Extracorporeal membrane oxygenation: a breath of fresh air or yesterday's treatment?

Extracorporeal oxygenation during cardiopulmonary bypass has become a routine procedure during the last 30 years, though a "pump oxygenator" for patients with respiratory failure was first developed as long ago as 1885.¹ Extracorporeal membrane oxygenation (ECMO) has been shown to be beneficial in selected cases of neonatal respiratory failure and the ECMO Central Registry in the United States has now documented over 800 neonates treated in this way with an overall survival rate of 79%.^{2,3} How effective is ECMO for acute respiratory failure in adults and is it likely to become a useful and widely applied therapeutic technique?

The deficiencies in conventional mechanical ventilatory support provided the initial spur for trials of ECMO in patients with the adult respiratory distress syndrome, particularly as evidence accumulated that mechanical ventilation might itself contribute to the pathophysiology of lung injury and influence the course of the disease adversely.⁴ The role of high peak inspiratory pressure in the development of barotrauma is generally accepted, but experimental work has also shown that peak inspiratory pressures as low as 30 cm H₂O may be associated with pulmonary damage.⁵ In addition, the high volume ventilation required for patients with the adult respiratory distress syndrome, regardless of whether the peak inspiratory pressure is high or low, may lead to increased lung microvascular permeability,⁶ or to exacerbations of pre-existing lung injury.⁷ The theoretical attractions of extracorporeal oxygenation are therefore considerable. Several studies have been carried out in patients with the adult respiratory distress syndrome in recent years using various approaches; but the success rate has varied considerably, suggesting that the precise indications for the technique have yet to be determined. As parallel advances are made with other techniques of respiratory support, the use of ECMO, with its high cost and complication rate, may never become widespread.

Extracorporeal gas exchange (ECGE) has emerged as the blanket term describing all techniques of extracorporeal respiratory support, but the specific approach for a particular patient depends on the desired therapeutic goal. In true ECMO oxygenation is the prime objective and the transfer of carbon dioxide occurs as a secondary effect. Blood flow rates exceeding 50% of cardiac output are required. The objective in extracorporeal carbon dioxide removal (ECCO₂R) is to reduce the need for alveolar ventilation, thereby diminishing the potential for further pulmonary injury due to barotrauma. Partial carbon dioxide removal (PECCO₂R) can be achieved with blood flow at as little as 0.8–1 l/min and only one gas exchanging membrane, whereas total removal of carbon dioxide (TECCO₂R) usually requires higher flow rates (1–2 l/min) and the use of two membranes in series. As this technique provides only 20–30% of total body oxygen requirements, some ventilatory support is still required. This can be provided in one of three ways: spontaneous ventilation with or without the aid of continuous positive airways pressure (the term extracorporeal lung assist has been used recently^{8,9} to describe this technique); controlled conventional positive pressure ventilation at low frequency (for example, 4–6 breaths a minute) with positive end

expiratory pressure; and "apnoeic" intratracheal oxygen insufflation with positive end expiratory pressure.

Vascular access

The route of vascular access is also vital in determining what can be achieved through the use of extracorporeal gas exchange. Femoral vein to femoral artery bypass (venoarterial bypass) permits high bypass flow rates (up to 80% of cardiac output), but may leave vital organs such as the heart and brain perfused with poorly oxygenated blood from the lungs. Venoarterial bypass reduces pulmonary blood flow, which may lead to stasis and thrombosis. As the terminal respiratory units are supplied primarily by blood from the pulmonary and not the bronchial circulation, this approach may compromise lung repair.¹⁰ Venovenous bypass is arguably the technique of choice at present. The high flow rates required for ECMO, however, are difficult to achieve with inferior vena cava to superior vena cava bypass, and the benefits of a reduction in inspired oxygen concentration and inflation pressures in ventilated patients cannot be achieved. If the inferior vena cava cannula is advanced into the right atrium so that the flow rate can be increased, substantial recirculation of oxygenated blood through the oxygenator occurs. Oxygenated blood can be returned to the right ventricle so that the tricuspid valve prevents recirculation and 80% of the venous return can then be passed through the extracorporeal circuit. The pulmonary circulation is therefore perfused with oxygenated blood at normal blood flow rates and this may aid pulmonary repair. It is theoretically attractive to combine the two routes described above (mixed venoarterial and venovenous bypass) so that pulmonary artery oxygen saturation and perfusion pressures may be controlled, but the system is complicated to run and requires considerable expertise.

Selection criteria for extracorporeal gas exchange

Extracorporeal gas exchange has effectively been given to two categories of adults. In one group the underlying lung pathology is assumed to be reversible and ECGE is used supportively while the injured lung recovers. Clearly, the general state of the patient is critical and multiple organ failure, especially if the central nervous system is affected, should be considered a strong contraindication. Others include the risk of bleeding, substantial and irreversible left heart failure, septic shock, and pre-existing degenerative or malignant disease. Respiratory indications for the initiation of some form of ECGE include life threatening arterial hypoxaemia and a rising arterial carbon dioxide tension in the face of maximal conventional ventilatory support. Inclusion criteria remain contentious, but the early initiation of ECGE before irreversible lung changes occur may be desirable.

The second group of patients includes those with irreversible end stage lung disease who are considered suitable for single lung or heart-lung transplantation. Such an invasive procedure should not be initiated unless there is an excellent prospect that organs will shortly become available.

Terms used in extracorporeal membrane oxygenation

ECGE	Extracorporeal gas exchange, the blanket term for all techniques of extracorporeal respiratory support
ECMO	Extracorporeal membrane oxygenation; oxygenation is the prime objective of this technique, the transfer of carbon dioxide occurring as a secondary effect
ECCO ₂ R	Extracorporeal carbon dioxide removal; the removal of carbon dioxide is the primary objective, thereby reducing the need for conventional mechanical ventilatory support
P/TECCO ₂ R	Extracorporeal carbon dioxide removal may be partial (PECCO ₂ R) or total (TECCO ₂ R), depending on the blood flow rate and the area of the gas exchanging membrane

Current experience

How effective are these techniques and what are the principal complications? By comparison with conventional treatment in patients with the adult respiratory distress syndrome, extracorporeal gas exchange was not successful in reducing mortality in early controlled trials.^{11 12} This may reflect criteria for selecting patients, the severity of the underlying disease, and the continued use of conventional ventilatory support, which may have exacerbated pre-existing lung damage. This tendency to use ECGE as a supportive measure of last resort has been a feature of most studies and survival figures of around 10% reported in a recent informal study in United States centres are therefore not surprising.¹³ Eighty per cent of the patients had received ECGE for cardiopulmonary failure after cardiac surgery and 17% for the adult respiratory distress syndrome, where the expected mortality with conventional treatment is high. The best results published so far have been in studies from Italy using ECCO₂R with positive pressure ventilation at low frequency and venovenous bypass, where a reduction in mortality from 90% to 50% has been claimed.^{10 14} These results are surprisingly good, particularly as the mean duration of pulmonary insult before ECGE was instituted in survivors was 7.86 (SD 11.7) days. By contrast, in the collaborative ECMO (veno-arterial) study from the United States patients with more than one week of acute respiratory failure had a less than 4% chance of survival regardless of the type of treatment.¹² Other results from large series have so far been published only in abstracts, where survival rates of 56–70% have been reported in up to 100 patients with severe adult respiratory distress syndrome.^{15 16} The main difficulty of evaluating ECGE in a scientifically acceptable fashion in respiratory failure is the absence of controlled trials. In the studies published so far, the problem has been addressed by quoting historical control data from the United States national ECMO study. Within these limitations partial carbon dioxide removal and extracorporeal lung assist appear to be emerging as the most successful forms of ECGE for patients with the adult respiratory distress syndrome.

The use of extracorporeal support as a bridge to transplantation deserves special comment. Although the results of the multicentre trial organised by the National Institutes of Health in the United States did not show any difference in overall survival between those treated with ECMO and those treated conventionally, survival between days 2 and 11 was greater in the group having ECMO.¹² Extracorporeal gas exchange may therefore increase the time available to search for suitable donor organs. We have found this approach useful on several occasions. Although only three of six patients treated left hospital after transplantation, all but one survived until organs became available.^{17 18} As two patients died after transplantation,

prolonged support with ECGE may lead to irreversible tissue damage, thereby compromising the patient's chance of surviving transplantation; but it is at present impossible to obtain evidence on this.

Complications

Bleeding related to anticoagulation and disseminated intravascular coagulopathy have proved to be major sources of morbidity and mortality with ECGE and recent reports suggest that survival rates are higher in patients who do not bleed.¹⁴ New anticoagulants and antithrombogenic surfaces are now being assessed.^{16 19} Infection at multiple cannulation sites and bacterial colonisation of the bronchial tree in ventilated patients make antibiotic treatment unavoidable. Renal failure and the management of fluid and electrolyte abnormalities often require pump assisted haemofiltration or dialysis. Finally, even in centres with experience in extracorporeal support the allocation of resources and cost needs to be firmly established. The technique of positive pressure ventilation at low frequency with partial carbon dioxide removal has been estimated to cost about twice that of conventional intensive care for a critically ill patient.¹⁰

New modes of ventilatory support

Will the use of ECGE become more widespread? This will depend on the effectiveness of alternative modes of ventilatory support currently under development. These are based largely on the principle of maintaining an adequate mean airway pressure to provide oxygenation while high peak inspiratory pressures are avoided. Two examples are pressure controlled inverse ratio ventilation and airway pressure release ventilation; both have attractive features applicable to patients with the adult respiratory distress syndrome and are currently undergoing trials.²⁰ Ultra high frequency ventilation with ventilatory rates at or near the resonant frequency of the lung (about 5 Hz) is also being evaluated in patients with the adult respiratory distress syndrome and pilot studies have provided encouraging results.^{21 22} Probably the most innovative approach, however, is the development of an intravascular oxygenation device (IVOX). In essence, this consists of a miniaturised hollow fibre oxygenator designed to provide prepulmonary exchange of oxygen and carbon dioxide in venous blood when it is placed in venous structures from the confluence of the iliac veins through the inferior vena cava and right atrium to the superior vena cava. Oxygen is drawn through the fibres (under subatmospheric pressure to prevent air embolism) while anticoagulated (venous) blood flows between them. Oxygen diffuses passively down its concentration gradient into the blood while carbon dioxide diffuses out. In animal studies more than 150 ml/min of oxygen can be exchanged, thus providing a substantial portion (about 70%) of resting oxygen requirements. The need for conventional mechanical ventilatory support is therefore greatly reduced, and the danger of barotrauma and the toxic effects of high inspired oxygen concentrations are consequently much less. Blood entering the lungs is oxygenated, which may stimulate the pulmonary repair processes. Initial trials with IVOX are under way; published experience so far is confined to case reports.²³

Conclusions

The future of ECGE in the adult respiratory failure is clearly linked to the effectiveness of other new modes of ventilatory support. Though theoretically attractive as a means of "resting" the injured lung and avoiding the

damaging effects of mechanical ventilation, the technique is costly and fraught with complications and has not yet been shown to be effective in controlled trials. Possibly parallel developments in related areas will consign ECGE as currently practised to the therapeutic history books.

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