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The journey of pediatric ECMO

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Introduction: Extracorporeal membrane oxygenation (ECMO) is an adaptation of conventional cardiopulmonary bypass techniques used for long-term support of respiratory and/or cardiac function.

It provides physiologic cardiopulmonary support for patients with acute, reversible cardiac or respiratory failure. The term "extracorporeal life support" (ECLS) was proposed to describe prolonged but temporary (1 – 30 days) support of heart or lung function using mechanical devices. Technically, ECMO terminology is used for modalities that provide pulmonary support system involving oxygenation and carbon dioxide removal, and ECLS is used for both cardiac and pulmonary support systems, but these terminologies are still used interchangeably.[1,2]

Over the past 30 years, due to significant advances in the understanding of physiology, improvement in clinical care, innovation of novel therapies for primary diseases, and technological advances, there have been major changes in indications, cannulation, duration of treatment, and outcome for the children being treated with ECMO. Patient selection remains key to a successful outcome since ECMO is a supportive therapy utilized while waiting for a reversible condition to resolve through other treatment strategies.

According to the registry report of the Extracorporeal Life Support Organization (ELSO), over 78,000 cases have been reported until July 2016. Of these cases, 29,153 are newborn infants with respiratory failure, 74% of which survived to hospital discharge; 18,153 of them are patients managed with ECMO for severe respiratory failure in the pediatric (7,552) and adult (10,601) age groups with survival to a hospital discharge rate of 58% in each group. All other cases relate to cardiac support in neonates, children, and adults with rates of survival to hospital discharge ranging between 40 and 50%.[3]

History: Bubble oxygenators, used in early cardiopulmonary bypass systems, were characterized by a direct interface between blood and gas. However, significant hemolysis caused by these oxygenators limited prolonged exposure.[4] Long-term support was made possible by the development and introduction of membrane oxygenators, which physically separated the blood and gas phases and thus minimized the problem of hemolysis.[5] In 1972, the first successful use of prolonged cardiopulmonary bypass was reported by J. Donald Hill.[6] The patient was supported for 3 days with venoarterial extracorporeal bypass support for a ruptured aorta following a motorcycle accident.

Neonatal evidence: In 1976, Bartlett et al.[1] reported on baby Esperanza, the first successful neonatal ECMO survivor. She was supported for 3 days on ECMO for respiratory failure secondary to meconium aspiration. Dr Bartlett led the first prospective randomized, controlled trial (RCT) that evaluated neonatal respiratory ECMO against conventional management, which was conducted at the University of Michigan in 1985.[7] This study was published to demonstrate the benefit of ECMO by comparing cases in which all patients supported with ECMO survived, while conventionally treated patients died. The study faced much criticism. This led to a second larger study by Dr Pearl O'Rourke at Boston Children's Hospital in 1989. Of 10 patients who were conventionally supported, only 6 survived, whereas of 29 patients who were supported with ECMO, 28 survived.[8] In 1996, the UK Collaborative ECMO Trial Group published a 55-center conventionally designed RCT. Neonates with PPHN were randomized to either stay in their referral center for standard therapy or be transferred to a regional ECMO center. Survival was found to be higher in those receiving ECMO than in those who did not receive it (60% vs. 40%). Follow-up at 1 year showed a significantly lower death rate or severe disability in the ECMO group.[9] A Cochrane review (2008) by Mugford and colleagues evaluated four trials by comparing ECMO and conventional management for neonatal respiratory failure. Increased survival to hospital discharge with ECMO support was demonstrated by all the four studies when compared with conventional therapeutic strategies. Of a total of 244 infants, 77% survived in the ECMO group whereas only 44% survived in the conventionally managed group.[10] Bartlett et al.[11] attributed the success of ECMO in newborns to the fact that the lungs require only a short time for recovery in neonates with respiratory failure. The data from the prospective randomized controlled trial from the UK showed rigorous evidence of the cost-effectiveness of neonatal ECMO during childhood.[12]

Pediatric evidence: In the 1980s, the benefit of ECMO for pediatric patients was subject to discussion in the medical community.[13,14] Concerns were raised about the application of the new, expensive, and potentially dangerous technology in children in whom pulmonary injury could be due to widely unknown mechanisms. To gain further acceptance of ECMO in children, performance of a RCT was considered mandatory. However, this approach was postponed due to ethical considerations. In 1996, Green et al.[15] published the results of a retrospective multicenter cohort analysis in 331 pediatric patients. Evaluation of factors associated with survival was done with a multivariate logistic regression analysis. ECMO was found to be associated with a reduction in mortality. An additional matched-pairs analysis revealed 74% survival in the ECMO group ($n = 29$) and 53% in the non-ECMO group ($n = 53$) ($P < 0.01$).

In the review of ECMO utilization in neonatal and pediatric respiratory failure between 2002 and 2012, survival was found to be consistent at 57%, despite increasing comorbidities. However, for patients without comorbidities, survival increased from 57 to 72% over the study period. Children supported with ECMO for status asthmaticus, aspiration pneumonia, and respiratory syncytial virus pneumonia had higher survival rates (between 70 and 83%). Poor prognostic indicators included patient age between 10 and 18 years, hepatic or renal failure, evidence of immune dysfunction, and diagnosis of fungal pneumonia, pertussis, or ARDS secondary to sepsis.[16]

For children with severe cardiac failure, ECMO is used to provide temporary circulatory support for patients with potentially reversible disease or as a bridge to decision, either device or transplant. In a prospective multicenter study involving 17 pediatric cardiac centers, children who underwent implantation of the pediatric Ventricular Assist Device (VAD) as a bridge to transplantation were compared with a historical control group of children who received circulatory support with ECMO. Significantly higher survival rates were associated with VAD when compared with ECMO (88–92% vs. 75–67%). However, VAD use is not without complications, with the most common ones being bleeding, infection, stroke, and hypertension. This makes balancing when (or if) to institute the support even more challenging.[17]The way forward:

With the success of less-invasive respiratory support measures, the demographics of pediatric ECMO patients will continue to change with increasing numbers of support for patients with cardiac dysfunction and less for those with respiratory failure.[18–20] Improving results will encompass highly complex patients, and those with single-ventricle physiology will not be denied support and, in fact, will contribute a large percentage of ECMO patients.[21] Smaller and more efficient cannulas[22] are increasingly available for effective and rapid peripheral cannulation,[23,24] and can potentially trigger an upsurge in ECMO-CPR in children.[18,25]
Remarkable advancement in pumps, oxygenators, and heparin coating of artificial surfaces has resulted in higher biocompatibility and lower rates of complications. Furthermore, improvements in monitoring anti-coagulation and control of bleeding[24] through the development of rapid and accurate point-of-care devices will make ECMO safer for children. A key factor leading to complications in small bodies is the exposure to large volumes of fluids. Experimental miniature pumps that diminish priming volumes and circumvent hemodilution could eventually provide a solution.[26]
Upcoming generation of centrifugal pumps using magnetic levitation appears to improve end-organ recovery where supported patients show a trend toward better hospital survival and significantly higher late survival.[27] It is essential that future ECMO devices should make support much simpler, safer, and to a great extent automatic, while decreasing the need for anticoagulation. ICU nurses rather than ECMO specialists should manage the system, reducing the cost while maintaining ease and safety.[20,28]
Continued education with the help of regulated training of all participants and use of simulation should be part of in-service activities within each institution committed to advance the service.Pediatric cardiac transplantation will hopefully be available in the Gulf area, but is not currently a treatment strategy. Technological advances in implantable centrifugal and axial flow pumps have yet to be miniaturized for suitable use in infants and neonates, which is proven difficult until now.[29] On the flip side, significant advances to provide successful ECMO support for weeks or months have been achieved.[19] Reduction in sedative use and keeping patients more awake,[19] together with improvement in ventilator support to the point of extubation, could potentially lead to ambulatory ECMO. It could therefore potentially evolve into a definitive component of mechanical heart failure therapy in this region.Data and registry need to be widespread and garnered from multicenter experiences to provide understanding to the quality of life after ECMO in children. It could also guide us to develop criteria for the use of ECMO as a resuscitative tool in cardiac arrest,[19] and provide an answer to the controversial relationship between volume and outcome, and whether service regionalization would deliver the promise of improved results.
Conclusion: ECMO is used as a standard of care for neonates and children with severe cardiac and pulmonary dysfunction refractory to conventional management. A lot of wisdom has been gained through research and experience with a resultant change in practice in the field of neonatal and pediatric ECMO over the past three decades with many promising advances awaiting support with robust evidence.

Keywords: ECMO, ELSO, neonatal, pediatric

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