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The role of extracorporeal membrane oxygenation in congenital diaphragmatic hernia

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The aim of this paper is to review the role of extracorporeal membrane oxygenation (ECMO) in neonates with severe acute hypoxemic respiratory failure secondary to congenital diaphragmatic hernia (CDH). The difficulties in identifying patients with fatal lung hypoplasia are highlighted and the role of adjunctive therapies on ECMO (surfactant, inhaled nitric oxide, high-frequency ventilation and liquid lung distension) as well as the timing of surgical repair is discussed. Survivors of severe CDH who have been supported on ECMO have significant late mortality and morbidity. There remains a need for a randomized controlled trial of the role of ECMO in neonates with severe CDH.

The overall treatment strategy and the role of ECMO in the management of patients with severe acute hypoxemic respiratory failure (AHRF) secondary to congenital diaphragmatic hernia remain controversial. Over the past 3 decades we have seen treatment strategies evolve from urgent surgical correction (1970s), to delayed repair with aggressive preoperative hyperventilation (1980s), to the current era of delayed repair with permissive protective ventilation.

High-frequency oscillation ventilation (HFOV), surfactant, inhaled nitric oxide (iNO) and ECMO have all been tried with varying success and there are few randomized controlled trials. Disappointingly, the mortality from CDH remains significant, with the latest survival rate in the international CDH Study Group registry being 63%.[1]

ECMO is an invasive form of life support based on the principles of cardiopulmonary bypass which can be used to support patients with intractable cardiorespiratory failure. Its role in the setting of CDH is to treat potentially reversible pulmonary hypertension[2] and to provide the "ultimate" protective ventilation strategy. These potential benefits must be weighed against the inherent risks of ECMO, which include the need to instrument major neck vessels, exposure to blood products and the risk of bleeding from heparinization. It should be emphasized that ECMO is a form of life support and as such cannot cure fatal lung hypoplasia secondary to CDH.

The aim of this paper is to review the evidence for the use of ECMO in infants with CDH. Selection criteria, use of adjuvant therapies while on ECMO, timing of repair and long-term outcome of these patients are also discussed.

What is the evidence for ECMO in CDH?

Several retrospective reviews have reported an improvement in survival of patients with CDH with the use of ECMO.[3,4] It is difficult, however, to isolate the effect of ECMO from that of other simultaneous advances in modes of ventilation, surgical practice and treatment protocols.

In the only randomized controlled trial evaluating the role of ECMO in neonates with acute hypoxemic respiratory failure (OI>40),[2] none of the 17 patients with CDH ran-

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domized to conventional treatment survived, while 4 of the 18 patients in the ECMO group survived. These numbers are clearly too small to be conclusive.

In 1997, the *Journal of Pediatric Surgery* published the landmark "Tale of Two Cities" papers.[5,6] These side-by-side papers compared the outcomes of neonates with CDH treated at two large tertiary care pediatric centers between 1981 and 1994. One center used high-frequency ventilation as the primary rescue therapy after failure of conventional ventilation and used ECMO in only 3 of 223 patients. The overall survival rate in this cohort was 54.7%. The other center used ECMO as its preferred rescue therapy (98 of 196 patients) with a similar survival rate of 53%.

While there was no difference in survival between these two centers in 1997, it is interesting to note that in the current era, the center favoring ECMO has recently reported an improved overall survival rate of 93% in their patients with CDH.[7] This has been associated with a treatment protocol emphasizing gentle ventilation, aggressive treatment of pulmonary hypertension, and judicious use of ECMO (36% of all CDH patients). The improvement in survival does not appear to be due to altered case selection, as survival was significantly higher than that predicted (68%) using the CDH Study Group formula for prediction of outcome.[8] The survival of patients treated with ECMO in this series was 86% despite a predicted survival of 52% using the same CDH Study Group formula. This is also much higher than the latest Extracorporeal Life Support Organization (ELSO) figure of 53% survival in 4491 CDH infants treated with ECMO.[9]

It is of note that improved outcomes have also been reported recently in centers which rarely or never use ECMO, with survival rates in the range of 75 to 90%.[10,11] Comparisons of small, single center retrospective reviews to identify the effect of a single intervention such as ECMO will always be limited by potential differences in patient population and overall treatment strategy. It is thus impossible to reach a definitive conclusion regarding the role of ECMO in improving outcome in these patients. There therefore remains the need for a randomized controlled trial in neonates with severe CDH.

Selection criteria for ECMO in patients with CDH

The traditional entry criteria for ECMO in neonates with severe AHRF have been oxygenation index (OI) greater than 40, severe barotrauma/air leak, and/or refractory hypercarbia.[2] The OI is a ratio relating the level of ventilatory support (mean airway pressure × Fi02) to efficacy of oxygenation (Pa02). Historically, an OI>40 has been associated with 60 to 80% mortality in term neonates with AHRF. It has been argued that, in neonates with CDH, more lenient criteria should be applied in view of their lung hypoplasia and the higher mortality in this group when the OI is greater than 40[12,13]

General criteria for exclusion from ECMO have included prematurity (GA <34 weeks), weight below 2 kg, intracranial hemorrhage and contraindication to anticoagulation. Patients are also excluded if they are believed to have irreversible organ failure.

There have been numerous attempts to identify fetuses and newborns with CDH and fatal lung hypoplasia to avoid the futile use of invasive therapies and to develop selection criteria for trials of new therapies. None of these have been successful in reliably predicting mortality.

One of the oldest measures suggested to predict fatal pulmonary hypoplasia in CDH is the inability to achieve a preductal PO_2 greater than 100 mmHg at some stage of resuscitation. Failure to demonstrate this level of oxygenation (the so-called "honeymoon period") is still considered a reason to exclude a patient from ECMO in some centers today.[10,13,14] This number is originally based on a study of infants with CDH treated between 1966 and 1973[15] in which all 5 surviving patients of a group of 8 patients studied had a best preductal PO_2 greater than 100 mmHg. Of note, one of the three nonsurvivors had also demonstrated a preductal $PO_2 > 100$ mmHg.

Several papers have now shown survival of patients who would be deemed "unsalvageable" and excluded from therapy by this measure[7,16,17]

Unfortunately, we still lack physiological measures by which to predict fatal pulmonary hypoplasia with certainty. In the absence of such measures, it is our practice to offer ECMO to patients with CDH who fail conventional ventilation strategies (preductal saturation <85% or OI > 25 to 40), who have signs of severe barotrauma/air leak or who require cardiac support.

Management of CDH patients on ECMO

Mode of support: venoarterial versus venovenous

Venoarterial (VA) ECMO has been the traditional support mode used in patients with CDH; the 1995 worldwide ELSO Registry database figures reported the use of VA ECMO in 94% of CDH patients treated with ECMO.[18] With the introduction of the double lumen venovenous cannula (DLVV) and increased confidence with use of venovenous (VV) ECMO, the proportion of neonates supported with VV ECMO has increased in recent years[9] The advantages of VV ECMO include sparing of the carotid artery, delivery of oxygenated blood to the lungs, and preservation of pulsatile blood flow.

A recent multicenter survey using ELSO Registry data reviewed outcomes of CDH patients treated with ECMO between 1990 and 1999.[19] Of 2628 patients, 86% were treated with VA and 14% with VV. The level of pre-ECMO support was similar in each group. Patients treated with each mode had similar survival rates (58.4% versus. 52.2%, respectively), with a possible trend toward higher survival in