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ECMO in CDH: Is there a role?

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ABSTRACT

Despite wide use and decades of experience, survival of congenital diaphragmatic hernia (CDH) patients treated with extra-corporeal membrane oxygenation (ECMO), as reported by the extra-corporeal life support organization (ELSO), remains unchanged at 50%. High-survival rates both with and without utilizing ECMO have been reported, fueling questions about the utility of ECMO support in this difficult population. This review looks at data from the Congenital Diaphragmatic Hernia Study Group and individual center reports, to evaluate the role of ECMO in CDH, focusing on defining the patients most likely to benefit, and discussing how those benefits can best be achieved. These data show that ECMO improves survival in those CDH patients who are most severely affected, but potential complications of ECMO delivery outweigh benefit in patients with less severely affected. Improved results can be expected by minimizing ECMO complications, and by improving rates of CDH repair in patients that require ECMO.

Introduction

In 1977, German et al.[1] reported the first four CDH patients supported with ECMO, of which one survived. Four decades later, CDH is the most common indication for ECMO in neonates.[2] Despite its wide availability and use, however, many remain unsure of the utility and benefit of this invasive support in this most difficult population. Multiple centers report excellent survival results using ECMO in 35–50% in their CDH population, but in stark contrast, other centers report very good results using ECMO sparingly, if at all. Are these experiences comparable? Several monographs specifically addressing this question of utility of ECMO in CDH have failed to derive clear conclusions.[3,4]

The goal of this review is to first address then go beyond the binary question of whether ECMO improves survival in CDH, asking for which CDH patients does ECMO increase survival, how are those results best obtained, and can those results be improved? Is there an outcome difference in veno-venous (VV) versus veno-arterial (VA) ECMO in CDH? What is the optimal timing for CDH repair in the ECMO patient? Unfortunately, reporting of risk stratification data to allow direct comparison of results between series is insufficient in most reports. The task is further complicated by the fact that the ultimate survival success of ECMO in CDH is affected not only by the quality of the ECMO, but also by what comes before and after the ECMO run.

In addressing these questions, we will look to published data from the Congenital Diaphragmatic Hernia Study Group, and from individual center reports focusing on contemporary series that report high-survival rates both with, and without utilizing ECMO. We will also look at how overall treatment strategies affect CDH–ECMO outcomes, specifically the role of patient selection, ventilator support strategies, type of ECMO, and importantly, how timing of surgical repair affects CDH–ECMO outcomes.

History

ECMO was first used in 1977 and expanded in the 1980s to rescue neonates suffering from life-threatening hypoxemia and hypercarbia following emergent surgical repair of CDH, their courses also complicated by the ravages of aggressive ventilator support. Langham, Stolar, Newman, and many others demonstrated the life-saving potential of lung rest along with the resolution of pulmonary hypertension, which often occurred with the use of veno-arterial ECMO post-repair.[4–6] In those three early reports, 32 of 46 ECMO treated patients (69.6%) survived to discharge, and the future of ECMO support in CDH appeared bright.

Since then, the CDH diagnosis and treatment background has changed. Ventilation strategies have evolved and improved, vastly decreasing the potential for ventilator induced lung injury.[5–7] Affected newborns, for better or worse, are now stabilized for days or longer before surgical repair, and as a result the vast majority requiring ECMO arrive unrepaired, rather than

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post-repair as in the early years.[8,9] Pulmonary vasodilators including nitric oxide and others have become ubiquitous in the management of CDH, although their effect on improving, or perhaps worsening CDH outcomes is similarly questioned.[10–12] It is possible that contemporary CDH patients requiring ECMO, as a result of better non-ECMO management, are more severe than in previous eras. It is also possible, since the majority of CDH patients are now diagnosed prenatally, terminations of more severe CDH fetuses could be truncating the CDH severity spectrum.[13] No data currently exist to clarify if the underlying severity of CDH patients has changed over time, but it is clear that the survival of those supported by ECMO, as tracked by the extra-corporeal life support organization (ELSO), has not improved over the past few decades and remains at just 50%.[14] After 30 years of great effort, either the limitations of ECMO benefit in CDH have been reached, or there still remains significant opportunity for improvement.

CDH spectrum of disease

In 1999, a seminal report from the CDH Study Group defined the relationship between CDH disease severity, and the survival benefit from ECMO. Compared to conventional therapy alone, ECMO support significantly improved survival for those CDH neonates with a predicted mortality greater than 80%, as defined by a logistic regression equation based on birth weight and 5-min Apgar scores.[15] In contrast, when ECMO was used on patients with less severe disease, ECMO support exerted either an equivocal or negative effect on survival, the negative effect increasing as disease severity decreased (Figure). Since support with ECMO adds risks to the CDH patient, including bleeding from anticoagulation, these risks must be offset with greater benefit before additional CDH survival accrues. Utilizing ECMO in less severe patients increases mortality due to added risk without benefit, and only in the more severe patients is the added risk offset by increased survival opportunity. Future opportunities for improving survival must include minimizing ECMO in those patients with less severe disease, and minimizing the risks of ECMO, that is, doing better ECMO, in those on the severe end of the spectrum that require ECMO.

Understanding and defining CDH disease severity, therefore, is central to understanding the potential benefits of ECMO in CDH.

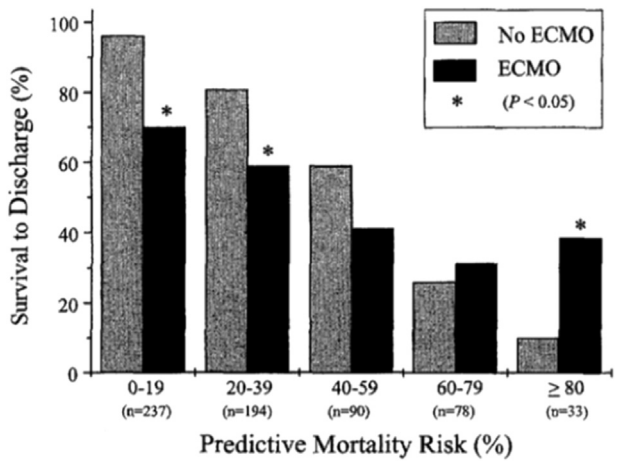

Fig. Difference in actual survival rate to discharge between those CDH neonates who received ECMO therapy compared with those who did not (i.e., no ECMO) when categorized into quintiles of predictive mortality risk. For predictive mortality risk of 80% or greater, ECMO neonates have a higher survival rate compared with the no ECMO neonates. *$p < 0.05$ by χ^2 and logistic regression analysis.

Following the original CDH Study Group predicted survival equation based on 5-min Apgar and birth weight, additional work on prenatal anatomical and postnatal physiologic markers of severity have added considerable granularity to our understanding of CDH disease severity.[16–19] Of physiologic markers, birth physiology and early blood gases provide more discrimination of underlying disease severity than later blood gases or pre-ECMO physiology.[20] This occurs because blood gases tend to improve over the first 12–24 h of life for most CDH patients, and the levels of physiologic derangement immediately before ECMO are similar for the majority of CDH patients. This "homogenization over time" diminishes the power of those physiologic markers, at those time points, to differentiate the underlying levels of disease severity. In contrast, anatomic measures of CDH severity including prenatal lung measurements, liver position, and percent liver herniation, along with the postnatal measures of defect size and patch rate, are not affected by treatment factors or clinical course. Anatomical measures are, therefore, more useful for comparing disease severity between studies where treatment strategies may differ. Of these, thoracic liver position (liver-up), especially for left CDH, has proven an important and relatively simple risk stratifier, correlating strongly with increased risk for ECMO and for mortality.[19,21,22] A meta-analysis of liver herniation in CDH showed survival rates of 74% with liver down CDH, which dropped to 45% in liver-up CDH.[21] Finally, defect size correlates strongly with survival and risk for ECMO, and "patch rate" functions as a reasonable surrogate for larger defect sizes.[23–25] In addition, outborn patients as a group represent a less severe cohort compared to inborn, as the most severe outborn patients do not survive birth and transfer, effectively pruning the severity spectrum. These proven correlations to CDH severity; inborn status, liver position, and patch rate can help inform population severity as we compare historical series.

Trials and series

Randomized controlled data on the role of ECMO in CDH is limited to two early ECMO studies, and the UK ECMO trial.[26–28] In the UK ECMO trial, randomization to conventional ventilation versus ECMO occurred at an oxygenation index of 40. Seventeen of 17 CDH infants randomized to conventional management died, while 4 of 18 in the ECMO arm survived (0% survival versus 22% survival). One of those survivors subsequently died at 2 years of age.

In 2006, Morini et al.[4] published a systematic review of ECMO in CDH, identifying 658 publications of which 21 (2043 patients) met entry criteria. Looking at the most rigorous of the non-randomized studies, the authors concluded ECMO use was associated with a reduction in CDH mortality. Zalla et al. recently reviewed a single center CDH experience dividing 16 years of treatment into four eras, the latter two with ECMO availability. Post hoc analysis suggested a 73% reduction in risk of death in the ECMO eras compared to the pre-ECMO eras despite increases in CDH disease severity ($p < 0.001$).[29]

The Table shows a compilation of single center publications since 2000 that show high survival, from centers reporting either low or higher ECMO usage that were assembled for this publication. These reports were chosen because they document very good results, appear to have minimal selection bias, and provide some anatomical data for risk stratification. While all the results are excellent and the authors are to be congratulated, it appears notable that the highest survival rates and the highest severity, as reflected in the higher patch rates, were reported in the centers with higher ECMO use. While hardly definitive, these data support