7–9.3 kPa. Paralytics are not used and sedatives are minimised so as not to depress respiratory drive. Wung et al reported 100% survival of 15 infants treated this way, who had had a predicted mortality of 80%. Dworetz et al reported 90% survival in 10 patients. Both series were non-randomised and uncontrolled.

**High frequency ventilation**

This form of positive pressure ventilation uses extremely small tidal volumes (less than anatomical deadspace) provided at very rapid rates to produce gas exchange at lower mean airway pressure than conventional ventilation. High frequency jet ventilation (HFJV) uses a jet injector to deliver a high velocity gas flow at rates of 240–660 breaths/min. Expiration is passive. High frequency oscillatory ventilation (HFOV) uses either a piston or vibrating diaphragm to deliver tidal volumes at rates of up to 3600 breaths/min. Both inspiration and expiration are active.

HFJV has had some success when applied to ECMO candidates. Baumgart et al reported 100% survival if applied to infants with an oxygenation index (mean airway pressure (cm H₂O) x fractional inspired oxygen/PaO₂ (mm Hg)) <0.4, and 84% survival in 38 patients with respiratory distress syndrome or pneumonia. Similarly, Hart et al described a 48% survival rate over a three-year period in an ECMO centre. Using HFOV, Carter et al successfully managed 50% of near term infants with severe respiratory failure who had met ECMO indications. Although high frequency ventilation is relatively easy to use, it requires careful analysis of the strategy to be utilised, based on the homogeneity of the lung disease, lung volume, and whether the primary deficiency is ventilation or oxygenation.

**Volume cycled ventilation**

Volume cycled ventilation refers to the delivery of a preset tidal volume delivered at whatever pressure is necessary to do so. Although it was used frequently in the late 1970s and early 1980s, design flaws and insufficient monitoring capabilities led to its disappearance from neonatal nurseries. Now, however, microprocessor based technology and state of the art monitoring has enabled the use of volume cycled ventilation in infants as small as 2000 g. Bandy et al reported on a non-randomised, quasiexperimental series of ECMO candidates treated with volume cycled ventilation after time cycled pressure limited ventilation failed. All six of the infants showed dramatic improvement in oxygenation, at the same mean airway pressure, and all avoided ECMO. Pulmonary mechanics testing revealed much more consistent tidal volume delivery during volume cycled ventilation, perhaps stabilising lung volumes and decreasing ventilation-perfusion mismatch.

**Liquid ventilation**

This technique, which must still be considered investigational, involves the use of a liquid medium, a perfluorocarbon, to inflate the lungs and serve as a medium for gas exchange. Perfluorocarbons are able to do this because of low surface tension and high oxygen solubility; they are also biologically inert. Human neonatal experience to date has been minimal. Shaffer et al reported the use of liquid ventilation in three dying infants. Before death improved compliance was demonstrated in all three, and improved oxygenation in two. Although much more study is required, it appears that some patients might derive benefit from the technique.

**Nitric oxide**

Nitric oxide has been identified as the long elusive endothelial derived relaxing factor, which binds to haemoglobin and results in relaxation of vascular smooth muscle cells. Animal experience has demonstrated that inhaled nitric oxide is a potent pulmonary vasodilator with a sustained effect which does not decrease systemic blood flow. Early human neonatal experience in ECMO candidates has been favourable. Roberts et al and Kinsella et al successfully treated a total of 15 patients during short term evaluation. Marked improvement in predural arterial oxygen tension suggests a selective lowering of pulmonary vascular resistance and right-to-left shunting. Wider experience and careful attention to longer term toxicity will be necessary, but early indications are very exciting.

**Magnesium sulphate**

Abu-Osba and colleagues recently reported a series of cases in which newborns with severe persistent pulmonary hypertension unresponsive to conventional treatments and with predicted mortalities ranging from 94–100% were treated with high dose intravenous magnesium sulphate. Seven of nine infants survived. Treatment was associated with improvements in arterial oxygen tension and haemoglobin saturation, decreased arterial carbon dioxide tension, and increased pH. The mechanism believed responsible for the observed changes was reduced pulmonary pressure from muscle relaxation. This intriguing treatment will require more study.

**Summary and conclusions**

The past decade has witnessed technological advancements which are unparalleled in neonatology. ECMO has been demonstrated to be a powerful rescue treatment, but has perhaps been overutilised and is not universally available. Alternative treatments have been shown to be both safe and efficacious in the management of infants with respiratory failure. Direct head to head clinical trials will probably be necessary to establish appropriate criteria and indications for use, given the wide diversity of pathophysiology these unique patients present.

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