Application of Venovenous Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Failure: Situations, Issues, and Trends

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Extracorporeal membrane oxygenation (ECMO) is a type of extracorporeal life support (ECLS), and technological advances have expanded the use of this technique from the confines of the operating room by producing a compact system that could revolutionize the treatment of different types of respiratory failure.[1] The use of ECMO for severe acute respiratory failure (ARF) has evolved over the past two decades, and venovenous-ECMO (VV-ECMO) has been found to be safe and successful, especially during the H1N1 influenza epidemic, with good survival rates. ECMO has been used as salvage or rescue therapy for acute respiratory distress syndrome (ARDS) by providing oxygenation, CO_2 removal, or both. It is not curative for ARDS and is used mainly as a bridge until the lungs recover from the underlying disease or as a bridge to lung transplantation for severe irreversible lung diseases.

Evolution of Extracorporeal Membrane Oxygenation for Acute Respiratory Failure

Three major prospective trials of ECMO have been conducted in the past 40 years in patients with severe ARF. However, because the initial study sponsored by Zapol *et al*.[2] using venoarterial-ECMO in 1979 and the Morris trial[3] performed in 1994 were both disappointing, the use of ECMO in adults has exhibited a different trajectory. The CESAR trial, which was a randomized multicenter trial comparing conventional ventilation to ECMO for 180 severe ARF patients published in 2009, showed a significantly higher rate of disability-free survival at 6 months, 63% in patients referred for an ECMO protocol versus 47% in the conventional care group.[4] A further surge in the use of ECMO occurred during the H1N1 influenza pandemic in 2009, which caused a significant mortality in otherwise healthy young people due to ARDS, in whom conventional ventilation was often not successful.[5] The ongoing randomized Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome trial will likely provide more concrete answers regarding the effectiveness of ECMO in severe ARDS patients (ClinicalTrials.gov Identifier: NCT01470703).[6]

Although ECMO has been performed for many years in our country, it has mainly been used for cardiac support; the increased use of ECMO as a rescue therapy for ARF due to H1N1 influenza began in 2009 and increased in 2013 due to the H7N9 influenza outbreak.[7-9] Although the number of hospitals that have performed VV-ECMO for ARF rescue is increasing rapidly, the quantity in each center is limited, and no unified registration network exists in our country. This situation hinders the standardization and management of ECMO and leads to poor outcomes. However, VV-ECMO has been used for the treatment of more than 80 cases of

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severe ARF in our center, with a survival rate of more than 70% in the last 2 years, which is similar to that of larger ECMO centers abroad.[10,11]

Noticeable Problems during Extracorporeal Membrane Oxygenation

When to initiate extracorporeal membrane oxygenation

We are also faced with much confusion, such as when ECMO initiation is appropriate and how to manage and prevent complications. According to the Extracorporeal Life Support Organization (ELSO) registry data, over 16,430 adult patients have received ECLS as of July 2016. Of these, the need for respiratory support accounted for 10,601 cases (47%) followed by cardiac support in 9052 (40%) cases, and 2885 cases (13%) involved extracorporeal cardiopulmonary resuscitation.[12]

The common indications for the use of VV-ECMO in patients with ARDS include profound refractory hypoxemic respiratory failure with or without hypercapnia despite maximal ventilator support and the inability to tolerate lung protective strategies.[13] The ELSO guidelines, which we followed, recommend transfer to specialized ECMO centers when the mortality risk is 50% or higher, and transfer is indicated when mortality is equal to or exceeds 80%.[14] However, physicians are now often faced with the dilemma of when to initiate and terminate therapy. This can prove to be ethically challenging. The optimal timing for the initiation of ECMO also remains unclear, which makes the entire process challenging for physicians.

Management during extracorporeal membrane oxygenation

The daily care of an ECMO patient is a complex multidisciplinary task. Similar to other critically ill patients, ECMO-supported patients must be re-evaluated for the primary disease, which can lead to Intensive Care Unit (ICU) admission, and for the possible development and treatment of other organ failures. The complex relationship between the patient and the ECMO circuit sometimes makes patient assessment difficult. Other tasks include monitoring of the ECMO circuit and the prevention of complications.

Very little is known about the optimum ventilator settings while using VV-ECMO. The new "ultra-lung protective strategy" adopted the use of even lower tidal volumes and pressures to minimize ventilator-induced lung injury.[15] An important dilemma in these patients is the question, "Should we let the lungs collapse or should we try to keep them open?" The details such as the mode of ventilation, breath type, respiratory rate, positive end-expiratory pressure (PEEP), and FiO_2 are still unknown. A study of new ventilation strategies guided by transpulmonary pressure in ECMO to determine the optimal PEEP to limit atelectrauma is ongoing in our center (ClinicalTrials.gov Identifier: NCT02439151).[16] Our previous study found that, compared to the traditional "lung rest" strategy, the transpulmonary pressure-guided ventilation strategy can better maintain lung volume to limit atelectasis and provide more effective lung protection.

Another method includes potentially extubating patients while on ECMO, the so-called "awake ECMO" mode,[17] thereby avoiding the damaging effects of ventilator-induced lung injury and the risk of ventilator-associated pneumonia. Patients undergoing this method will require minimal to no sedation and can ambulate, participate in physical therapy, and remain on ECMO until the lungs recover.

The potential benefit of ECMO can be offset by numerous complications. Bleeding is one of the major and most dreaded complications, with an incidence ranging between 10% and 30%. Intracranial hemorrhage is the most serious and potentially fatal bleeding complication, occurring in approximately 10–15% of ARDS patients on ECMO. These potential complications require close monitoring and necessitate the presence of a specially trained ICU team who are constantly available to troubleshoot the system at the bedside 24 h a day.[18]

Heparin is the most commonly used anticoagulant in EMCO. Targets for anticoagulation are monitored using different methods such as the activated partial thromboplastin time, anti-Xa activity, activated clotting time, anti-Xa levels, and viscoelastic tests (Thromboelastography [TEG®] or rotational thromboelastometry).[19] However, the most reliable technique for monitoring anticoagulation and the ideal range of anticoagulation to prevent thrombosis or bleeding are both unknown. It is noteworthy that novel centrifugal pumps, polymethylpentene oxygenators, and heparin-coated circuits ensure fewer clotting challenges. Large cannulas with higher flows also reduce the risk of thrombosis.

Expansion and Standardization

Recently, the increasing application of ECMO in ARF patients has expanded the clinical practice of ECMO in our country. However, blind expansion in every hospital is not appropriate. Centralization of patients to a few selected, specifically equipped centers and establishing a registration network to share resources may help improve clinical management by physicians and the outcome of patients, which should be our primary effort. Moreover, the CESAR trial indeed indicated that significantly more patients with severe ARDS survived without severe disability if they were transferred to a single ECMO center compared with patients who were managed conventionally at remote hospitals.[4] ECMO instituted at referral centers allows stabilization of an unstable patient, otherwise unmovable, and thus a safer transportation to the targeted destination. Nevertheless, adding an ECMO system makes transportation more complex, requiring a specialized multidisciplinary ECMO team, trained and equipped to stabilize patients at the referring hospital, to apply and manage ECMO, and to assist patients during transportation up to the treatment

center. Besides, as ECMO is an expensive investment and advanced technology life support modality; introduction of a qualification assessment system should be recommended in large medical centers.

Several questions remain to be considered when planning a national or regional ECMO network with structured interhospital transport. Interhospital transportation of critically ill patients to referral centers is required when local resources and technology are insufficient for adequate management. The process requires a specialized team and resources dedicated to retrieval. Therefore, as ECMO is an invasive, intensive form of support; it requires considerable institutional commitment. Consequently, its use is advocated only in those patients who are believed to be at substantial risk of death.

Conclusion

Overall, the application of VV-ECMO for ARF in the mainland of China is still in the development phase. Based on the above-mentioned standardized management experience and shared resources, we can implement a system that is consistent with that of the international community.

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