

## Extracorporeal membrane oxygenation (ECMO) in South Africa

Extracorporeal membrane oxygenation (ECMO) is an advanced modality of life support for neonatal, paediatric and adult patients with cardiopulmonary compromise resistant to conventional critical care management. This edition of *SAJCC* features a position statement proposing guidelines for the use of ECMO in South Africa. The authors correctly point out that ECMO is not a novel therapy, the first adult patient having been treated in 1972. For more than 30 years, ECMO has been a controversial subject in the intensive care community. For most of that time it has only been practised in a few specialist centres worldwide, usually concentrating on neonatal and paediatric patients. Even these centres were generally handling less than 20 cases per year. After publication of the 1979 National Institutes of Health<sup>[1]</sup> and subsequent Morris<sup>[2]</sup> studies there was even less enthusiasm for adult ECMO, and only a handful of centres continued to offer it worldwide. Neither of the abovementioned studies is relevant to current practice, however, for many reasons related to changes in both ECMO and conventional care management, and several other observational studies have demonstrated its benefits.<sup>[3,4]</sup>

The recent upsurge in interest in this subject has been precipitated by the coinciding of several factors: firstly the technological improvements in oxygenator, pump and cannula design; secondly the CESAR trial of adult ECMO<sup>[5]</sup> and thirdly a worldwide H1N1 influenza A pandemic. This pandemic produced a significant cohort of young, critically ill adults, despite the mortality for older patients actually being lower than usual.<sup>[6]</sup>

Until recently (around 2007), ECMO was generally practised using a roller pump controlled by a bladder box and a solid silicone membrane oxygenator. It was soon obvious to all concerned that achieving an acceptable standard using these circuits was difficult and time consuming, and that occasional ECMO was to be avoided. Because of the limited demand for long-term use devices, there was little industry research into improving technology. However, when the improvements started to appear, developments came quickly.

Firstly, there was the introduction of polymethylpentene (PMP) hollow-fibre oxygenators. These were long lasting and had much lower resistance to blood flow than earlier devices. These new PMP oxygenators have no protein leakage over time, which did occur and compromised durability with the previous generation of membranes. Secondly, highly efficient and durable magnetically operated centrifugal pumps were developed, which were also in use as ventricular assist devices and much better suited to the new lower-resistance gas exchange devices. The final component that made ECMO much more attractive, particularly for use in adults, was the development of purpose-built Silastic wire-reinforced double-lumen cannulas with low recirculation characteristics. The combination of these improvements makes for a circuit that is durable and efficient, requiring much less bedside interaction than its predecessor. The new double-lumen cannula allows for single-catheter insertion, simplifying initiation and improving the efficiency of venovenous (VV) ECMO. It is also a circuit that will not blow apart, because there is no occlusive roller pump, although air entrainment and embolisation can still be a complication. Superficially, therefore, it appears much simpler and safer, and for this reason many clinicians are being

tempted to use it without engaging in the necessary training, development of management protocols and planning necessary for providing this prolonged circulatory support. The main issue causing meltdown for inexperienced users is the occurrence of haemorrhage, often arising from something simple like an intercostal chest drain insertion. Experience and understanding are required, both to prevent such events and to manage them before they precipitate an untenable clinical situation.

The Heart Link ECMO Centre in Leicester, UK, was involved in two major ECMO trials. The first was the UK collaborative trial for respiratory failure in neonates, which showed a clear benefit for transfer of critically ill babies from a regional neonatal centre to an ECMO centre to receive ECMO support.<sup>[7]</sup> In the UK this led to the setting up of a national neonatal ECMO service based in four centres and providing for the UK as a whole. It has functioned successfully for over 20 years and is ongoing.

The second was the CESAR trial for adult respiratory failure, which randomised patients from established intensive care units to either continuing conventional intensive care in the original hospital or transfer to a single specialist ECMO centre (Glenfield Hospital, Leicester).<sup>[5]</sup> This trial reported a statistical benefit for transferring patients with a Murray score of more than 3.0 for ECMO. There were, however, confounding factors with respect to the number of successful conventionally treated patients in the ECMO arm, and significant mortality during transfer of patients, which had not been a feature of earlier practice.

An important feature of both UK trials was that the end-point was not survival; instead, it was intact survival after an interval. In the case of the UK Collaborative Neonatal Trial it was 1-year intact survival based on a neurological assessment. In the case of the CESAR trial it was functional independence at 6 months after treatment. An important, often unrecognised, aspect of ECMO support is that the quality of both neonatal and adult survivors is excellent and there is little long-term functional disability. Provided they are otherwise healthy before their severe illness, they go on to have a long and productive life in society.<sup>[8]</sup>

Coinciding with publication of the CESAR trial was the H1N1 influenza A pandemic, which behaved in an unusual way. Instead of causing major mortality in older patients, particularly those with pre-existing respiratory disease, it produced a small number of severely compromised young adults. Typically, these patients were between the ages of 18 and 35, and they were often obese and/or pregnant. This was first apparent in Australasia, where there was acute demand for ECMO beds over a 3-month period.<sup>[6]</sup> When the pandemic reached the Northern Hemisphere the pattern of infection was of a 'slow burn', i.e. a similar number of patients were treated, but over a longer period of time. The Northern Hemisphere had a further hit from H1N1 in the winter of 2011/12, with a similar pattern to the Australasian experience in 2010.<sup>[9]</sup> Unlike in the CESAR trial, the circuits used were almost exclusively centrifugal pumps with PMP oxygenators.

Out of the H1N1 pandemic came some case-controlled studies with prospectively controlled data.<sup>[10]</sup> As has been pointed out by the authors, these showed significant benefit from accessing ECMO.

Although case-controlled studies have their limitations, we believe that interpreted together with the CESAR trial data they provide sufficient information to recommend ECMO for some carefully selected adult patients with acute lung injury. During this period of emergency, co-ordination between experienced and other centres both in the Northern and Southern hemispheres showed the benefit of experience in case selection and patient management. The other development from the H1N1 outbreak was the much more frequent transfer between centres of patients on ECMO. The new technology makes transfer much easier and safer, and a hub-and-spoke approach can be possible, depending on the geography and healthcare system involved.

The recently published Xtravent study<sup>[11]</sup> confirmed that hypoxaemic patients treated with an ultraprotective ventilation strategy (tidal volumes 2 - 3 ml/kg) have a significantly shorter ventilation period, which suggests that early initiation of ECMO is important in those with critical acute lung injury. Another aspect that may improve results is the concept of 'awake ECMO'<sup>[12]</sup> – a good example would be a patient with status asthmaticus or acute exacerbation of chronic bronchitis. 'Awake ECMO' allows for earlier extubation and mobilisation, with markedly decreased complications.

The design and results of the small number of randomised ECMO trials have been controversial and have met with criticism. The reality is that such trials are ethically and practically difficult to design, expensive and time consuming. Given the type of patient being studied, it is also likely that the results may show confounding factors. We believe that it is unrealistic to expect any further meaningful data derived from randomised ECMO trials to guide decision making in the future. There are currently sufficient data to suggest that any new trial would have to involve an option for crossover to justify ethical approval. This is also true for the French EOLIA (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome) study currently in progress.<sup>[13]</sup> Any future data accruing from randomised trials may therefore have major built-in limitations. We believe that individual case series of adult patients with acute respiratory failure managed with ECMO, conducted in the setting of ongoing technological advances, should guide future management protocols.

In the UK, the response to the CESAR trial and the H1N1 flu pandemic has been to commission a five-centre adult ECMO service in addition to the four-centre neonatal and paediatric service. This is now operating on a regional basis, with transport of patients on ECMO as part of the contract.

From the available experience and literature, we believe that there is sufficient evidence to support the selective use of ECMO in specific clinical situations, provided that the centres offering the service have done the necessary planning, preparation and training.<sup>[14]</sup>

According to the ELSO Guidelines,<sup>[14]</sup> the indications for ECMO that are supported by evidence include:

1. Severe neonatal respiratory failure refractory to medical management
2. Support for severe respiratory failure in older children and adults with a potentially reversible cause, not responsive to optimal conventional management along the guidelines recommended (however, we have found peri-resuscitation iatrogenic drowning/fluid overload of such patients to be a depressingly frequent event). A useful severity guide for smaller children is an oxygenation index >40, and for larger patients a Murray score >3.0.
3. Support for cardiorespiratory failure after surgery for congenital heart disease

4. Bridge to heart, lung, and heart-lung transplantation<sup>[15]</sup>
5. Support for reversible right heart failure in acute pulmonary embolism, and postoperative pulmonary hypertension in acquired heart disease.

Beyond these general considerations, one should not be too prescriptive. Key to the assessment is potential reversibility. Each case should be judged on its merits, as case selection depends not only on patient factors but also on the experience and expertise of the centre offering treatment. Clearly, patients with specific contraindications such as severe neurological injury, disseminated malignant disease and severe chronic lung disease should be excluded. However, beyond that, individualised assessment needs to be made. In practice there will be uncertainties, not least because the most common indication in adults is pneumonia. In our experience, the most difficult group of patients to assess are those with treatable malignancies, such as leukaemia, when they may or may not be salvageable depending on the stage of the disease, its treatment and the ability to treat underlying infection. For example, varicella in a lymphoma patient will usually be treatable, but cytomegalovirus infection in a bone marrow transplant patient is usually not. Other challenging decisions are patients with *Pneumocystis* pneumonia or HIV/AIDS. These are often young people with single-organ failure who, should they recover, may have reasonable survival rates, provided they are compliant with their treatment. Similarly, an experienced centre might be able to manage a patient with acute trauma or sepsis, where an inexperienced one may end up with uncontrollable haemorrhage.<sup>[16]</sup>

In general, if a disease process has a specific treatment or is self-limiting, the patient should be offered support. In the new Berlin definition of acute respiratory distress syndrome (ARDS), ECMO is included in the treatment algorithm of severe ARDS.<sup>[17]</sup>

The mode of ECMO is an important consideration, and we would like to correct the assertion that veno-arterial ECMO (VA-ECMO) produces better gas exchange than VV-ECMO for respiratory failure. ECMO is not synonymous with cardiopulmonary bypass, in that the heart is normally filled (often overfilled!) and ejecting. Unless the return cannula is in the aortic arch, as with neonatal VA-ECMO, this will not be true. Typically, femoral artery cannulation results in a patient with one very pink opposite leg and abdomen up to the waist, while the head and chest are blue ('harlequin effect'). Also, with VA-ECMO the high returning arterial pressure in the aorta may cause 'cardiac stun', because the heart is ejecting against an increased afterload. We have always favoured VV-ECMO, which has the advantage that the whole arterial system, including the coronary arteries, will have similar oxygenation. Although 100% oxygen saturation may not be achieved, >85% is adequate and achievable even with no lung function. VA-ECMO is reserved for situations when there is additional right heart failure in cases of pneumonia, and conditions such as pulmonary embolism or postoperative pulmonary hypertension.

Removal of carbon dioxide can be done in two ways, either with VV-ECMO or with the arteriovenous pumpless extracorporeal lung assist (PECLA) system.<sup>[18]</sup> The predominant feature here is low blood flow allowing CO<sub>2</sub> removal. Complications with placement of this device have been quite common and usually relate to the too-low positioning of a rigid arterial cannula. Using a smaller cannula may limit the complication of limb ischaemia.<sup>[19]</sup>

The high cost of ECMO as described in the CESAR trial is always argued as a reason why it is not a viable treatment option in developing countries. Although the cost of the circuit is expensive, the largest cost of ECMO lies in staffing the service. CESAR was performed with the

previous generation circuits, and the nurse staff-to-patient ratio in the ECMO arm was two to one (ECMO specialist and critical care nurse to one patient). At the same time the conventional arm had one-to-one nurse staffing. With modern technology this is no longer necessary, and a one-to-one ratio is also possible with an ECMO patient. In addition, costs of the disposable circuits are decreasing, plus blood priming of the circuit can be avoided. The cost during the CESAR trial therefore does not reflect modern practice. Cost can be put into perspective when comparing a young patient with reversible acute lung injury on ECMO and a patient with leukaemia receiving chemotherapy, radiotherapy and a bone marrow transplant.<sup>[20]</sup>

In future, it is likely that use of the conventional methods of respiratory support such as positive-pressure ventilation may decrease, while the use of non-invasive methods of oxygenation such as extracorporeal circuits may increase. For instance, a young patient with H1N1 viral pneumonia has good lung mechanics, with bad gas exchange and oxygenation. Intubation and positive ventilation may therefore not be the ideal treatment in this patient. Compare this with the polio epidemic, where patients had bad lung mechanics and weakness, with preserved lung parenchyma. After all, 30 years ago renal replacement therapy for renal impairment had a very bad outcome, while today it is commonplace. Everything depends on further technological advances.

In conclusion: ECMO should be available for selected cases in advanced healthcare systems, and it should be performed in centres that have done the necessary planning, preparation and training. The exact method of achieving this goal depends on the particular healthcare system and the balance between public and private providers. In general, we believe that neonatal and paediatric ECMO should be available in centres doing large numbers of congenital heart operations (>300 cases per year). The organisation for adult ECMO is more problematic, owing to the low turnover of cardiac surgical cases requiring ECMO support. The concept of a specialised ECMO centre is central to a successful ECMO programme. ECMO should not be encouraged in low-volume centres (<20 cases per year), which should rather refer to high-volume centres, ideally with mortality rates under 50%, where expertise increases exponentially. Rather than a free-for-all developing, there should be a formal discussion between the public sector, private sector providers and medical aids about whether ECMO should be supported as a treatment modality, and if so where and how it would be best provided.

We should not be predicting present outcomes from ECMO on the basis of studies conducted in the distant past. It is likely that future case series of patients treated with VV-ECMO will show considerably improved outcomes compared with past studies, since there have been major improvements in gas exchange devices, centrifugal pumps and advanced double-lumen cannulas. It is in everyone's interests, particularly those of our patients, that if ECMO is to be done at all, it is done as well and as cost-effectively as possible. It would be a significant and major achievement if a coherent strategy were agreed on for the greater good.

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*S Afr J Crit Care* 2013;29(1):3-5. DOI:10.7196/SAJCC.165