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EDITORIAL

Extracorporeal lung assist: more than kicking a dead horse?

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Up to now, the history of extracorporeal lung support has been a tale of great expectations and even greater disappointments. In 1972, HILL *et al.* [1] published the first case report on the use of extracorporeal membrane oxygenation (ECMO) in a young patient who suffered from acute respiratory distress syndrome (ARDS) after trauma. At that time, mortality rates from ARDS were extremely high and thus this report was embraced with great enthusiasm. However, only 2 yrs later reality caught up when the results of a randomised controlled trial using ECMO in ARDS were published showing mortality rates of >90% in both treatment arms [2].

Despite these sobering results, several groups of investigators continued to work on extracorporeal devices. GATTINONI and co-workers [3, 4] were the first to introduce the use of extracorporeal CO_2 removal to support protective ventilation strategies, now with survival rates of ~50% among patients with ARDS. However, once again a randomised controlled trial failed to show a survival benefit in ARDS patients treated with extracorporeal CO_2 removal [5] although the survival rates (33% in the extracorporeal group *versus* 42% in the conventional ventilation group) were now substantially better than in the 1970s.

The reasons for the failure to demonstrate a survival benefit with extracorporeal lung support were certainly manifold. The study by MORRIS *et al.* [5] included only 40 patients and was gravely underpowered (for comparison, the ARDS Network trial on low tidal volumes recruited >800 patients before a survival difference of 22% became statistically significant [6]). More importantly, the technical devices used at these times were not sufficiently developed and therefore prone to complications, such as thrombosis, haemorrhage and infections. In addition, protective ventilation strategies differed substantially from what is being used today. For example, in one of their first studies, GATTINONI *et al.* [4] used a ventilatory concept based on low breathing frequencies and high tidal volumes. Nowadays, this approach wouldn't be considered lung protective as it has been shown that low tidal volumes and airway pressure gradients are the key determinants of a protective ventilatory strategy [6–8].

So, why is it that extracorporeal devices are probably being used more frequently than ever before in modern intensive care units? There are several explanations for this including the availability of much better devices which are less prone to complications and more convenient to use. In addition, we have a better understanding of the physiology of extracorporeal devices and can tailor their use to the needs of individual patients. Conventional veno-arterial ECMO is now utilised mainly in patients in need of full cardiopulmonary support. Patients with severe oxygenation failure are candidates for veno-venous lung support. Patients presenting predominantly with hypercapnic respiratory failure may be treated with an arterio-venous assist device. Both the veno-arterial and the veno-venous approach require the use of a pump to generate flow rates of 3–5 $L \cdot min^{-1}$ to ensure sufficient organ perfusion and oxygenation, respectively. In contrast, no pump is needed for the arterio-venous approach since low-resistance devices are available which allow sufficient blood flow driven by the patient's own blood pressure. These so-called pumpless extracorporeal lung assist (pECLA) devices achieve flow rates of 0.8–1.5 $L \cdot min^{-1}$ which is sufficient to allow effective CO_2 removal. Vascular access is usually obtained with 13–15F arterial cannulas and 15–17F venous cannulas inserted into the femoral vessels.

The pumpless arterio-venous approach is increasingly being used in patients with ARDS, although there is still no data from randomised controlled trials to support this concept. However, the results of the ARDS Network have demonstrated that a less invasive ventilation strategy with low tidal volumes of 6 $mL \cdot kg^{-1}$ and inspiratory plateau pressures of 30 cmH_2O (3 kPa) resulted in a better survival rate than what was considered conventional ventilation at that time, *i.e.* tidal volumes of 12 $mL \cdot kg^{-1}$ and inspiratory plateau pressures up to 50 cmH_2O (5 kPa) [6]. Data from experimental models suggest that even lower tidal volumes and plateau pressures might be more beneficial [9] but in real life, protective ventilation is often limited by hypercapnia and respiratory acidosis. Although hypercapnia by itself has not been associated with adverse consequences, it may be extremely distressing for the patient, resulting in poor patient-ventilator interaction, the need for intensified analgosedation or even relaxation and an increasing use of catecholamines.

BEIN *et al.* [10] have reported the largest series on the use of pECLA in 90 patients with ARDS. Although this study was

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noncontrolled, it confirmed the concept that pECLA can be used to ensure protective ventilation. In that study, survival rates were lower than expected but this does not prove that pECLA was responsible for improved survival. Another study demonstrated that pECLA can be used successfully to bridge patients with end-stage lung disease to transplantation [11]. However the use of pECLA may be harmful as it is associated with significant complications, foremost lower limb ischaemia, compartment syndromes and cannula thrombosis [10].

In the present issue of the *European Respiratory Journal*, HOMMEL *et al.* [12] report on four patients with ARDS and bronchopleural fistulas with persistent air leakage despite surgical interventions. These patients usually have a poor prognosis if they develop respiratory failure and require mechanical ventilation with high airway pressures. In all four patients, the use of pECLA corrected hypercapnia and enabled the reduction of airway pressures, and all patients were eventually discharged from the hospital. As HOMMEL *et al.* [12] point out in their paper, there is no proof that the use of pECLA was responsible for the good outcome but there are compelling pathophysiological reasons supporting this hypothesis.

What are the main obstacles for the future development of extracorporeal lung assist? Many would argue that we need data from randomised controlled trials to warrant the use of such invasive, costly and potentially dangerous devices. In fact, such trials are currently underway but it will take years until results become available and the question remains as to whether these trials are adequately designed and powered to demonstrate an improved outcome. Unfortunately, those patients who might benefit the most from extracorporeal lung support may be too ill to be eligible for randomised controlled trials. Even in modern intensive care medicine many of our decisions are based on experience and pathophysiological considerations rather than on evidence from rigorous trials, and this must not necessarily be a bad thing. In the setting of intensive care medicine, randomised controlled trials often enrol heterogeneous patient populations. If those trials fail, a drug or intervention is usually considered not effective although it may still be useful in selected patients. The study by HOMMEL *et al.* [12] is a good example of a judicious use of an experimental device based on a sound clinical and pathophysiological rationale. Until further data become available it seems to be crucial to limit the use of such devices to well-equipped intensive care units with extensive experience in managing patients with severe ARDS. Similar to other areas in medicine, volume matters and the whole team needs substantial experience with the use of these devices to avoid the numerous pitfalls and to manage potentially dramatic complications.

Extracorporeal lung assist is not dead; in fact it seems to be more alive than ever. However, for the time being, the use of pumpless extracorporeal lung assist and other extracorporeal devices should be restricted to specialised centres, mostly tertiary care hospitals. It is likely that such devices improve the management of selected patients with respiratory failure as described in the case series by HOMMEL *et al.* [12] but they may also cause substantial harm when they are not being used in a proper setting.

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