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Interventional Lung Assist – Effective Removal of Carbon Dioxide in Acute Respiratory Failure

a report by
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Acute respiratory failure is still one of the most important diagnoses in intensive care therapy. Although recent years have seen major advances in ventilator techniques, pharmacological treatment and general intensive care, the overall mortality rate in acute respiratory failure leading to mechanical ventilation is still high.1 The most effective intervention to reduce mortality has been the reduction of tidal volumes and the application of an adequate positive end-expiratory pressure level to prevent further ventilator-induced lung injury.2 This protective ventilation mode has been widely accepted for clinical use in recent years.3 However, in the most severe cases of acute respiratory failure profound hypoxaemia or respiratory acidosis may contradict the sole use of protective ventilation strategies and necessitate additional strategies such as positioning manoeuvres, inhaled vasodilators, partial liquid ventilation or high-frequency ventilation techniques.4–6 Another approach is the application of extracorporeal gas-exchange devices to facilitate oxygenation and carbon dioxide (CO2) removal without the harm associated with aggressive mechanical ventilation. Depending on its technical modifications, the blood flow rate and the route of extracorporeal blood flow, these techniques are called extracorporeal lung assist (ECLA), extracorporeal membrane oxygenation (ECMO) or interventional lung assist (ILA).

History of Extracorporeal Lung Assist

With the first successful application of a modified cardiopulmonary bypass system for a young patient with traumatic lung injury, the concept of ECLA/ECMO was introduced to clinical practice.7 A milestone in the technical evolution of cardiopulmonary bypass and ECLA was the development of membrane oxygenators instead of bubble oxygenators in the 1960s, leading to increased short- and long-term biocompatibility.8 Promising results in different case reports led to the first prospective, randomised, controlled study in the early 1970s,9 in which 90 patients with severe acute respiratory distress syndrome (ARDS) were randomised to either conventional therapy with mechanical ventilation or to additional ECMO therapy; there was no significant effect on mortality, which was as high as 90 and 92% in the respective groups. A veno–arterial perfusion with reduced pulmonary blood flow, no adjustment of mechanical ventilation to protect the lungs after starting ECMO, high-dose heparinisation with a daily blood loss of 2.5l and termination of ECMO after five days regardless of lung function are possible reasons for the disappointing results in this trial.

Gattioni et al. developed an alternative approach: a veno–venous perfusion route and a blood flow of only 20–30% of cardiac output combined with low-frequency mechanical ventilation and additional oxygen insufflations, known as extracorporeal CO2 removal (ECCO2R).10 Forty-three patients with severe ARDS according to the same entry criteria as used in the first ECMO study were treated with ECCO2R, demonstrating a 51.2% mortality rate. A subsequent prospective, randomised trial failed to confirm these results, but an injurious ventilation strategy during the extracorporeal treatment, a low blood flow despite ongoing hypoxia and high blood loss were profound technical problems in the ECMO group.11 For newborns with severe respiratory failure, a prospective, randomised study clearly demonstrated that ECMO improved clinical outcome and is cost-effective compared with conservative therapy.12,13

Despite two negative randomised trials, different ARDS centres enhanced ECMO therapy for most severe cases of ARDS with life-threatening hypoxaemia, demonstrating an average mortality of 44% in various case studies.5,6,14–18 In a single-centre case study with 255 adult ECMO patients, age, gender, pH ≤7.10, partial pressure of oxygen (paO2)/fraction of inspired oxygen (FiO2) ratio and number of ventilator days before ECLA correlated with mortality.15 An ongoing prospective, randomised, multicentre study (CESAR Trial) is reassessing this clinical concept, comparing conventional protective ventilation versus ECMO therapy for severe ARDS.19 However, one of the most important limitations when using ECLA or ECMO is the technical complexity and the personnel required to install and maintain the technique at the bedside without causing major complications such as bleeding, clotting and complement activation as a result of mechanical and contact activation blood trauma. Therefore, the development of miniaturised systems with improved bioactive and heparin-bound surfaces must be viewed as a necessary step towards the widespread clinical use of extracorporeal support systems.

Arterio–Venous Pumpless Interventional Lung Assist

In this context, the recently developed approach of an arterio–venous pumpless ILA driven by the patient’s arterial blood pressure is most interesting. In the past, a blood pump was necessary to overcome flow resistance of cannulae and oxygenators and to achieve sufficient blood flow. Using newly designed oxygenators with a markedly reduced pressure drop,20 the difference between arterial and venous blood pressure is sufficient to achieve adequate extracorporeal blood flow. Mathematical analysis for arterio–venous ILA demonstrated that total extracorporeal CO2 removal is possible with a blood flow of...
10–15% cardiac output, a gas flow ≥5l/min and an adequate diffusing capacity of the oxygenator. Blood flow depends on the diameter and resistance of cannulae, as well as mean arterial pressure (MAP). Although the membrane could act as the perfect oxygenator, oxygen transfer is limited due to the fact that arterial blood is flowing into the oxygenator. Therefore, the main mechanism of the device is CO₂ removal. However, in profound hypoxaemia the oxygenation effect becomes more obvious when the inflowing arterial blood is no longer completely oxygenated. The cannulae are inserted percutaneously using a standard Seldinger’s technique and the filling volume is as low as 500ml, so the technical installation of the device is rather simple for physicians trained in vascular access modalities. All tubing as well as the membrane itself are bioactive, with a modified heparin coating that allows the device to be used with only minimal systemic heparinisation.

The first clinical studies demonstrated the feasibility and safety of arterio-venous ILA. The mean blood flow with ILA was 0.5–1.0l/min with the Affinity Oxygenator (Medtronic) and 2.0±0.44l/min with the Novalung Oxygenator. Hypercapnia could be significantly reduced after initiation of both devices, demonstrating adequate CO₂ elimination. The Novalung membrane was specifically designed for pumpless ILA with a reduced maximum blood flow and lower pressure drop compared with oxygenators developed for cardiopulmonary bypass.

The advantages of ILA are the avoidance of all pump-related complications, reduced blood contact with surfaces and simplified clinical management. Disadvantages are: indirect control of blood flow, which is the result of the arterio-venous pressure gradient; low oxygen transfer capacity, since the already oxygenated arterial blood is flowing into the device; arterial cannulation, which might pose local problems to the cannulated vessel and distal blood flow; and arterio-venous shunt perfusion up to 25% of cardiac output, which needs to be sustained by the left ventricle. Accordingly, the contraindications for ILA are heart failure, septic shock with low mean arterial pressure and severe peripheral arterial occlusive disease. Indications for ILA are not formally established in well controlled clinical trials, but patients with severe acute respiratory failure and severe hypercapnia seem to benefit most. ILA enables a more protective ventilation strategy with reduced airway pressures and tidal volumes, while providing adequate gas exchange in many of the most severe cases of respiratory failure, such as chest deformation, chest trauma, post-surgery, bronchospasms and asthma. The device is even transportable over long distances when necessary. In cases of severe head injury and concomitant chest trauma, the dilemma occurs between lung-protective ventilation with permissive hypercapnia and increased intracranial pressure requiring normo- or hypocapnia. In such a scenario, ILA and low-dose heparinisation lower CO₂ concentration and establish lung-protective ventilation without increasing CO₂, thereby maintaining control of intracranial pressure when necessary.

Although the technique is fascinating, and many case reports and small series have shown the clinical feasibility and physiological benefit of the ILA technique, more and bigger clinical studies are necessary to evaluate the advantages, complications and indications as well as contraindications of arterio-venous ILA. Larger-scale clinical studies must aim to define the role of ILA as a device facilitating lung-protective ventilation rather than testing it as a stand-alone gas exchanger, which has been a major interest of past studies in extracorporeal support. Two randomised controlled
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studies in acute lung injury are ongoing. A completely open field worth investigating is severe hypercapnia in forms of acute on chronic respiratory failure. One of the as yet unanswered questions in this field will be whether the extracorporeal CO₂ removal would result in a clinically significant unloading of the breathing pump.

Further Development of Extracorporeal Lung Assist

New concepts for minimised and highly integrated veno–venous ECMO are being developed using the experience of the already evaluated mini-ECMO.37 Here, the oxygenator and blood pump are coupled, reducing foreign surface area and priming volume even more, and the blood is warmed by the pump motor housing instead of a heat exchanger. The compact design should further simplify clinical management.38 Another concept for a compact assist device is the insertion of oxygenators into the vena cava. These intravascular oxygenators (IVOX) use the pressure difference inside the vena cava for blood flow.39 New concepts of intravascular lung assist are being designed with a combination of a cross-flow oxygenator and an intravascular microaxial blood pump to improve blood flow and gas exchange.40 Additional efforts are being made to use ECLA for long-term lung assist and as a bridge to transplant. Using an oxygenator with further decreased flow resistance creates the opportunity of using the right venticile as the driving force for blood flow after paracorporeal implantation of the artificial lung in series or parallel to the biological lungs.41 An oxygenator with a pressure gradient of 7.5mmHg and an oxygen transfer of 350ml/min at a blood flow of 40ml/min has been developed,42 and in an animal model with adult sheep successful paracorporeal implantation has been demonstrated.43 The first clinical studies are being planned.

Conclusion

Over the past few decades, veno-venous ECLA has been an important therapy for the management of severe ARDS. However, ECLA has always been a rescue therapy for the most severe ARDS cases, since it is highly demanding in terms of technical and personnel requirements. Accordingly, no clinical data support the use of ECMO as a standard treatment in ARDS. However, fascinating technological progress has provided us with newly developed devices such as highly integrated minimised systems or arterio–venous pumpless Ila. Indications and contraindications will depend on the route of perfusion as well as the site of cannulation and must be weighed against the harm of conventional therapy. Therefore, well designed clinical studies must guide the implementation of extracorporeal support into clinical work.