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Extracorporeal life support

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Extracorporeal life support (ECLS) is a variation of cardiopulmonary bypass. Whereas cardiopulmonary bypass facilitates open heart surgery for a number of hours, extracorporeal life support maintains tissue oxygenation for days to weeks in patients with life threatening respiratory or cardiac failure (or both).

As technology advances, indications increase, and the numbers of specialist centres rise, more doctors are likely to find themselves assessing patients for early referral, discussing this support option with relatives, directly or indirectly managing patients on extracorporeal life support, and providing follow-up outpatient and community based care. During the recent H1N1 influenza A pandemic, one third of patients admitted to the intensive care unit with severe respiratory failure required extracorporeal life support.[1]

Evidence from case series, cohort studies, registry database analyses, and randomised controlled trials form the basis of this overview.

Table 1 | Commonly used terms

Abbreviation	Definition	Details
ECLS	Extracorporeal life support	Encompasses all extracorporeal technologies and life support components including oxygenation, carbon dioxide removal, and haemodynamic support; renal and liver support may also be incorporated
ECMO	Extracorporeal membrane oxygenation	Older traditional term for extracorporeal life support that omits reference to inherent additional life supports such as haemodynamic support and carbon dioxide removal
VV ECLS	Venous-venous extracorporeal life support	Deoxygenated blood is drained from one or more major vein and oxygenated blood returned to the right atrium; supports respiratory function only and requires native heart function to deliver oxygenated blood to the tissues
VA ECLS	Venous-arterial extracorporeal life support	Deoxygenated blood is drained from one or more major vein and oxygenated blood pumped back into a major artery, thus providing tissue perfusion in the absence of adequate native heart function
ECPR	Extracorporeal cardiopulmonary resuscitation	Extracorporeal life support instituted during, and as an adjunct to, conventional cardiopulmonary resuscitation
ECCO2R	Extracorporeal membrane carbon dioxide removal	Selective carbon dioxide removal

SUMMARY POINTS

- Extracorporeal life support is a type of cardiopulmonary bypass that supports the lungs, heart, or both for days to weeks in patients in intensive care with reversible life threatening respiratory or cardiac disease
- Venous-venous cannulation is used for respiratory failure and venous-arterial cannulation for cardiac failure (with or without respiratory failure)
- Bleeding and thrombosis are the most common serious complications
- Extracorporeal life support is used in children and adults; neonates with respiratory failure have the highest survival rates
- Timing of extracorporeal life support is important—the specialist centre should be consulted early in the course of illness

What happens during extracorporeal life support?

The circuit consists of tubing taking deoxygenated blood from the patient, a pump, an artificial lung, a heat exchanger, and tubing returning oxygenated blood to the patient (fig 1). Venous-venous cannulation is used for isolated respiratory failure (tissue hypoxia secondary to hypoxaemia), whereas venous-arterial cannulation is used for cardiac failure (tissue hypoxia secondary to hypoperfusion) with or without respiratory failure (table 1).

Venous-venous

A double lumen cannula is commonly placed in a major vein. Deoxygenated blood flows from the venae cavae and oxygenated blood is returned to the right atrium (fig 1). Alternatively, separate inflow and outflow cannulas may be used (fig 2A).

Blood is removed distal to the right atrium and returned directly into the right atrium in an attempt to reduce mixing of deoxygenated with oxygenated blood, and to reduce recirculation of oxygenated blood within the circuit. It is impossible to prevent all mixing and recirculation, and so, in the absence of pulmonary gas exchange, arterial oxyhaemoglobin saturation as low as 80% is common. Adequate oxygen delivery to the tissue, therefore, requires a sufficiently high cardiac output and a haematocrit above 40%.[2]

Venous-arterial

Cannulas are placed in a major artery and one or more major veins. Venous blood is oxygenated and pumped back directly into the arterial circulation, bypassing both the heart and lungs.

Femoral arterial cannulation is common in adults (fig 2B), whereas the carotid artery is commonly cannulated in infants (fig 2C). In femoral artery cannulation a distal down flow cannula may be needed to prevent leg ischaemia, whereas in carotid cannulation, collateral circulation must be relied on for adequate brain perfusion.

Existing transthoracic cardiopulmonary bypass cannulas may be used where extracorporeal life support is needed immediately after open heart surgery (fig 2D).

In the presence of native heart function, oxygenated blood may not reach the proximal aorta, and this results in cardiac and upper body hypoxaemia (fig 2B). An increase in blood flow rate, a change to venous-venous extracorporeal life support, or placement of an extravenous return cannula may be needed.

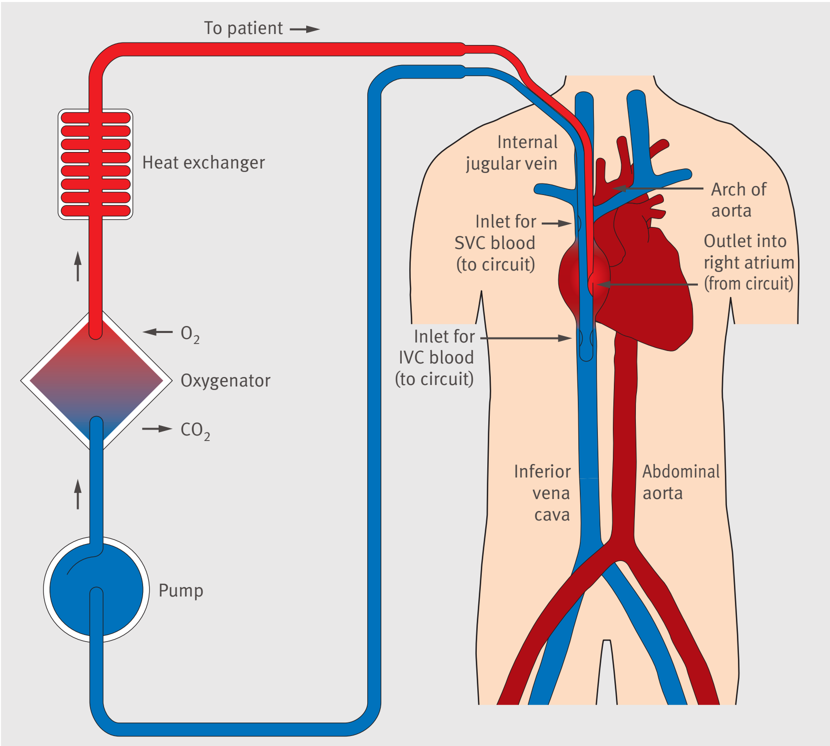

Fig 1 | Double lumen cannula version of venous-venous extracorporeal life support for respiratory failure: deoxygenated blood from both the superior and inferior venae cavae passes into one lumen of the double lumen cannula. Blood flows in tubing to a pump and on to an oxygenator and heat exchange unit, before being returned to the right atrium through the second lumen with an oxyhaemoglobin concentration approaching 100%. Here, oxygenated blood mixes with deoxygenated blood that has bypassed the double lumen cannula. This mixture of oxygenated and deoxygenated blood (oxyhaemoglobin saturation of around 80%) is pumped by the heart through the non-functioning lungs into the aorta and on to the organs and tissues of the body. Blue: intravascular deoxygenated blood; red: intravascular oxygenated blood; dark red: intravascular and intracardiac mixed oxygenated and deoxygenated blood; IVC: inferior vena cava; SVC: superior vena cava

Anticoagulation
Because of blood-surface interaction, an infusion of unfractionated heparin is necessary to prevent thrombosis within the circuit and embolism to the patient.

Ventilation
Positive end expiratory pressure is applied to the lungs and the ventilator is set to deliver low tidal volumes, low inspiratory pressures, and a low inspired oxygen fraction. These so called rest settings help to prevent ventilator induced lung injury, oxygen toxicity, and ventilator associated haemodynamic compromise.[3] Prevention of further lung injury may be the major advantage of extracorporeal life support.

Which patients benefit?
Extracorporeal life support is a support modality rather than a treatment in itself. Its use is restricted to highly specialised centres. It is invasive, complex, resource intensive, and can be associated with serious complications. Extracorporeal life support is, therefore, mostly reserved for patients with a high risk of death who have failed conventional management and where the underlying respiratory or cardiac disease is reversible. It has also been used as a bridge to transplant and placement of a ventricular assist device, to aid weaning from cardiopulmonary bypass, and as an adjunct to cardiopulmonary resuscitation.

The greatest number of cases and highest survival rates have been reported in neonates with respiratory failure (table 2). Most of the evidence supporting extracorporeal life support for other age groups and indications consists of case reports, case series, and analyses of the Extracorporeal Life Support Organization database, although some randomised controlled trials have been reported. Randomised controlled trials are difficult to conduct given the relatively low numbers of patients requiring extracorporeal life support across many centres, the heterogeneity of underlying pathologies, and the speed of technological advances.

Children
The first cases of successful extracorporeal life support management of "moribund infants" were reported in 1974.[4] Thereafter, case series and cohort studies reported improved outcomes, when compared with standard care, in neonates supported with extracorporeal life support for respiratory and cardiac failure. Analysis of cases registered with the Extracorporeal Life Support Organization showed similar improved outcomes.[5-8]

Four randomised trials met inclusion criteria for a recent Cochrane Collaboration review of extracorporeal life support for severe respiratory failure in newborn infants.[9-13] Risk of mortality was typically reduced by 44% in infants given extracorporeal life support. The authors concluded that a policy of using extracorporeal life support resulted in "significantly improved survival without increased risk of severe disability."

Extracorporeal life support undertaken for cardiac failure constitutes less than a quarter of reported cases in children. No prospective randomised controlled trials have assessed effectiveness in this population. However, case series and registry analyses suggest that extracorporeal life support, where available, benefits children with severe life threatening cardiac failure.

Adults
Extracorporeal life support was first used successfully in an adult patient in 1972.[14] In 1979, a randomised prospective multicentre trial of conventional ventilation versus the addition of venous-arterial extracorporeal life support in 90

Table 2 | Survival after extracorporeal life support (ECLS)[25]

Group	Number of ECLS episodes	Survival to discharge or transfer (%)
Neonatal*		
Respiratory	24 017	75
Cardiac	4103	39
ECPR	586	38
Paediatric*		
Respiratory	4635	56
Cardiac	5026	47
ECPR	1128	39
Adult*		
Respiratory	2121	53
Cardiac	1238	34
ECPR	476	29

Neonatal: <1 month; paediatric: 1 month to 18 years; adult: >18 years.
ECPR: ECLS as adjunct to cardiopulmonary resuscitation.

Table 3 | Most common underlying diagnoses needing extracorporeal life support[25]

Age group	Diagnosis
Respiratory system	
Neonates	Meconium aspiration syndrome
	Congenital diaphragmatic hernia
	Sepsis
	Persistent pulmonary hypertension of the newborn
	Respiratory distress syndrome
Children and adults	Viral pneumonia
	Bacterial pneumonia
	Aspiration
	Adult respiratory distress syndrome (ARDS)
	Acute respiratory failure (non-ARDS)
Cardiac system	
Neonates, children, and adults	Congenital defect
	Cardiac arrest
	Cardiomyopathy
	Myocarditis

adults with severe acute respiratory failure reported high mortality (about 90%) in both groups. This is probably a reflection of the deleterious ventilatory strategies used at the time, venous-arterial rather than venous-venous cannulation, and older technologies.[15] Since then, many case series have shown improved success in adults.[16-19] Recently, a multicentre randomised controlled trial of conventional ventilator support versus extracorporeal life support for severe adult respiratory failure in 180 patients was published (the conventional ventilation or extracorporeal membrane oxygenation (ECMO) for severe adult respiratory failure (CESAR) trial).[2] Of patients allocated to consideration for extracorporeal life support, 63% survived to six months without disability compared with 47% of those allocated to conventional care. Those randomised to the intervention arm were managed in a single centre where 75% went on to receive extracorporeal life support. Patients in the control arm received conventional ventilation in the referring centres.

No randomised controlled trials have compared extracorporeal life support with conventional care in adults with cardiac failure. Most evidence supporting adult cardiac extracorporeal life support comes from non-randomised trials, case series, and the Extracorporeal Life Support Organization registry database, as is the case for children.

A PATIENT'S PERSPECTIVE

I heard about swine flu but just regarded it as something other people got and serious for people with an underlying medical condition. I was healthy.

I woke up one night with a temperature, aches, pains, a cough, and I felt weak. Things got worse as the week went on. I coughed up blood and had diarrhoea. On the tenth day my lips and hands turned blue. I was admitted to hospital, then sedated and ventilated. My lungs continued to deteriorate and the only option left on day 20 was extracorporeal membrane oxygenation (ECMO). My family told me that signing the consent form was the most difficult decision they had ever made.

The colour of the blood in the tubes frightened them at first. I remained on extracorporeal membrane oxygenation for 60 days. My only memory is of my mum and sister on one occasion.

When the sedation was stopped I was frightened and confused. I was shocked to find out that swine flu had caused this.

I find it very difficult to comprehend the severity of my illness. I get tired quite easily and breathless from simple everyday tasks but I will make a full recovery and lead a normal life, which I find amazing.

Cardiopulmonary resuscitation

Extracorporeal life support has been instituted emergently during in-hospital cardiopulmonary resuscitation in children and adults. Case series have reported variable survival rates, and overall survival to hospital discharge rates of 29% in adults, 38% in neonates, and 39% in paediatric patients are reported in the Extracorporeal Life Support Organization registry database (table 2).[19-21]

Cost effectiveness

Where randomised controlled trials have incorporated economic evaluations into the study design, extracorporeal life support has been demonstrated to be as cost effective as other life extending technologies in common use in intensive care units in developed countries.[29 22-24]

What are the main complications?

Bleeding (7-34%) and thrombosis (8-17%) are the most common serious complications.[25] Because of blood-surface interaction, clots can form in the circuit and embolise with potentially devastating consequences. Systemic infusion of unfractionated heparin and the use of heparin bonded circuits help to reduce thrombus formation but bleeding risk is then increased. The delicate balance between haemostasis and thrombosis requires frequent clinical and laboratory monitoring with replacement of coagulation factors, fibrinogen, platelets, and antithrombin III, as necessary. Monitoring and appropriate treatment for disseminated intravascular coagulation (2-5%), haemolysis (7-12%), and fibrinolysis is also needed. Cannulation (7-20%) and surgical site bleeding (6-34%) are common. Invasive procedures and operations should be avoided.[26] Intracranial bleeding (1-11%), especially in neonates; gastrointestinal haemorrhage (1-4%); and pulmonary haemorrhage (4-8%) may also occur.[27]

All organ systems can be affected by hypoxia and hypoperfusion before and during extracorporeal life support.

The brain is particularly vulnerable to damage by each of the above mechanisms and so, in addition to haemorrhage, seizures (2-10%) and infarction (1-8%) are common complications.

Despite these problems, extracorporeal life support is becoming ever safer, especially when appropriately selected patients are managed in specialised units with well trained and experienced staff supported by multidisciplinary teams.

When should patients be referred?

Extracorporeal life support should be considered in patients with severe, life threatening respiratory or cardiac failure that does not respond to conventional intensive care management. The disease process must be reversible or, failing this, the patient should be a candidate for transplantation or ventricular assist device placement.

Table 3 lists the most common underlying diseases in patients reported to the Extracorporeal Life Support Organization registry. Indications and contraindications vary among centres and continue to change as experience accrues and technology improves. Extracorporeal life support may be relatively contraindicated in patients who: are considered to be too far into the course of their disease; have been on conventional treatment for too long (usually >7-10 days); have pre-existing conditions that

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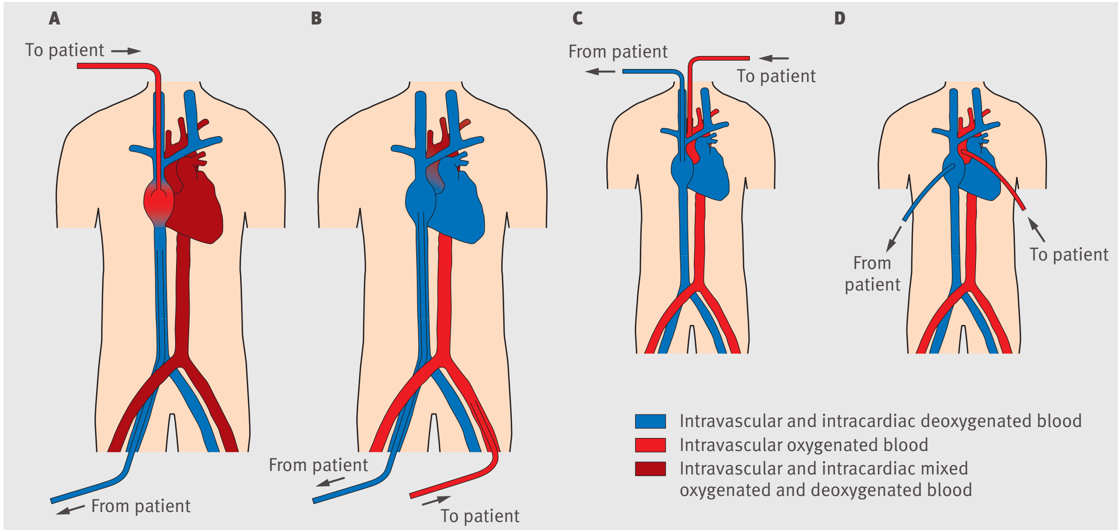

Fig 2 | A: an alternative venous-venous extracorporeal life support (ECLS) cannulation; deoxygenated blood is drained from the femoral vein with oxygenated blood being returned to the right atrium. B-D: various venous-arterial configurations. B: blood is drained from the femoral vein and returned to the femoral artery where oxygenated blood flows in a retrograde direction up along the aorta; when some residual cardiac function remains, oxygenated ECLS blood mixes with deoxygenated blood ejected from the left ventricle. C: a cannulated carotid artery, a site often used in infants. D: transthoracic right atrial and aortic cardiopulmonary bypass cannulas. Blue: intravascular and intracardiac deoxygenated blood; red: intravascular oxygenated blood; dark red: intravascular and intracardiac mixed oxygenated and deoxygenated blood

affect quality of life or that may be incompatible with normal life if the patient recovers (for example, brain injury, end stage malignancy, risk of systemic bleeding with anticoagulation); or are too young or too small (<32 weeks' gestational age, <2 kg).[28]

Although there are indices and scoring systems that help clinicians to determine the most appropriate time to consult with referral centres or to start extracorporeal life support (table 4), these serve only as guides and are neither rigidly nor universally applied. Referring hospitals should become familiar with their local specialist centre's referral guidelines. In all cases, early discussion with the specialist centre is imperative to ensure appropriate patient selection and timely transfer.

What are the long term effects?

Survivors of extracorporeal life support are more likely than the general population to have neurodevelopmental deficits, behavioural problems, and respiratory morbidities. However, when compared with the conventional care arms of randomised controlled trials, no between-group differences are seen for these outcomes.[2 29] Patients require rehabilitation and multidisciplinary follow-up after discharge from hospital. A high index of suspicion for late manifestations of neurodevelopmental problems must be maintained.

Table 4 | Respiratory failure severity scores

Indicators	Extracorporeal life support considered	Extracorporeal life support initiated
Oxygenation index (neonates) = ((FiO_2 x MAP)/PaO_2) x 100	20	40
PF ratio: PaO_2/FiO_2	<150 on 90% oxygen	<80 on 90% oxygen (and Murray score of 3-4)
Murray score[30]	2-3	3-4
Average score over all four parameters:		
1) PF ratio (mm Hg) on 100% oxygen: 300=0; 225-299=1; 175-224=2; 100-174=3; <100=4		
2) Chest radiograph: normal=0; 1 point per quadrant infiltrated		
3) Positive end expiratory pressure (cm H_2O): 5=0; 6-8=1; 9-11=2; 12-14=3; 15=4		
4) Lung compliance (ml/cm H_2O): 80=0; 60-79=1; 40-59=2; 20-39=3; 19=4		

FiO_2: fraction of inspired oxygen
MAP: mean airway pressure (cm H_2O)
PaO_2: partial pressure of oxygen in arterial blood (mm Hg)
mm Hg: millimetres of mercury
cm H_2O: centimetres of water

ONGOING AND FUTURE RESEARCH

- Research into the modification of extracorporeal life support surfaces is ongoing with the goal of preventing thrombosis in the absence of heparin anticoagulation
- Although the conventional ventilation or ECMO (extracorporeal membrane oxygenation) for severe adult respiratory failure (CESAR) trial showed that management of adults with severe respiratory failure in an extracorporeal life support referral centre is superior to conventional management in referring centres, further trials are needed to confirm increased survival attributable to extracorporeal life support alone
- Trials are needed to define the use of extracorporeal life support in acute myocardial infarction (MI)
- Trials of whole body cooling during extracorporeal life support to prevent neurological disability are ongoing
- Trials are warranted to compare outcomes between extracorporeal life support and high frequency oscillatory ventilation

Conclusion

Extracorporeal life support is a life saving intensive care resource when used in appropriately selected patients by well trained personnel in well organised centres. Advances in technology and development of antithrombogenic surfaces will continue to lower the complication rates associated with extracorporeal life support, allowing more patients to benefit from its use.

ADDITIONAL EDUCATION RESOURCES

Resources for healthcare professionals

Extracorporeal Life Support Organization (ELSO) (www.elso.med.umich.edu)—International consortium of extracorporeal life support specialists and centres. Maintains a registry database of patients managed with this technique; develops and publishes patient management, training, and organisational management guidelines; produces reports to participating centres

Van Meurs K, Lally KP, Peek G, Zwischenberger JB, eds. ECMO: extracorporeal cardiopulmonary support in critical care. "The red book". 3rd ed. Extracorporeal Life Support Organization, 2005

Resources for patients

University of Michigan. Family guide to neonatal extracorporeal membrane oxygenation (ECMO) (www.med.umich.edu/ecmo/patient/NeoECMO.pdf); Family guide to pediatric ECMO (www.med.umich.edu/ecmo/patient/PedECMO.pdf); Family guide to adult ECMO (www.med.umich.edu/ecmo/patient/AdultECMO.pdf)—Provide family and friends of patients with easy to understand information regarding extracorporeal life support

SOURCES AND SELECTION CRITERIA

We searched PubMed, Embase, and the Cochrane Library for systematic reviews, randomised trials, large population based studies, case controlled studies, case series, scientific and clinical reviews, evidence based guidelines, and published consensus statements between 1996 and 2010. We used the search terms "extracorporeal membrane oxygenation", "extracorporeal circulation", and "extracorporeal life support". We also consulted the registry database of the Extracorporeal Life Support Organization, personal databases, reference collections, and contemporary textbooks.

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