

Extracorporeal Membrane Oxygenation (ECMO): a review of its status and practice

Richard K Firmin, FRCS, FRCPH (Hon)

Emeritus Cardiothoracic Surgeon, Leicester, UK.

Visiting Surgeon, Karapitya Hospital (Teaching), Galle, Sri Lanka.

Correspondence : Dr Richard K Firmin; rkfirmin@hotmail.com

ORCID ID : <https://orcid.org/0000-0002-5119-7742>

Competing interests : None declared

Key words : ECMO development, evidence for ECMO, review of ECMO

Introduction

Extracorporeal Membrane Oxygenation (ECMO) is a temporary cardio-respiratory support technique usually employed in the Intensive Care Unit (ICU) to provide cardiac, respiratory, or cardio-respiratory support in life-threatening clinical situations. It is one of several techniques that come under a wider umbrella of Extra-corporeal Life Support that include Ventricular Assist Devices (VAD) and Extra-Corporeal CO₂ Removal (ECCOR). These techniques became possible with the development of reliable blood pumps and gas exchange devices, more usually called Oxygenators (even though CO₂ clearance is as important as oxygenation).

The first clinically applied oxygenator was developed by John Gibbon in the early 1950's [1]. Thereafter, other devices were developed by other groups interested in developing cardiac surgery. Until then, the only other techniques that could be used for cardiac surgery were surface hypothermia with brief circulatory arrest or cross circulation, usually involving a child with a parent.

All the oxygenators developed in that era whether screen, disc or bubble oxygenators, had two intrinsic problems that made their use for longer than an hour or so impossible. The first was that oxygenation and CO₂ clearance were achieved by direct contact between blood and gas phases that caused haemolysis, thrombocytopaenia and leucopenia. The second was foaming of the blood. Taken together, these issues caused particulate and gaseous emboli.

Despite these issues, improved bubble oxygenators with arterial line filters were widely used for cardiac surgery until about 1990. However, long-term use (i.e. more than six hours) was not possible with these devices due to excessive blood cell damage. Pumping of blood round bubble oxygenators was usually by means of occlusive roller pumps, although the French company, Rhone-Poulenc, developed a non-occlusive pump that was also effective.

The device that allowed for long-term extracorporeal circulation was the membrane oxygenator in which the blood and gas phases were separated by a semi-permeable membrane. This was derived from the observation of Kolff [2], who was researching dialysis membranes, and noticed that venous blood that passed across certain membranes, notably silicone rubber, changed colour and became pink even when exposed in just air. This allowed Theodor Kolobow [3] and his group at the National Institute of Health, Bethesda, USA to develop a solid silicone rubber, spirally wound membrane oxygenator. This functioned well for many days and its commercial production allowed research groups to pursue the concept of prolonged extracorporeal support in the intensive care setting.

Although these solid silicone membrane oxygenators functioned effectively and could be used for both cardiac surgery and prolonged circulatory support with minimal blood damage, they were expensive, difficult to manufacture and had a high resistance to blood flow.

The next important development, initially for cardiac surgery, was the development of low resistance hollow-fibre membrane oxygenators with polypropylene membranes. Polypropylene membrane devices revolutionised cardiac surgery and soon completely replaced bubble oxygenators.

Although these membranes could and were used for prolonged support in the ICUs, they tended to fail due to plasma leakage, particularly if the patient was jaundiced. This problem was corrected by the development of polymethylpentene (PMP) hollow-fibre membrane oxygenators that are as efficient at transferring gas but rarely leak plasma. PMP oxygenators are produced by several companies with different surface coatings and are licensed for up to 30 days in some jurisdictions, but often last much longer.

The last technical advance that improved the current techniques of extracorporeal circulation was the development of impeller blood pumps to replace occlusive roller pumps. A number of these are now available from different manufacturers of which the most widely used are those manufactured by Levitronix and Macquet.

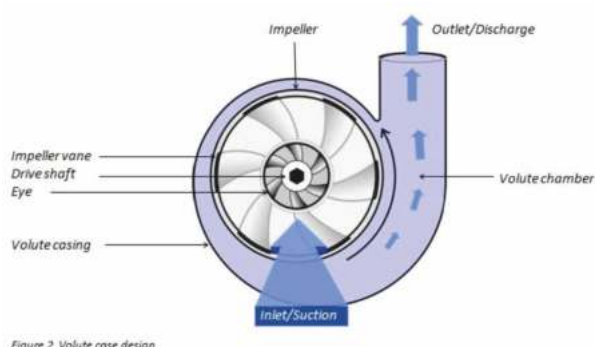


Figure 2. Volute case design

Fig.1 : Impeller pump

Other important developments were in cannula design and anticoagulation management. As was soon discovered, walking the tightrope of clotting of the circuit on the one hand and bleeding in the patient on the other was a very difficult thing to do for prolonged periods, as compared to performing cardio-pulmonary bypass for cardiac operations for short periods.

These developments took more than 50 years of research by many different groups with the support of Industry. The developments were both technical and clinical, with the clinical often being controversial as discussed below.

Prolonged support

Having developed a technology that could produce prolonged respiratory and cardio-respiratory support, the next issue was in what circumstance was it appropriate to use? The first report of clinical success was of an adult patient with post-traumatic lung injury treated at Pacific Medical Centre, San Francisco, USA by Dr Don Hill and colleagues in 1973 [4].

Shortly thereafter, the first successful case of neonatal respiratory failure treatment was reported by Dr Robert Bartlett from Orange County Children's Hospital, California [5].

Dr Bartlett subsequently moved to the University of Michigan Medical Centre and became the pre-eminent researcher and clinician in the development of ECMO with his hospital being the world's largest unit for more than 20 years.

Trials and Tribulations

Because of the dramatic nature of ECMO intervention, its resource implications and cost, there was pressure to perform clinical trials to assess its efficacy. Doing trials in which the end point is death is ethically, morally, and practically difficult and all the trials that have been done have created controversy. I will briefly describe these trials and illustrate how much thought and effort was put into them. Despite this, all were still criticised before, during or after their completion.

National Institute of Health (NIH) Adult Trial

This trial was a fully randomised trial (RCT) between ECMO, and conventional care conducted between 1975 and 1978 [6]. Some of these centres had never used ECMO before and care was not

standardised. Many of the patients had Influenza A and only veno-arterial ECMO support was used. The trial was stopped early as it became obvious that there was no benefit to ECMO support. The results of the trial are illustrated below (fig. 2).

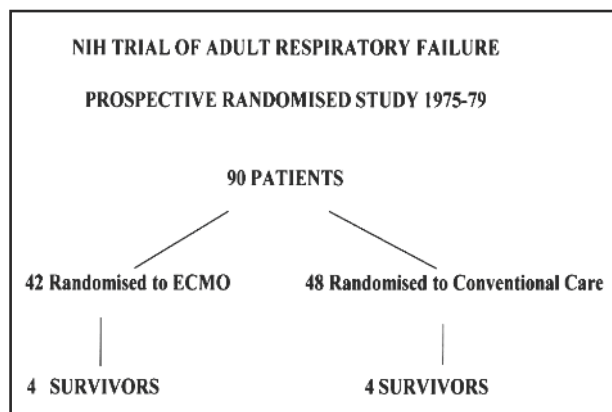


Fig. 2 : Summary of NIH trial

One of the main issues with this trial related to the lack of experience with ECMO before the trial started. Unlike in a drug trial, experience is necessary with what is essentially a surgical technique. One needs to be able to perform such a procedure reproducibly before it can be trialled. Experience in neonatal ECMO has suggested that it takes between 10 and 20 cases for this level of expertise to be achieved. The other issues were 1) the exclusive use of veno-arterial ECMO rather than veno-venous that is now known to be more appropriate for adult respiratory failure and 2) that there was no concept of lung rest. Patients on ECMO received high pressure, high volume and high inspired oxygen ventilation.

The negative outcome of this trial effectively stopped the use of ECMO worldwide for adult patients for 25 years.

University of Michigan Neonatal Trial

In parallel with work on adult respiratory failure, neonatal respiratory failure was also being investigated by Dr Bartlett, treating babies with a very high predicted mortality (90%). In early reports, he showed increasing success with neonatal patients as compared to historical controls [7]. A registry was established for neonatal ECMO patients

under the aegis of the Extracorporeal Life Support Organisation (ELSO), which confirmed improving results from all groups using this technique[8].

In 1984, Dr Bartlett's group at the University of Michigan Medical Centre organised a single-centre randomised controlled trial (RCT) of neonatal ECMO using a modified 'Play the Winner' design under which, after a random start, the next patient was allocated to whichever treatment had been successful for the previous patient. After 12 patients had been randomised, the trial was stopped. Only one patient had been allocated to conventional treatment and had died. Eleven patients had been allocated to ECMO, all of whom had survived (fig. 3) [9].

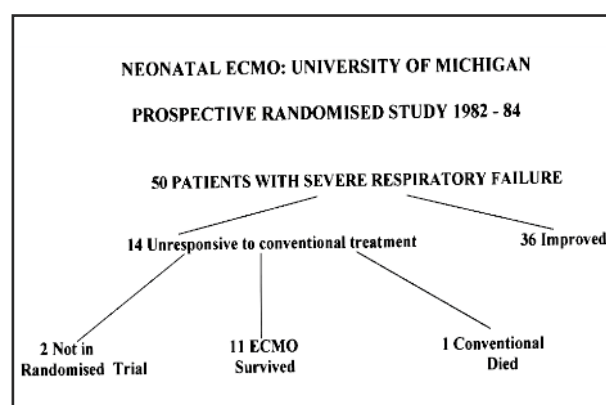


Fig. 3 : Summary of University of Michigan Neonatal Trial

There was widespread criticism of the trial design by both statisticians and clinicians [9]. Many neonatologists did not believe that the trial advanced the evidence base for the technique.

Boston Neonatal Trial

To address the criticisms of the University of Michigan trial, O'Rourke and colleagues in Boston designed a further modified RCT [10]. Randomisation continued until there were four deaths in either treatment arm. The more successful treatment (ECMO) was then given to a further 20 patients (fig. 4).

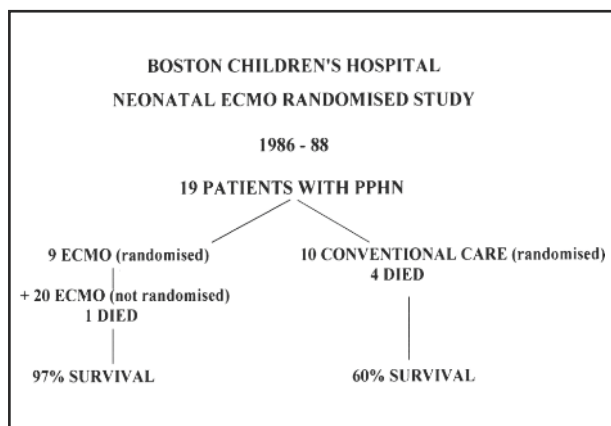


Fig. 4 : Summary of *Boston Neonatal Trial*

Although there was further criticism of this study [11], appearing even in the lay press [12], most clinicians were, now more convinced. Certainly, with the ELSO Registry data and these two trials, it was now considered by many to be ethically impossible to mount a fully randomised study, at least in the USA.

UK Collaborative Trial (Neonatal)

Although neonatologists in the USA had accepted ECMO as a treatment for neonatal respiratory failure, their colleagues in Europe, Scandinavia and Australasia were more sceptical. Thus, after an ECMO service was started in Leicester, UK in 1989 using charitable funds, government funding was made available to conduct a randomised controlled trial. The end points for this trial were significantly different from other trials. As well as hospital mortality being assessed, the primary end point was 'intact survival' at one year of age, with 'intact' being a neurological and development assessment by a paediatric neurologist. Also, ECMO was being provided in four ECMO Centres, whereas conventional care was being provided in separate multiple Regional Neonatal Units. All the patients treated with ECMO required inter-hospital transfer whereas a majority of conventionally treated patients did not. This reflected the realities as to how the treatment would be delivered in practice and was, therefore, a pragmatic trial design. The UK Collaborative Trial ran from 1993-5, being stopped early by the data monitoring committee because of

obvious benefit. The first report from the trial gave the hospital mortality for all 185 patients with the one-year intact survival data of 67 (fig. 5) [13].

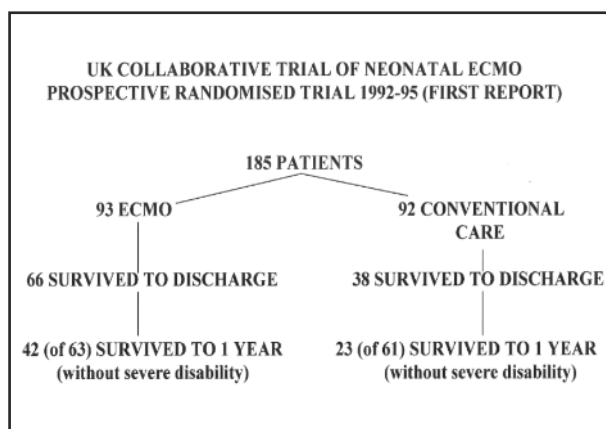


Fig 5 : Summary of UK Collaborative Trial (Neonatal)

A second report of the data on all 185 patients was subsequently published (fig. 6) [14].

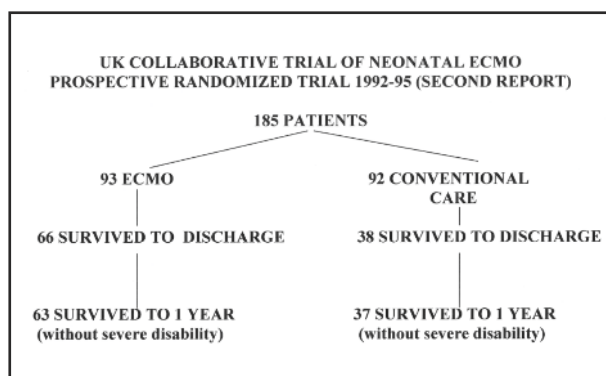


Fig. 6 : Summary of the second report of UK Collaborative Trial (Neonatal)

Both reports confirmed the efficacy of ECMO with respect to hospital mortality and 'intact survival' at one year.

A third paper from this trial has also been published on the cost-effectiveness of ECMO compared to conventional care to the trial endpoint of one year [15]. These economic data were an integral part of the trial.

Finally, a late follow-up fourth paper was produced in which a pre-school assessment was made of their neurological, behavioural, and respiratory health

[16]. In essence, the neurological morbidity was similar in the two groups of survivors, suggesting that any damage was more likely due to the initial birth asphyxia and its sequelae rather than the mode of treatment. The respiratory morbidity in terms of hospital admission and use of bronchodilators was greater in the conventional group, suggesting that longer periods of high-pressure ventilation used in this group were deleterious.

ECCOR Study

Although the case for the effectiveness of neonatal ECMO was getting stronger by the year, adult ECMO was all but abandoned. The exceptions were Gattinoni and his colleagues in Milan, Italy, who had put the hypotheses of Kolobow concerning lung rest and extracorporeal CO₂ removal (ECCOR) into clinical practice. Gattinoni had reported much higher than expected survivals for patients with severe ARDS, although the study was not randomised [20]. Morris and colleagues further tested this technique in an RCT which compared ECCOR to a computer driven algorithm adjustment of ventilator settings. Although there was no significant difference between the randomised groups, both groups had a much better survival than in the earlier NIH trial (fig. 7)[17].

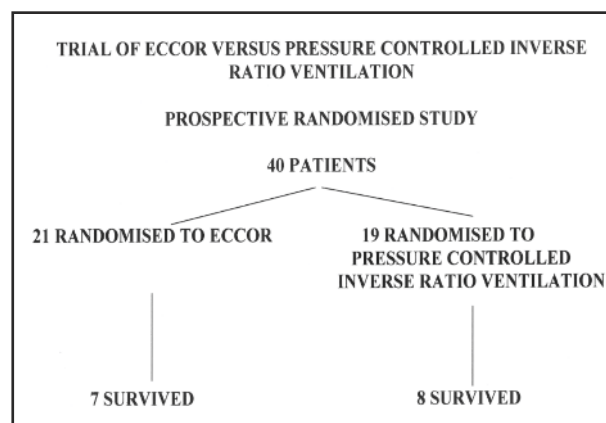


Fig. 7 : Summary of *ECCOR Study*

CESAR Trial (Adult)

The CESAR Trial was an UK based RCT based on similar precepts to the UK Collaborative Trial of Neonatal ECMO [18]. It was of pragmatic design with a primary end point of 'intact survival' at six months as well as just hospital survival. The definition of 'intact' was a functional one of independent living, reflecting both neurological and respiratory function. ECMO was provided in one centre (Leicester) and included transport as part of the equation and was based on intention to treat so not all the patients sent for ECMO received it. Conventional care was provided in designated large ICUs. Most patients did need transport to such units. The results are shown in the diagram below (fig.8).

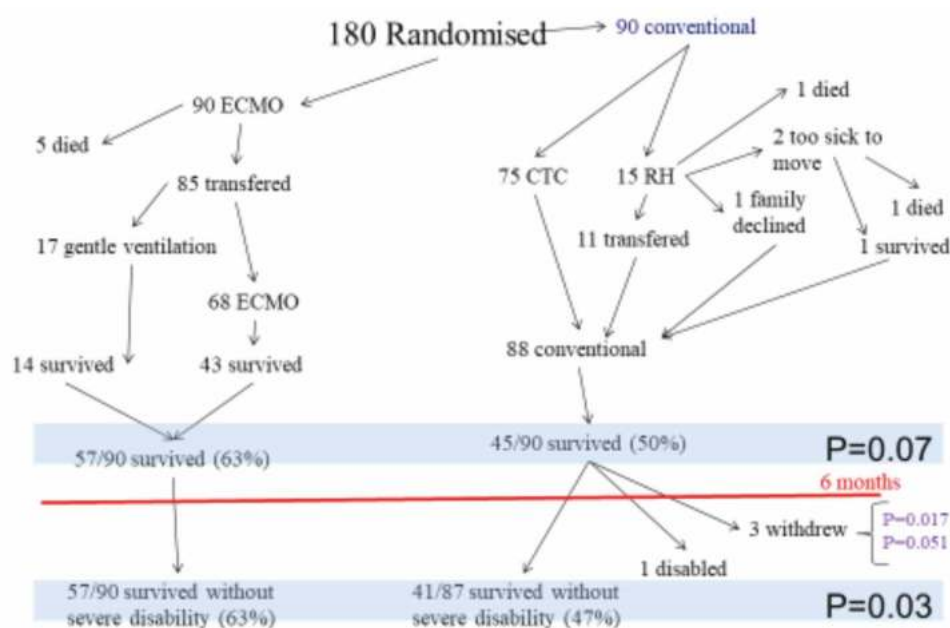


Fig. 8 : Summary of *CESAR Trial (Adult)*

Again, there was controversy related to such issues as transport and the fact that a significant group of ECMO patients did not receive ECMO. It did, however, make an impact on the subject such that when H1N1 influenza became a serious issue, the capacity for adult ECMO provision was significantly ramped up in the UK and elsewhere. The UK response to this emergency included increasing the availability of ECMO nationally and auditing all the

cases that were treated in these centres and conventional treatment centres prospectively. When the data were analysed the benefit for ECMO provision in the severest cases of respiratory failure was clearly seen. The analyses were done in two ways, both of which provided clear evidence of benefit from being able to access ECMO (figs 9 and 10) [19].

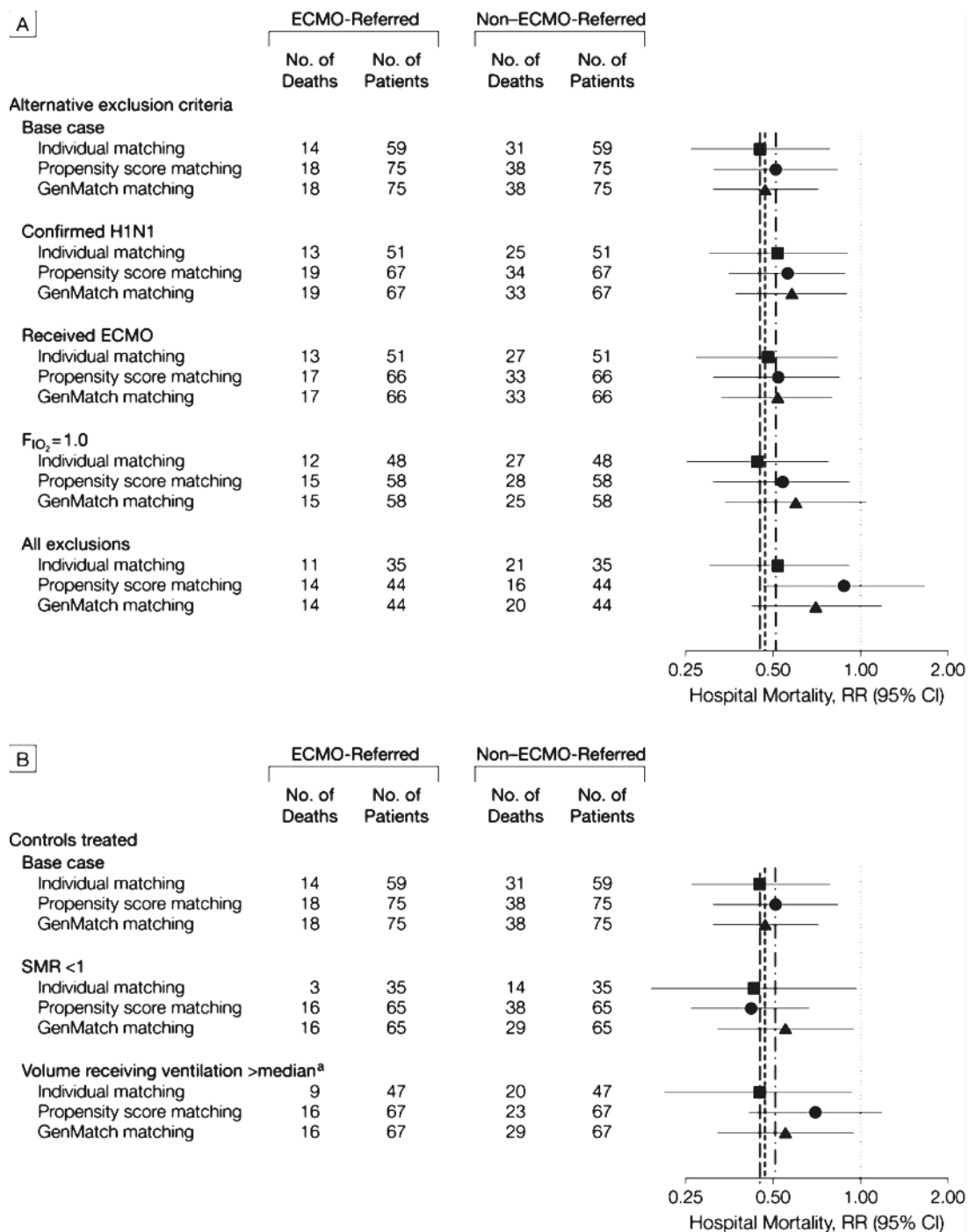


Fig 9 : Sensitivity Analyses for ECMO-Referred Patients vs Matched Non-ECMO-Referred Patients

Table 2. Deaths Analyzed by Matching Methods

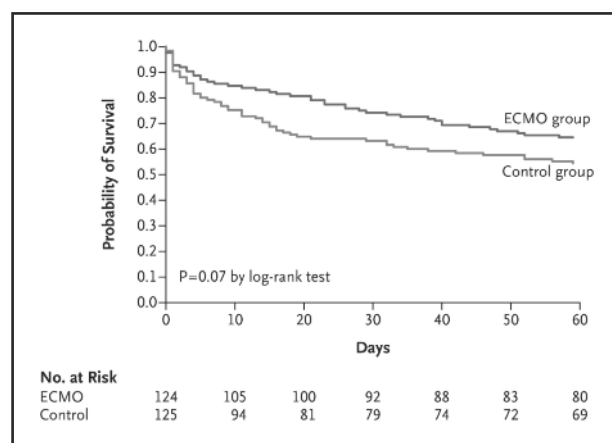
	No. of Deaths/ Total No. of Patients (%)		RR (95% CI)	P Value
	ECMO-Referred	Non-ECMO-Referred		
Matching method				
Propensity score	18/75 (24.0)	35/75 (46.7)	0.51 (0.31-0.84)	.008
GenMatch	18/75 (24.0)	38/75 (50.7)	0.47 (0.31-0.72)	.001
Individual	14/59 (23.7)	31/59 (52.5)	0.45 (0.26-0.79)	.006

Abbreviations: ECMO, extracorporeal membrane oxygenation; RR, relative risk.

Fig 10 : Deaths Analyzed by Matching Methods

EOLIA (ECMO to rescue Lung Injury in severe ARDS) Trial (Adult)

Despite all the above, a European based adult RCT was commissioned, and its results published (fig. 11) [20].

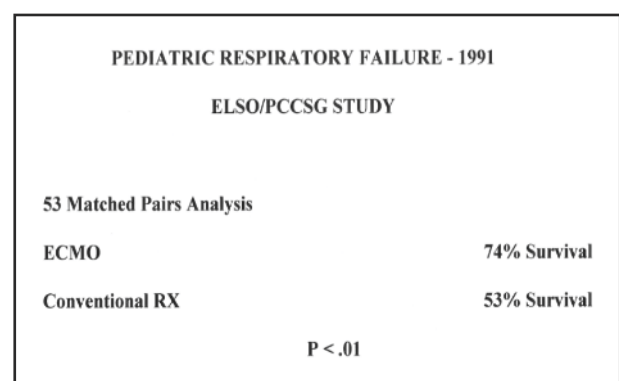
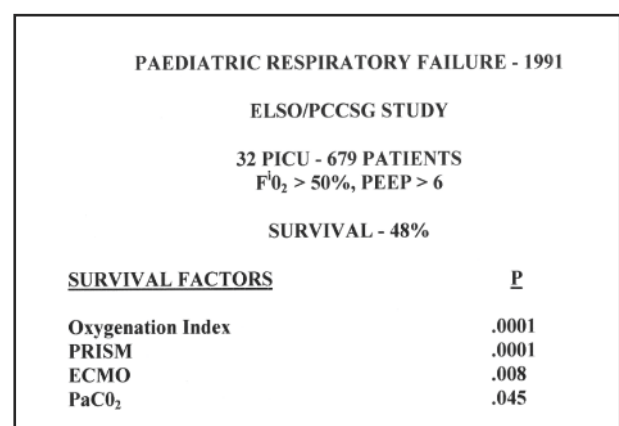
**Fig 11 :** *EOLIA Trial (Adult)*

These data added little to what was already known as the design allowed cross-over to ECMO if the patient deteriorated. When cross-over is allowed in such a trial it is being acknowledged that there is no longer equipoise in the assessment being made and the trial is being performed too late.

Audit on Children on ECMO

There has been no RCT performed on children outside the neonatal period. The only available data are from registry audits using matched pair data (fig.

16) and data derived from assessing the performance of Paediatric Intensive Care Centres that could access ECMO as opposed to those who could not (fig.17) [21].

**Fig. 12 :** Paediatric Respiratory Failure study. Case matching in ELSO and Paediatric Critical Care Study Group (PCCSG) joint database analyses.**Fig. 13 :** Factors determining survival in PCCSG database.

Both assessments indicated benefit from being able to access ECMO support.

Considerable efforts were made to do an RCT in the USA, but it proved impossible. However, it is reasonable to assume that ECMO is likely to benefit children with severe respiratory failure as clear benefits have been shown for those both younger and older.

Despite ECMO being used widely in neonates and children post-cardiac surgery and it being assumed to be a standard of care in paediatric cardiac centres, there is only limited audit information and no trial data to support this enthusiasm.

Indications

It should be clearly understood that ECMO is a support technique and not a treatment per se. It can be reasonably applied when there is a potentially reversible illness associated with severe cardio-respiratory compromise. If used inappropriately in irreversible pathology, ECMO will merely prolong death. Due to the invasiveness, cost, and resource implications, it should only be used in severe disease when conventional care has failed or is failing.

In practice there are two types of patients. Those that cannot be stabilised and continue to deteriorate rapidly within a few hours despite escalating treatment such that death is inevitable. There are others who can be stabilised on conventional treatment but at a very high level of inotropic and/or ventilatory support. In these latter patients a value judgement must be made as to whether it would be better to institute ECMO to reduce the level of support, (particularly ventilatory support), and obviate the risk of progressive ventilator induced lung injury (VILI). A long period of high-pressure ventilation is a relative contraindication to ECMO as both VILI and increasing risk of nosocomial infection lead to worse outcomes and this needs to be factored into any patient assessment.

In neonatal practice, the Oxygenation Index [22] gives a reasonable guide as to when ECMO should

be considered. An OI > 40 indicates severe compromise and is an important guide. In adult practice the Murray Score [23] also gives guidance. A Murray Score > 3 indicates severe respiratory failure. However, experience with H1N1 influenza when ECMO availability was limited, showed that most patients with Murray Scores between 3 and 3.5 can be managed conventionally. Above a Murray score of 3.5, ECMO is certainly indicated.

In cardiac indications, unresponsive low-output syndrome with acidosis is the usual indication. This may be in the operating theatre when bypass cannot be discontinued or in the ICU when increasing inotropic support (and/or balloon pump) proves ineffective.

The main contraindications to ECMO relate to active bleeding and futility in a brain damaged or otherwise irreversibly compromised patient (e.g. disseminated cancer). Surgery is only a relative contraindication, as many patients undergoing cardiac or transplant surgery have been successfully managed. This is because of a greater understanding of how to manage anticoagulation and bleeding in such patients.

Equipment

The standard modern ECMO circuit comprises of a polymethylpentene (PMP) hollow fibre oxygenator with an impeller blood pump and a heater cooler.

Some centres still use a roller pump with a negative pressure controller, such as a bladder box or negative pressure inflow control system, for neonatal patients (fig.14).

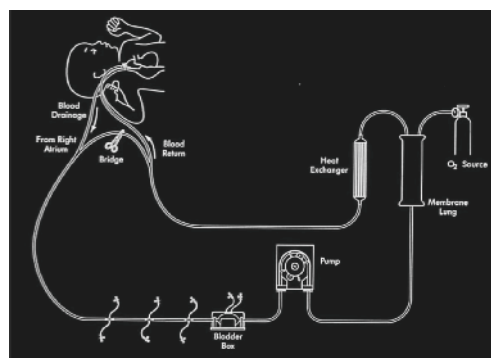


Fig. 18 : ECMO circuit with roller pump

Modes of ECMO and cannulation

Veno-arterial (VA) ECMO will support both the lungs and circulation. Veno-venous (VV) ECMO supports only the lungs. VV ECMO is the preferred method for respiratory support as it avoids complications related to distal organ perfusion after cannulation of a major artery. In children below two years as their femoral vessels are too small, VA ECMO requires cannulation of the right carotid artery; in older children and adults, cannulation is usually of a femoral artery. In or after cardiac and transplant surgery, cannulation may be through the incision and trans-thoracic.

Veno-venous ECMO can be achieved with multiple single lumen cannulae draining from the femoral vein(s) and returning to the right internal jugular vein, or a double-lumen cannula usually inserted into the right atrium via the right internal jugular vein. Cannulation for VV ECMO is usually percutaneous under ultrasound and/or fluoroscopic guidance. VA ECMO may be done surgically but is increasingly being done percutaneously under ultrasound guidance. Whereas right common carotid artery cannulation in an infant is well tolerated, femoral artery cannulation in older children and adults often causes distal limb ischaemia and a separate distal perfusion cannula is typically necessary.

Anticoagulation

Prolonged support with an extra-corporeal circuit requires anticoagulation to prevent it from clotting. The main anticoagulant historically has been heparin, monitored by the Activated Clotting Time (ACT) which is a near patient whole blood testing system. More recently, heparinoids such as Argatroban and Lepirudin monitored by Factor Anti-Xa assay have been used. This requires access to an advanced haematology laboratory or advanced near patient testing.

For most units, heparin monitored by ACT is the starting point, with the ACT's being run in the range 160-220 seconds depending on the type of cartridge

and machine used rather than the 400 + seconds used when performing cardiopulmonary bypass.

In addition to these regular monitoring tests for heparin/heparinoids, full anticoagulation profiles also need to be done, to monitor other clotting factors such as prothrombin and fibrinogen. It should be remembered that adequate fibrinogen levels are necessary for ACT testing to operate. Additional information from TEG (thromboelastography) or ROTEM (Rotational thromboelastometry) analysers is also useful, particularly when there is bleeding.

Each unit must work out what their anticoagulation protocol for ECMO is going to be, in line with the available haematological expertise. A detailed review of this issue can be found in an Extra-corporeal Life Support Organisation (ELSO) publication [24].

Management of ECMO patients

The successful management of ECMO patients is five-fold:

- a) The circuit needs to be adequately anticoagulated and supervised. This requires planning, protocols, and training of all the staff looking after the patient, whether medical, nursing, or technical. It is not something that can successfully be done as a one off or occasional pastime.
- b) The management of the patient should acknowledge that the patient is heparinised such that needle sticks and surgical procedures should be minimised and only done when the anticoagulation is being tightly controlled.
- c) Low frequency, low pressure, low volume, low oxygen ventilation should be instituted as far as possible-i.e. the 'lung rest' strategy. During VV ECMO, some ventilation may be necessary to maintain adequate oxygenation. During VA ECMO with femoral cannulation some ventilation may also be necessary to avoid differential oxygenation of the upper and lower

body ('Harlequin Syndrome'). Carbon dioxide clearance should never be an issue as the sweep gas flow through the oxygenator can easily control it. However, hollow-fibre oxygenators are so efficient in this respect that great care may be necessary reducing the PaCO₂ slowly to avoid rapid shifts in blood and tissue pH particularly if it is very high as in an asthmatic patient.

- d) All patients with lung injury should have their fluid balance optimised. This may be achieved with fluid restriction and diuretics or with haemo-filtration and dialysis as appropriate. Excessive fluid goes to areas of inflammation and dependency and reducing it nearly always improves lung function.
- e) Finally, and most importantly, the underlying condition should be actively and intensively treated. This may mean antibiotics, antivirals, steroids or other drugs together with mechanical adjuncts like prone positioning, bronchoscopy and tracheostomy.

Results

As has been indicated before, ECMO is a support technique, not a therapy and the results of its use depend on the condition for which it is used. The most comprehensive information on the results and complications of ECMO use is from the Extracorporeal Life Support Organisation's International Registry [25] which is the development of the earlier registry for neonatal respiratory failure. There is now information of more than 176,000 cases for a wide variety of conditions at different ages and their complications. It represents the majority of ECMO cases performed worldwide.

The data is very comprehensive with respect to hospital mortality, patient related and circuit related complications. The feared complications being bleeding in the patient and clotting in the circuit. There is also graphical data illustrating the change in the use of ECMO over time.

The variation in outcome according to the condition treated is best seen in neonatal respiratory failure patients. For meconium aspiration syndrome, the worldwide survival is 91% whereas that for diaphragmatic hernia is 58%. The other neonatal indications have mortalities between these figures. Despite these usually good outcomes, the overall use of ECMO in neonates is declining as recorded in the ELSO Registry, maybe reflecting more options in conventional treatment being available.

There has been a significant increase in the use of ECMO for cardiac surgery in all age groups. Similarly, there has been a significant increase in ECMO use in adult respiratory failure since the publication of the CESAR Study and the H1N1 pandemic in 2009. The mortality in this age group has varied from 56% to 81% according to the indication with the best results being in aspiration pneumonia. The recent experience with Covid 19 has given results similar to other adult pneumonia cases with the best results in younger patients with short periods of pre-ECMO ventilation and without comorbidities [26, 27].

Another indication that has significantly increased ECMO use has been in resuscitation; so-called extracorporeal resuscitation (ECPR). This has been mainly in hospital emergency departments and post cardiac surgery. In some countries, ECPR is being applied for outside-hospital cardiac arrests as well.

Future developments

ECMO is likely to be used more widely in the future as more sophisticated auto-regulated pumping systems are developed that require less anticoagulation and supervision. Implantable artificial lungs are also under development that are based on the oxygenator technology that we currently use and will likely complement organ transplantation in the future.

References

1. Miller BJ, Gibbon JH, Greco VF, Cohn CH. The production and repair of interatrial defects under direct vision with the assurance of an extra-corporeal pump-oxygenator circuit. *J Thorac Surg.* 1953;4:29-33.
2. Kolff WJ, Berk TTJ. Artificial kidney: A dialyzer with great area. *Acta Med Scand.* 1944; 117:121. <https://doi.org/10.1111/j.0954-6820.1944.tb03951.x>
3. Kolobow T, Bowman RL: Construction and evaluation of an alveolar membrane artificial heart lung. *ASAIO Trans* 1963;9:238.
4. Hill JD, O'Brien TG, Murray JJ, et al: Extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome): Use of the Bramson Membrane Lung. *N Engl J Med* 1972;286:629-34. <https://doi.org/10.1056/NEJM197203232861204>
5. Bartlett RH, Gazzaniga AB, et al: Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. *ASAIO Trans* 1976;22:80-8.
6. Zapol WM, Snider MT, Hill JD, et al: Extracorporeal membrane oxygenation in severe respiratory failure. *JAMA* 1979;242:2193-6. <https://doi.org/10.1001/jama.1979.03300200023016>
7. Bartlett RH, Gazzaniga AB, Toomasian JM, et al: Extracorporeal membrane oxygenation (ECMO) in neonatal respiratory failure: 100 cases. *Ann Surg* 1986;204:236-45. <https://doi.org/10.1097/0000658-198609000-00003>
8. Toomasian JH, Snedecor SM, Cornell RG, Cilley RE, Bartlett RH. National experience with extracorporeal membrane oxygenation for newborn respiratory failure: data from 715 cases. *Trans Am Soc Artif Intern Organs* 1999;988;34:140-7.
9. Bartlett RH, Roloff DW, Cornell RG, Andrews AF, Dillon PW, Zwischenberger JB: Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective Randomized Study. *Pediatrics* 1985;4:479-87.
10. O'Rourke PP, Crone R, Vacanti J, et al: Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the new born. A prospective randomized study. *Pediatrics* 1989;84:957-63. <https://doi.org/10.1542/peds.84.6.957>
11. Chalmers TC. A belated randomised control trial. *Pediatrics* 1990;85:366-8. <https://doi.org/10.1542/peds.85.3.366>
12. Boston Globe; Issue of 8.7.89.
13. UK Collaborative ECMO Trial Group, UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet* 1996;348:75-82. [https://doi.org/10.1016/S0140-6736\(96\)04100-1](https://doi.org/10.1016/S0140-6736(96)04100-1)
14. UK Collaborative ECMO Group. The Collaborative UK ECMO Trial: Follow-up to 1 year of age. *Paediatrics* 1998;101(4):e 1-10. <https://doi.org/10.1542/peds.101.4.e1>
15. Roberts TE and the Extracorporeal Membrane Oxygenation Economics Working Group. Economic evaluation and randomised controlled trial of extracorporeal membrane oxygenation: UK collaborative trial. *BMJ* 1998;317:911-6. <https://doi.org/10.1136/bmj.317.7163.911>
16. Bennett CC, Johnson A, Field DJ, Elbourne D. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation: follow-up to age 4 years. *Lancet* 2001;357:1094-6. [https://doi.org/10.1016/S0140-6736\(00\)04310-5](https://doi.org/10.1016/S0140-6736(00)04310-5)
17. Morris AH, Wallace CJ, Clemmer TP, et al: Randomised clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994;149:295-305. <https://doi.org/10.1164/ajrccm.149.2.8306022>
18. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe respiratory failure (CESAR): a multicentre randomised trial. Peek GJ, Mugford M, Tiruvoipati R, Wilson, A, Allen E, Thalanany MM et al. *Lancet* 2009;374;1351-1363. [https://doi.org/10.1016/S0140-6736\(09\)61069-2](https://doi.org/10.1016/S0140-6736(09)61069-2)
19. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, Sadique MZ, Sekhon JS, McAuley DF, Firmin RK, et al. Referral to an extracorporeal membrane oxygenation and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011;306:1659-1668. <https://doi.org/10.1001/jama.2011.1471>
20. Coombes A, Hajage D, Capellier G, Demoule A, Lavoue S, Guervilly C et al. Extracorporeal membrane oxygenation for acute respiratory distress syndrome. *N Engl J Med.* 2018;378:1965-1975. <https://doi.org/10.1056/NEJMoal800385>
21. Green TP, Timmons OD, Fackler JC et al: The impact of extracorporeal membrane oxygenation on survival in pediatric patients with acute respiratory failure. *Pediatric Critical Care Study. Crit Care Med* 1996;24:323-9. <https://doi.org/10.1097/00003246-199602000-00023>

22. Durand M, Snyder JR, Gangitano E, Wu PY. Oxygenation index in patients with meconium aspiration: conventional and extracorporeal membrane oxygenation. *Crit Care Med* 1990;18:373-7.
<https://doi.org/10.1097/00003246-199004000-00005>
23. Murray JF, Matthay MA, Luce JM et al. An expanded definition of adult respiratory distress syndrome. *Am Rev Respir Dis* 1988;138:720-3.
<https://doi.org/10.1164/ajrccm/138.3.720>
24. McMichael ABV, Ryerson LM, Ratano D, Fan E, Faraoni D, Annich GM. 2021 ELSO Adult and Pediatric Anticoagulation Guidelines. *ASAIO J* 2021;68:303-310
<https://doi.org/10.1097/MAT.0000000000001652>
25. Extracorporeal Life Support Organisation ECLS International Summary, October 2022.
26. Bertini P, Guarracino F, Falcone M, Nardelli P, Landoni G, Nocchi M, Paternoster G, ECMO in COVID-19 Patients: A Systematic Review and Meta-analysis. *J Cardiothorac Vasc Anesth*. 2022;36:2700-2706.
<https://doi.org/10.1053/j.jvca.2021.11.006>
27. Makhoul M, Keizman E, Carmi U, Galante O, Ilgiyaev E, Matam M, Slomka A, Sviri S, Eden A, Soroksky A, Fink D, Sternik L, Bolotin G, Lorusso R, Kassif Y. Outcomes of Extracorporeal Membrane Oxygenation (ECMO) for COVID-19 Patients: A Multi-Institutional Analysis. *Vaccines*. 2023;11:108.
<https://doi.org/10.3390/vaccines11010108>