Extracorporeal membrane oxygenation (ECMO)

G A Richards,[1] MB BCh, PhD, FCP (SA); **I Joubert**,[2] MB BCh, FCA (SA); **on behalf of the Critical Care Society of South Africa**

[1] *Department of Critical Care, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; Departments of Critical Care and Pulmonology, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Departments of Critical Care and Anaesthesiology, University of Cape Town, South Africa*

Corresponding author: *G A Richards (Guy.richards@wits.ac.za)*

Extracorporeal membrane oxygenation (ECMO) is increasingly being employed in South African intensive care units for the management of patients with refractory hypoxaemia and for haemodynamic support, particularly following cardiothoracic procedures. ECMO is expensive, however, and there is a danger that this rescue modality may be abused or utilised unnecessarily or in situations where further intensive therapy is futile. This brief review provides an overview of the techniques available, and the recommended indications and exclusions for venovenous ECMO in particular.

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Extracorporeal membrane oxygenation (ECMO) is not a novel therapy in the true sense of the word. The first case report appeared in 1972 and described a 24-year-old who had sustained blunt thoracic trauma that was successfully treated using ECMO.[1] Thereafter, the first randomised, prospective study of ECMO in severe acute respiratory failure was published in 1979. In the latter study, 90 adult patients received conventional mechanical ventilation (CMV) or CMV plus ECMO, with only 4 patients in each group surviving.[2] The author's conclusion was that ECMO could support respiratory gas exchange, but did not increase the probability of survival for severe acute respiratory distress syndrome (ARDS).

Modes of ECMO

Currently, there are 3 types of ECMO available: venovenous ECMO (VV-ECMO), which is indicated for severe but potentially reversible respiratory failure; veno-arterial ECMO (VA-ECMO), which allows haemodynamic support and is indicated for cardiac failure, with or without respiratory failure; and arteriovenous ECMO (AV-ECMO), which facilitates gas exchange, especially carbon dioxide removal, by using the patient's own arterial pressure to pump blood through the circuit.[3] The latter is sometimes referred to as an extracorporeal carbon dioxide removal ($ECCO_2R$) system, as it is more efficient at CO_2 removal than it is at correcting hypoxaemia. Low-flow VV-ECMO may also be used primarily for $ECCO_2R$.

The potential for improvement in oxygenation with VV-ECMO is less than that with VA-ECMO and is due to an increase in the central venous oxygen saturation, such that the shunted blood elevates overall arterial saturation despite a potential **increase** in shunt fraction from loss of hypoxic pulmonary vasoconstriction. This mode may, however, reduce pulmonary pressures and right ventricular strain through a similar mechanism.[3-5] VV-ECMO also has a lower risk of thrombo-embolic complications, and because the lung is perfused, in contrast to VA-ECMO, pulmonary endocrine function remains normal. This system allows for extracorporeal removal of carbon dioxide while providing lung rest, avoiding ventilator-induced lung injury. In addition, the dual-chamber cannula (Avalon Laboratories, Rancho Dominguez, CA, USA) drains the inferior and superior vena cava, returning the blood to the region of the tricuspid valve without significant re-recirculation (drainage of oxygenated blood injected by the return cannula when dual-catheter systems are utilised) and allowing better patient mobilisation.[3,6]

Despite VA-ECMO improving oxygenation more than VV-ECMO, and the fact that there is no loss of hypoxic pulmonary vasoconstriction, there are increased risks associated with this method. The technique requires arterial cannulation with large catheters and therefore has the potential for limb ischaemia, and if blood is returned to a femoral artery, brain oxygenation cannot be guaranteed.[3,4]

Outcome studies

Since the 1970s, the efficiency of ECMO in oxygen exchange has never been debated – it has been proof of efficacy regarding survival that has been lacking. Recently, however, a number of observational studies have reported improved outcomes with overall survival rates close to 50%.[7,8] The H1N1 influenza epidemic of 2009 in particular produced a number of publications describing outcomes, again observational, mostly with patients who had single-organ failure.[9,10] While the mortality rate in these patients was better than previously reported, these studies are retrospective and selection bias was a concern. In addition, patients who received ECMO had longer stays both in the intensive care unit (ICU) and in hospital, irrespective of outcome.

ECMO is an expensive therapy, so outcome should be unequivocally improved to justify its use. In the only prospective randomised trial involving ECMO, 180 patients either received CMV at their base hospital or were transferred to a centre offering ECMO as part of therapy. Intention-to-treat analysis showed benefit for ECMO, with a relative risk reduction for death at 6 months of 0.69 (95% confidence interval 0.05 - 0.97; p=0.03). There have been criticisms of this study, and it is of note that only 75% of patients referred for consideration of ECMO actually received it. In fact, 16 patients improved with lung-protective CMV alone. In this study, however, ECMO added a cost of £40 544 per patient and was again associated with a longer stay in both ICU and hospital, irrespective of outcome.[11,12] Estimation of cost is technically difficult because it involves total in-hospital,

transfer and pre-transfer costs and the cost per quality-adjusted life year saved. Currently cost analyses that have been reported in the literature are sparse and vary significantly in methodology, making direct comparisons between patient populations difficult.[13] In South Africa, costs related to ECMO, accessed from one medical aid, have increased dramatically over the past 3 years, indicating a significant increase in utilisation but with an associated high mortality rate (Discovery Health – personal communication) (Table 1).

As with all data of this sort, the problem is that there is no way of determining whether patients treated with ECMO would have survived with CMV alone, or whether costs would have been similar if evaluated as total hospital cost inclusive of all therapies and length of stay.

Another factor that confounds the consideration of cost-efficacy or quality-adjusted life years gained is that there is still controversy regarding the survival benefit of this technique, even in its primary indication, H1N1 influenza. Researchers using data from the large French REVA/SRLF H1N1 cohort study recently found no benefit when using a propensity analysis in patients with severe H1N1 influenza.[14] Of 123 patients treated with ECMO, only 52 could be matched using an exposed/non-exposed, one-to-one approach. Those who could not be matched were younger, had more severe respiratory failure, and had a markedly lower mortality rate. In the matched groups, ICU mortality did not differ significantly with ECMO versus CMV (50% v. 40%; p=0.32). However, when control subjects were used more than once in a sub-study, the authors were able to match 102 patients with and without ECMO and in this case demonstrated a significant (55%) reduction in risk of death (p<0.01). This method was also employed for a propensity analysis in a British study and may similarly have resulted in an overestimate of benefit.[15]

We are, then, left with a technology that has been proved to be efficient in improving oxygenation, but has substantial cost implications and scant evidence of survival benefit. We therefore need to ensure that ECMO is not just another expensive yet ultimately ineffective therapy like drotrecogin alpha, particularly in a cash-strapped healthcare environment such as that in South Africa.[16]

Table 1. Costs related to extracorporeal membrane oxygenation

	Average for 2010 and 2011
Overall hospital costs specific to ECMO	R31 883 306
Average cost per case/ event	R358 730
Mortality rate	41.5%

Patient selection

Despite the costs, the controversies and the high mortality, we have no doubt that VV-ECMO is an advance in medical technology, and that its application should be encouraged and its techniques more widely taught and refined. This should, however, be introduced without unnecessary expense, specifically by selecting the most appropriate patients in order to minimise mortality so that the use of this modality will not be compromised in the future.

Where the risk of death associated with the underlying disease is high, life expectancy after recovery is low, or CMV with or without salvage therapies (Table 2) would conceivably have a similar outcome, ECMO should be avoided. While studies are ongoing in Europe, and in Luciano Gattinioni's unit in Italy in particular, to determine whether ECMO would result in an overall reduction in ventilator-induced lung injury with decreased systemic inflammation and improved survival, it is not envisaged that ECMO should be a frequent intervention in South Africa. Only a few patients have hypoxaemia refractory to CMV, and most recover unless there is significant co-morbidity or multi-system disease. There is a balance, however – if ECMO is utilised too late, benefit is likely to be less, and if it is utilised too early, or without consideration of other interventions, expense will be greatly increased.[18]

Recommendations

Because the best survival rates in patients treated with ECMO are observed in respiratory failure due to non-necrotising viral pneumonia, probably because these are often younger patients with less co-morbidity and the associated lung injury is often reversible, we recommend that the following should be overall exclusions for ECMO:

1. Non-availability of a trained multidisciplinary team with access to a specialised intensive care and cardiothoracic and vascular surgical services
2. Pulmonary oedema from myocardial dysfunction, unless ECMO is a holding measure before transplantation, or the patient has acute myocarditis from which he or she is likely to recover
3. Exacerbations of chronic obstructive pulmonary disease with respiratory failure
4. Multiple-organ failure from severe sepsis or a systemic inflammatory response syndrome
5. *Pneumocystis jiroveci* pneumonia requiring ventilation
6. Severe co-morbid illness that will impact significantly on life expectancy, e.g. incurable malignant disease or liver failure
7. Inadequate recruitment and/or diuresis/dialysis in the presence of fluid overload
8. Any condition that is potentially irreversible

Table 2. Current salvage interventions for refractory hypoxaemia[17]

1. Optimisation of fluid balance
2. Recruitment, including proning, HFOV and APRV
3. Corticosteroids
4. Sedation and the use of neuromuscular blockade
5. Use of 'permissive hypoxaemia' accepting lower saturations (in the region of 70% with PaO_2 in the region of 40 - 50 mmHg) rather than using potentially injurious ventilatory techniques

HFOV = high-frequency oscillatory ventilation; APRV = airway pressure release ventilation; PaO2 = partial pressure of oxygen in the blood.

9. Technical difficulty associated with the procedure
10. Where systemic anticoagulation is contraindicated
11. Immunosuppression not likely to recover rapidly
12. Patients mechanically ventilated for longer than 7 days, as underlying lung damage might be irreversible
13. Age >75 years.

Specific indications: VV-ECMO

1. Primary ARDS with refractory hypoxaemia: severe pneumonia (particularly viral, but any pneumonia without multiple organ failure), pulmonary contusion, gas inhalation, aspiration, smoke inhalation
2. Status asthmaticus or reversible airway obstruction not able to be ventilated conventionally or rapidly ameliorated
3. Pulmonary embolism (if haemodynamically stable).

Specific indications: VA-ECMO

1. Weaning from cardiopulmonary bypass after cardiac surgery
2. As a bridge to cardiac transplantation
3. Acute myocarditis
4. Pulmonary hypertension (after pulmonary endarterectomy or following surgery on congenital heart defects).

Whereas these recommendations are not meant to be prescriptive, it is necessary that some degree of control is maintained over the burgeoning expense of this procedure nationally. It is envisaged, however, that as ECMO is more frequently employed and expertise is improved, new indications and exclusions may become apparent. This is a living science that will develop along with new technical developments.

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