

REVIEW

Pushing out the frontiers: single centre experience in 100 patients receiving extracorporeal membrane oxygenation

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Extracorporeal membrane oxygenation and its evidence in adults

Extracorporeal membrane oxygenation (ECMO) has been deployed for more than 40 years, first as a therapeutic option for circulatory shock and later also for the worst cases of acute respiratory distress syndrome (ARDS). However, as far as we know, no randomised trials have been performed that demonstrate the efficacy of ECMO for circulatory support. ECMO for respiratory support was found not to be superior to conventional treatment in two randomised controlled trials in the nineteen-nineties.^{1,2} Consequently, its use has long been restricted to neonates and small children. Due to major technological improvements in ECMO machines and catheters,³ ECMO has regained interest and the number of published case series has increased since the beginning of this century. Especially during the H1N1 pandemic, a dozen case series of patients who failed on conventional ventilation and were saved by ECMO therapy were published.⁴⁻⁸ In addition, a randomised trial was performed in which treatment in specialised ARDS centres (with ECMO capability) was compared to treatment in centres without ECMO capability.⁹ The study demonstrated a mortality benefit for patients treated in specialised ECMO centres. However, the study received criticism as it was the centres and not the treatment modalities that were compared. Moreover, in a recent propensity matched case-control study, ECMO did not demonstrate a survival benefit in H1N1-induced ARDS patients.¹⁰ Therefore, while ECMO is used as rescue therapy in certain centres, a survival benefit of ECMO is still lacking. Hopefully the recently started multicentre international randomised study, which will test the efficacy of early veno-venous-ECMO in patients with severe ARDS (EOLIA trial), will clarify this topic.

Physiology of ECMO

In veno-arterial extracorporeal membrane oxygenation (vaECMO), blood is drained from the caval vein and after

oxygenation blood is returned into the femoral artery. Blood flow through the ECMO system is mostly around 4-7 l/min and is thus capable of taking over the complete circulation, even when cardiac output is nil due to severe cardiac failure. vaECMO is suitable for circulatory support and less suitable for respiratory support, especially in patients with preserved native cardiac output.

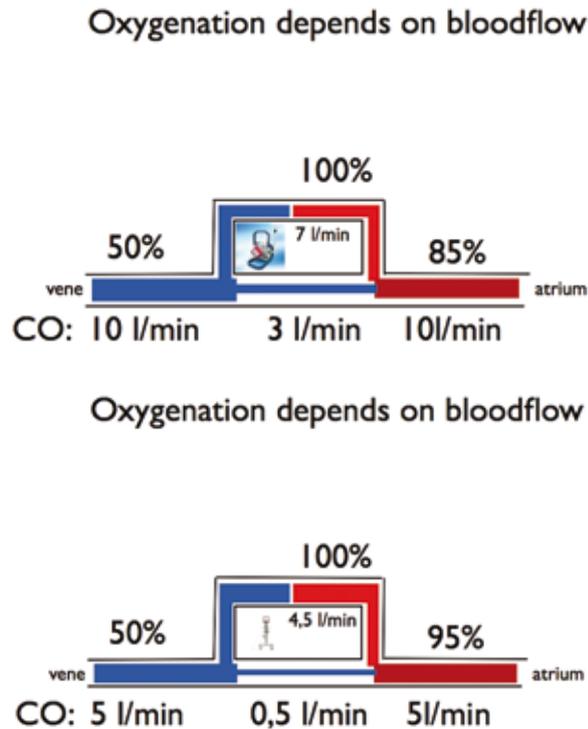
Veno-venous extracorporeal membrane oxygenation (vvECMO) drains blood from the inferior caval vein and returns oxygenated and decarboxylated blood in the right atrium via the superior caval vein. Without native gas exchange in the lung, vvECMO can achieve an arterial saturation of 90%. The arterial saturation depends on blood-oxygen saturation in the drainage canula, haemoglobin concentration, and the ratio blood ECMO flow / native cardiac output (*figure 1*).

Decarboxylation does not require a high ECMO blood flow as blood solubility of CO₂ facilitates a more rapid diffusion and higher clearance through the membrane lung. Therefore, CO₂ removal is primarily a function of the fresh gas flow through the membrane, provided a minimal ECMO blood flow of 1 l/min to allow complete clearance of the patient's CO₂ production.

Which patients should receive vvECMO?

Determining which patients should receive vvECMO therapy is still very difficult. Historically, oxygenation failure, assessed by a Murray score or oxygenation index, is used to decide whether to start vvECMO therapy. The Extracorporeal Life Support Organisation (ELSO) states that vvECMO can be considered with a PaO₂/FiO₂<150 mmHg and a Murray score 2-3, which represents an estimated mortality risk >50%.¹¹ vvECMO is indicated with a PaO₂/FiO₂<80 mmHg and a Murray score 3-4, representing an estimated mortality risk of 80%. Moreover, CO₂ retention due to asthma with a PaCO₂>80mmHg or the inability to achieve plateau pressure (Pplat) <30 mbar is also an indication for vvECMO, as well as severe air leak syndromes. Ventilation longer than one week at high settings

Figure 1a and 1b. Arterial oxygenation depends on ECMO blood flow and native cardiac output and venous saturation. In this figure, venous saturation is 50%. In the left figure, high native cardiac output (10 l/min) with an ECMO blood flow of 4.5 l/min results in a large amount of blood not going through the oxygenator and results in a low arterial saturation. In the right figure, cardiac output is lower, resulting in a higher arterial saturation. These figures are under the assumption of an absent recirculation.



($\text{FiO}_2 > 90\%$ or $\text{Pplat} > 30$ mbar), major immunosuppression (absolute neutrophil count $< 400/\text{m}^3$) and recent CNS bleeding are considered relative contraindications. Furthermore, an increased mortality risk with increasing age should be considered (no specific age criteria are set), weight > 125 kg, non-fatal co-morbidities and bridging to lung transplant can be a relative contraindication because of the limited number of donors.

Who should be excluded from vvECMO: predicting mortality while on vvECMO

As the criteria for withholding a patient from vvECMO therapy were based on expert opinion, the ECMOnet score has recently been developed, based on historical data.¹² The aim of the ECMOnet score is to identify predictors of mortality in patients treated with vvECMO in referral centres. The dataset contained 60 patients (82% H1N1 patients) and the validation set contained 74 patients (81% H1N1 patients). Using multivariate analysis, five significant predictors for death were identified (table 1). An ECMOnet score > 4.5 had an area under the curve of 0.69 in the receiver-operator-characteristics (ROC)

Table 1. The ECMOnet score.¹²

Pre-ECMO mortality predictor (ECMOnet)			
Bilirubin (umol/l)	Pt	PreECMO Hospital LOS (days)	Pt
<2,5	0	<3	0,5
2,6 - 11,1	0,5	4-7	1
11,2 - 19,6	1	8-11	1,5
19,7 - 28,2	1,5	>11	2
28,3 - 36,7	2	Hematocrite (%)	
>36,7	2,5	>40	0,5
Creatinine (umol/l)		36-40	1
<44	0	31-35	1,5
45 - 70	0,5	<31	2
71 - 97	1	MAP (mmHg)	
98 - 123	1,5	>90	0
124 - 150	2	61-90	0,5
151 - 176	2,5	<60	1
177 - 203	3		
>203	3,5		

MAP = mean arterial pressure, regardless of vasopressor use, LOS = length of stay.

of the validation set with a sensitivity of 51% and a specificity of 76% for survival on ECMO therapy.

Experience in the Erasmus Medical Center

Since 2004, 122 adults in the EMC have been treated with ECMO: 9 patients received vaECMO during cardiopulmonary resuscitation (ECP), 60 patients received vaECMO mainly due to ischemic cardiomyopathy and 54 vvECMO mainly due to bacterial or viral pneumonia (figure 2). The survival rate was 38%, 63% and 67%, respectively, and this was in accordance with the ELSO registry data. Figure 3 shows that the survival rate has decreased after vvECMO therapy during the last few years. However, the ECMOnet score increased, indicating that more severely ill patients have been treated over the years.

Whilst patients were receiving vvECMO, the causes of death on the ICU were multiple organ failure ($n=4$), intracerebral haemorrhage ($n=4$), massive bowel ischemia ($n=2$), cardiac arrest ($n=2$) and lack of respiratory improvement ($n=2$). Patients on the vvECMO frequently had renal failure, requiring renal replacement therapy (36%). Severe complications of vvECMO were intracerebral bleeding, which occurred in 7% of patients, cardiac tamponade and myocardial infarction, which occurred in 5% of patients. These severe complications required immediate neurosurgical or cardiothoracic intervention. These data may illustrate the severity of illness in vvECMO patients and the need for neurosurgical and cardiothoracic backup in an ECMO centre.

In the beginning, our indications for vvECMO were very strict and limited. In 2009, only patients with mono-organ failure were candidates for vvECMO treatment. One year later, also

Figure 2. number of adult patients per year treated with extracorporeal membrane oxygenation(ECMO) in the Erasmus MC. va-ECMO= veno-arterial ECMO, vv-ECMO= veno-venous ECMO, ECPR= ECMO during cardiopulmonary resuscitation.

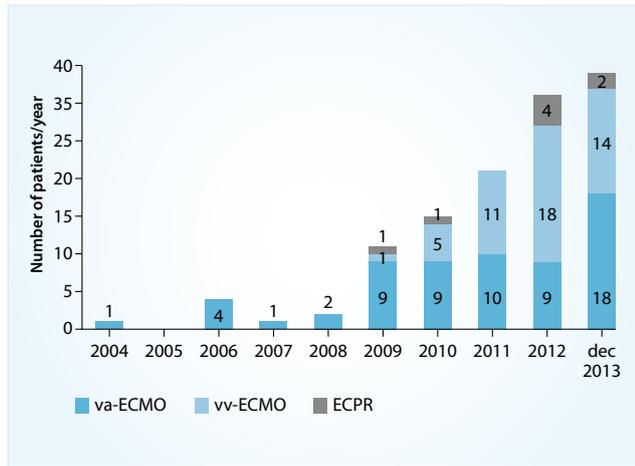
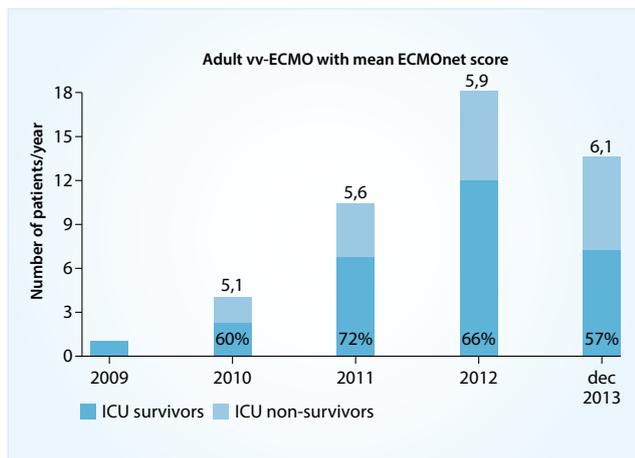


Figure 3. Number of patients/year treated with veno-venous extracorporeal membrane oxygenation (vv-ECMO). Numbers above bars is the mean annual ECMOnet score. Number in the bars is the percentage of ICU survivors.



young patients with systemic diseases were included and the need for renal replacement therapy was no longer a contraindication. In 2011, patients with septic shock were included for vvECMO. Thereafter, a patient with haemorrhagic shock due to trauma was included for vvECMO. Due to massive lung bleeding the patient was planned for vvECMO, but as the patient developed a cardiac arrest during the preparation phase, vaECMO was successfully instituted during resuscitation. In 2012, patients were receiving lung transplantation while on vvECMO. Recently, even duration of mechanical ventilation was no longer considered a contraindication. This is illustrated by the case of a young man with pneumosepsis, ventilated with peak pressures between 35 and 40 mbar (PEEP 10 mbar) for 37

days who underwent a successful vvECMO run for treatment of severe air leaks.

When analysing the *power to predict mortality* using the ECMOnet score in patients treated in the Erasmus MC, the ECMOnet score has the same area under the curve of 0.69, but with a higher optimal cut-off value of >6.5.¹³ In the Erasmus MC, an ECMOnet score above 6.5 has a sensitivity of 50% and a specificity of 80% for predicting mortality in patients on vvECMO. In our patients, the oxygenation index and APACHEII had an area under the curve of 0.54 for both variables.

Over the years, the ECMOnet score firmly increased in our centre, but mortality remained stable. As stated above, the indications for vvECMO expanded over the years and patients were found to be progressively more ill. *Figure 3* shows the progression of the ECMOnet score over the years in patients treated in the Erasmus MC and with the survival rate. Most likely, increasing expertise and the introduction of protocols has led to the relative increase in survival. In addition, bleeding complications have decreased dramatically due to percutaneous insertion of cannulas being carried out by an experienced team on the intensive care unit. Furthermore, a lower degree of anticoagulation is now accepted which results in a lower risk of bleeding complications. Just as in our intubated ICU patients, deep sedation of ECMO patients appeared to be superfluous and patients are now treated awake on ECMO, whenever possible. When they have a single, double lumen cannula in the internal jugular vein (*Figure 4 and 5*) and are awake on ECMO, patients receive physiotherapy and are mobilised. Mobilisation on vvECMO reduces mortality in patients awaiting lung transplantation.^{14,15} Due to our

Figure 4. Patient with methotrexate pneumonitis on full veno-venous extracorporeal membrane oxygenation, awake and cycling.



Figure 5. Patient awaiting a lung transplantation on full veno-venous extracorporeal membrane oxygenation walking to the corridor. The ECMO canulas are fixated on the patient's head with a cycling helmet.

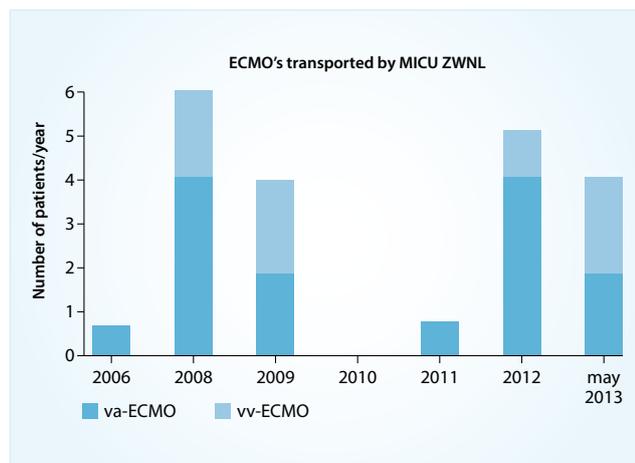


experience in the last five years, we strongly believe that ECMO should be centralised in expert centres where severe complications can be immediately be treated.

ECMO and transport

Patients on ECMO can be transported.^{16,17} 49 of the 101 patients who received ECMO were transported to the Erasmus MC to receive ECMO. Recently, we have started ECMO transport with our mobile intensive care units (MICU). The MICU Zuidwest Nederland is equipped with its own ECMO machine integrated on the trolley and 18 cases of transport of adults on ECMO have been done (*figure 6*), of which one was initiated by the MICU team in the referring hospital. Up until now, no complications during transportation have been reported.

Figure 6. Number of patients transported by the Mobile Intensive Care Unit (MICU) of the region South-SouthWest Netherlands (Z-ZWNL).



vaECMO=veno-arterial extracorporeal membrane oxygenation,
vvECMO= veno-venous ECMO.

The team caring for ECMO patients

The ELSO has made guidelines for ECMO centres.¹⁸ These guidelines mainly describe the minimal preconditions to which a centre has to comply and the training preconditions of each team member involved in ECMO care. The minimal preconditions of ECMO care are that it should be delivered in tertiary centres, located in geographic areas that can support an absolute minimum of 6 ECMO cases per year, and are actively involved in the ELSO registry.

According to the ELSO guidelines, the ICU should be staffed with experienced intensivists and experienced intensive care nurses. These intensivists and nurses must have followed a certification and re-certification programme containing didactic lectures, simulation sessions and bedside training, ending with an exam. Team members not involved in ECMO management for >3 months should be required to go through a re-certification programme. Moreover, support staff from the permanent hospital staff should include a:

- Cardiologist
- Cardiovascular surgeon
- General surgeon
- Cardiovascular perfusionist
- Anaesthetist
- Neurosurgeon
- Radiologist.

The adult intensive care unit of the Erasmus MC has put much effort into complying with these valuable guidelines. A training programme has been instituted as follows: a full day basic course is given to all staff, nurses and ICU-fellows containing lectures and an extensive simulation programme. Moreover, all team members receive a short hands-on training on every type of ECMO machine once every three months. This training mainly aims at practising the emergency procedures for each type of ECMO machine and all the alarms/screens. Fully ECMO trained physicians are immediately available at the bedside 24/7. At first glance, it might seem odd that the ECMO requires such an intensive training scheme. Other machines such as renal replacement, hemodynamic monitoring machines, echo machines do not require such training procedures. The reason for such intensive training is that an ECMO machine is a life-saving machine that is rarely used. In a normal intensive care setting, only two machines are considered to be immediately life-saving – the ventilator and infusion pumps. Frequent, very extensive training procedures with these machines are not required as the exposure by staff to these machines is large. For ECMO machines however, exposure is limited and malfunction of these machines may cause cardiac arrest in few seconds, for example, with vaECMO and (in our experience) also with vvECMO. Therefore, extensive training and a solid collaboration with the above named support specialties is crucial for a successful ECMO programme according to the ELSO guidelines.

Future Perspectives: How do we organise ECMO care in the Netherlands?

Paediatric ECMO has a long tradition in the Netherlands and is well organised. The Netherlands have two paediatric ECMO centres, one of them being the Children's Hospital of the Erasmus MC which has performed approximately 700 ECMO runs, with very good outcome. The adult ECMO however, has not yet been organised. Funding for adult ECMO is still unclear and which centres will be designated to perform ECMO is also unclear. Due to the lack of organisation, intensive care units tend to rent an ECMO machine and give it a go. This situation is comparable with Germany, where ECMO centres are appearing all over the place, most of them being low volume ECMO centres. It is supposed that the reason for this is the good reimbursement for ECMO treatment in Germany, and debate is going on in the larger German ECMO centres on how to tackle this problem. In contrast, in Sweden, ECMO care is strictly regulated where only the Karolinska institute provides ECMO treatment. This centre is a centre of excellence known in the ELSO registry and is famous throughout the world due to its high quality care and innovations.

In our view, Dutch ECMO centres should primarily comply to the ELSO guidelines, thus being a tertiary centre, with the capability of performing cardiothoracic surgery and neurosurgery. These ELSO guidelines also prescribe an extensive training programme with simulation and a hands-on

training every three months for the whole team (physicians and nurses). Centres complying with the ELSO guidelines should subsequently be reimbursed on the basis of real costs. For our centre, we aim at a minimum of 20 ECMO runs annually to maintain the experienced team¹⁹⁻²¹ and to pay off the investment of the extensive training programme.

Conclusion

Extracorporeal membrane oxygenation is a rarely used therapy that is regaining interest. Formulating the indications for ECMO and the best therapy during ECMO is still highly dynamic. Due to these rapid developments of a rarely used therapy and due to the relatively high complication rate, ECMO is best used in selected, specialised centres. The most important preconditions for ECMO centres is a large base of specialists, including a cardiovascular surgeon and a neurosurgeon and a solid training programme with a basic course including simulation and a refresher course every three months for the whole team.

Conflict of interests

D. Reis Miranda en D. Gommers have received fees from NovaLung GmbH.

Table 2. The experience of veno-venous extracorporeal membrane oxygenation (vvECMO), veno-arterial ECMO (vaECMO) and initiation of ECMO during cardiopulmonary resuscitation (ECPR). For vaECMO, most patients are in principle candidates for heart transplantation. Therefore, bridge to transplant patients are categorized by their underlying disease.

Underlying disease	ICU survivors	ICU deaths
VAECMO		
Ischemic	18	6
Post thoracic surgery	9	8
Transplant failure	5	4
Myocarditis	4	4
Pulmonary embolism	2	
VVECMO		
Bacterial	11	7
Viral	10	3
Pneumonitis	7	5
Bridge to transplant	6	1
Yeast		2
Trauma	2	
ECPR		
Ischemic		3
Hypothermia		2
Pulmonary embolism	2	
Trauma	1	
Total	77	45

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