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ECMO: Past, Present, and Future

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INTRODUCTION

The application of extracorporeal techniques to support the failing heart and lungs has a distinguished history as a bench-to-bedside technology that has continued to develop and integrate into our daily intensive care practice. While still largely limited to specialized medical centers, advances in technology and patient management are allowing the diffusion of this technology into an ever-increasing number of institutions. One could have imagined that the application of ECMO would have a limited lifespan; that with improvements over the past 5 decades in managing cardiopulmonary failure would obviate the need for its use. To the contrary, its application has been expanding, as evidenced by the increase in cases reported to the Registry of the Extracorporeal Life Support Organization, particularly in adults:

EARLY HISTORY

ECLS has its roots in operating room cardiopulmonary bypass, established in the 1950's by Gibbon and other early pioneers. By the early 60s, the ability to replace cardiac and pulmonary function during surgical procedures led to the interest in applying this technology to long-term support in the intensive care unit. Things we now take for granted, however, were largely unknowns at that time. The effect of the non-biocompatible circuit on blood elements during prolonged exposure was unknown. Anticoagulation with heparin had not been used for more than the duration of bypass procedures, and its long-term effects were unknown. The impact on organ blood flow (early ECMO was strictly venoarterial) was also unknown. These questions and more were addressed by Drinker, Bartlett, Gazzaniga, and others with modifications of the CPB circuit for long-term use in a number of animal experiments conducted in the 1960's.

The first reported clinical application of extracorporeal support was in 1971 for respiratory failure in a young adult with post-traumatic ARDS. He underwent 2 days of venoarterial support and survived. Interest in ECMO for adult respiratory failure following this case report resulted in a more widespread application.

In 1972, the first successful use of pediatric cardiac ECMO for post-operative management following a Mustard procedure for transposition of the great vessels was described. Moreover, in 1975, the first use of ECMO for neonatal respiratory failure was reported by Robert Bartlett and colleagues.[1,2]

CLINICAL TRIALS

The use of ECMO in adult respiratory failure was adopted in a number of medical centers following the 1971 report in ARDS. The National Institute of Health (NIH) funded a randomized

multicenter study conducted from 1975 through 1979, in which venoarterial ECMO added to standard therapy was compared to standard therapy alone. Both groups had poor survival of about 10%, with no apparent improvement due to ECMO. Following this report, the use of ECMO for adult respiratory failure essentially ceased.

In 1994, Morris and colleagues performed a single-center and randomized trial of extracorporeal CO_2 removal (ECCO2R) in adult ARDS, following an earlier report of a cohort trial from Gattinoni suggesting benefit. The Morris trial also resulted in no difference in survival, and seemed to reaffirm the lack of benefit of extracorporeal support in adult respiratory failure. However, the differences between low-flow ECCO2R and high-flow ECMO were not widely appreciated, and the prevailing thought was that this was the second "ECMO" trial that failed to show benefit, when in fact, it was not a trial of ECMO (with oxygenation support).[3]

A third randomized trial of ECMO for adult respiratory failure (CESAR) was conducted beginning in 2007 in the United Kingdom by Peek and colleagues. The design included patient referrals from all of the UK, and required all ECMO to be performed at Leicester (by transfer), with all controls maintained at their respective hospitals. There were treatment guidelines for conventional therapy, but no strict protocols. It was an intent-to-treat trial, and therefore included those enrolled patients dying during transport as well as those who did not receive ECMO if their condition improved before arrival. The trial demonstrated a significant reduction in death or major disability at 6 months. Because of its design, it received criticism as being more a trial of transfer to a center with ECMO capability versus treatment in local intensive care units. However, it is felt to be at least in part responsible for the resurgence in ECMO application in adult cardiopulmonary failure.

There have been three neonatal trials that have demonstrated significant improvements in survival in neonatal respiratory failure. Bartlett performed the first trial using a play-the-winner design. While statistically valid, the fact that it enrolled only one patient in the conventional arm led to criticism. O'Rourke and colleagues at Harvard performed an adaptive randomized trial in PPHN reported in 1989 in favor of ECMO. This was followed by a true randomized trial in the UK from 1993 to 1995, showing a highly significant improvement in survival. From this point on, ECMO was firmly established as a standard of care in the management of newborn respiratory failure.

There have been no formal randomized trials in the pediatric population, although small studies have suggested an improved outcome. In spite of this, ECMO is considered a standard of care in this age group, and it is unlikely that a randomized trial was performed.

TECHNOLOGY AND PATIENT MANAGEMENT

Inherent in the use of advanced support technology is the risk of the equipment and the associated patient management. It is likely that the equipment used in the early years of ECMO and the lack of understanding of concepts such as ventilator induced lung injury contributed to the poorer outcomes than seen today.

Early ECMO was performed with circuits that comprised a high extracorporeal volume, high surface area, and components that were highly incompatible with blood resulting in significant complement and platelet activation and systemic inflammation. Vascular access was obtained by surgical cutdown often using thoracotomy tubes, since dedicated vascular cannulae for peripheral access did not exist. Anticoagulation levels were kept high due to the higher thrombogenicity of the circuit, and bleeding complications were profound by today's standards. Blood loss of 1.5–1 l/day was not uncommon.

Substantial improvement in equipment has ensued over the past 40 years. Vascular access is now typically percutaneous using thin-walled cannulae with antithrombotic coatings. The introduction of the dual lumen cannula allowing for single site cannulation has simplified venovenous support for respiratory failure. This approach also permits awaking and mobilizing patients, now increasingly recognized as important conditioning steps to recovery. Bleeding from access sites is now distinctly uncommon, and the need for blood transfusions has dropped considerably. Some patients may be managed without blood transfusion. The original metal Bramson artificial lung was replaced by the solid silicone lung (with no air-blood interface), which dominated the field until recent years. Current oxygenators are now low-resistance, high-efficiency and low priming volume, and plasma resistant hollow fibers with antithrombotic coatings. The new generation of centrifugal blood pumps is now hemolysis-free with low priming volume and can run for weeks without need for replacement. Antithrombotic coatings reduce the level of systemic anticoagulation and greatly reduce bleeding complications.

We now have a better understanding of managing the failing heart and injured lungs, leading to a greater chance of recoverability. The concepts of protective lung ventilation were not introduced until after the NIH and Morris trials. Patients in these trials were subjected to injurious levels of ventilator support. These protective concepts were developed by the time of the CESAR trial and may have played a part in the improved outcome.

PRESENT DAY ECMO

The present day applications of ECMO include the traditional uses for support of cardiac and respiratory failure. Cardiac

ECMO is used in the neonatal and pediatric populations for a number of indications, including post-operative congenital heart support and acute myocarditis. In the adult population, it is rapidly becoming the preferred acute short-term therapy for post-cardiotomy syndrome as well as acute myocarditis as a bridge to recovery or bridge to decision. Ventricular assist devices (VADs) are now being reserved for bridge to transplant or destination, although some patients recover enough function during support to have their VAD explanted.

Support of respiratory failure remains the most common indication for ECMO. Historically, it was used for patients with acute reversible respiratory failure with expected recovery and this still remains its most common application. With recent improvements in technology, in particular with dual-lumen single cannulation of the internal jugular vein, patients are being provided support to transplant. With current management, patients can participate in physical rehabilitation, including ambulation, thereby improving their ability to successfully undergo transplantation.

The newest and among most rapidly growing indications are in support of cardiopulmonary arrest. extracorporeal cardiopulmonary resuscitation (CPR) entails the rapid deployment of femoral venoarterial ECMO in patients not responding to conventional CPR. Survival rates on the order of 30% and greater are being reported, higher than the historically reported rates of 12–15% with conventional CPR. Rapid deployment is facilitated by recent technological improvements, including hollow fiber oxygenators with centrifugal pumps, which can be rapidly primed with crystalloid solutions. Results for in-hospital cardiac arrest are encouraging and its use in out-of-hospital arrest is associated with improving poor outcomes. The challenge in the latter may be in selection of patients, since in-hospital arrest is usually witnessed, while out-of-hospital often is not.

THE FUTURE OF ECMO

The driving force for the future of ECMO has been the improvement in technology. Miniaturization and automation of support systems will move ECMO to the current status enjoyed by CRRT, with nurse-driven bedside management. A large step in this direction has been realized in the Maquet Cardiohelp® system and other commercial systems on the way. It also enhanced the mobility of patients, and even permit excursions outside of the hospital (a feat which has already been accomplished). The future systems would also allow the use of ECMO as a replacement for mechanical ventilation. Some ECMO centers actively pursue extubation of patients on ECMO, removing a source of further injury and infection. It is not inconceivable that ECMO could be first line therapy in selected patients, avoiding intubation altogether. This is particularly true for hypercapnic respiratory failure, such as chronic obstructive pulmonary disease exacerbation, for which dedicated CO_2 removal systems are currently hitting the market.

The greatest hurdle remaining is perhaps anticoagulation. The antithrombotic coatings of today can reduce heparin requirements but not eliminate its use, requiring complex monitoring and management. Advanced coatings have the potential to eliminate this restriction altogether. Promising coatings such as nitric oxide-releasing coatings are currently under development and show promise in pre-clinical studies.

Another exciting extension of ECMO is the artificial implantable lung for destination therapy of chronic lung failure. In this capacity, blood would be pumped by the right ventricle, eliminating the need and problems of a blood pump. Animal experiments had clearly demonstrated the feasibility, yet work remains on optimal hemodynamic configuration, oxygenator design, and antithrombotic coatings. With continued development, these advances should be realizable in the not-too-distant future.[4]

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