Recent advances in extracorporeal lung support systems

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The treatment of severe acut lung failure includes artificial ventilation with a lung protective concept, but in situations of life-threatening respiratory failure with persistent hypoxia/hypercapnia, the technique of extracorporeal lung assist has been employed. A veno-venous pump-driven extracorporeal membrane oxygenation (ECMO) is established in specialized centres - requiring extended equipment with technical and support staff and costs - for patients with severe ARDS , while the use of a new technique of a pumpless interventional lung assist (iLA) using a femoral arterio-venous pressure gradient as the driving force for blood flow through a gas exchange membrane has been reported in patients suffering from severe lung failure due to trauma, sepsis or brain injury. ILA is a new and promising strategy for extracorporeal lung support allowing a de-escalation of injurious ventilation, but it contains a risk for potentially severe complications. For assessment of clinical perspectives and precise indications for both strategies aimed at restoring adequate gas exchange and supporting lung protective ventilation will be elucidated by multicentric prospective randomized clinical studies in the near future.

Introduction

Acute failure of the lung resulting in impairment of the pulmonary gas exchange capacity is a frequent cause for admission of patients at the intensive care unit, often resulting in mechanical ventilation. Acute lung in-

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jury (ALI) is defined as a moderate decrease in arterial oxygenation, whereas acute respiratory distress syndrome (ARDS) is characterized by alveolar epithelial injury and destruction of alveolar architecture with severe hypoxemia and/or hypercapnia (1).

Therapeutic regimen include artificial ventilation and the consideration of a lung-protective strategy (2) by avoidance of high inspiratory pressure and large tidal volume. Although it has been shown that in patients suffering from severe ALI or ARDS a lung protective ventilation affects outcome and reduces mortality in comparison with "traditional ventilation", the mortality rate remains high in ARDS despite recent advances in treatment strategies (prone positioning therapy, fluid management using extended hemodynamic monitoring, inhalation of vasodilating drugs).

The concept of a pump-driven extracorporeal membrane oxygenation (ECMO) has been employed in recent years for situations of life-threatening forms of respiratory failure with persistent hypoxemia and or/hypercapnia unresponsive to "optimised" conventional therapy. In earlier randomized controlled studies using the ECMO technique in adults suffering from severe ARDS, no outcome benefit has been shown (3,4), whereas improved outcome has been demonstrated in children (5,6). A high complication rate due to systemic anticoagulation (bleeding) and the specific side effects of roller pumps (inflammation, destruction of blood components, hemolysis) contributed to the lack of a benefitial outcome. Furthermore, the ECMO technique requires extended equipment with technical and support staff and its routine use is limited to specialised centres. Actually, a prospective randomised multicentre study comparing conventional ventilation methods with extracorporeal membrane oxygenation (Conventional Ventilation or ECMO for Severe Adult Respiratory Failure [CESAR-trial] has shown a significant increase in the survival rate and/or the rate of severe disability in patients on ECMO in comparison with conventional treatment (7).

Extracorporeal membrane oxygenation (ECMO) – acute developments

Extracorporeal membrane oxygenation (ECMO) is a technique for providing life support for patients experiencing both pulmonary and cardiac failure by maintaining oxygenation and perfusion until native organ function is restored ("bridging organ failure")(8). ECMO is used for adults in select medical centers, which have reported favourable findings in patients with ARDS and other causes of severe pulmonary failure. ECMO is also rarely used as a rescue therapy in a small subset of adult patients with cardiac failure. "Traditional" roller-pump driven ECMO was characterized by high complication rates (dislocation of devices, oxygenator and pump failure, bleeding,

thromboembolism), while a new generation of "miniaturized" ECMO systems using centrifugal pumps and reduced filling volumes is advocated to drop down the complication rates (9).

A new pumpless extracorporeal interventional lung assist (iLA) using arterio-venous shunt

In recent years, a pumpless extracorporeal interventional lung assist (iLA) has been described in experimental and clinical investigations using the animals` arterio-venous pressure gradient as the driving force for blood flow through a gas exchange membrane. The clinical development of the iLA system has been performed at the University Hospital of Regensburg by an interdisciplinary working group consisting of perfusionists, cardiothoracic surgeons, and intensivists. A new membrane gas exchange system (Novalung GmbH, Talheim, Germany) is integrated in a femo-femoral shunt flow generated by the arterial blood pressure. The membrane system is based on heparin-coated hollow fiber technique (polymethylpentene) with optimised blood flow properties by reduction of resistance. The membrane is integrated in a shunt established via arterial and venous cannulae inserted by Seldinger`s technique into femoral vessels. iLA does not need extended technical and staff support, and the main advantage is easy handling. It is a single-use ultracompact extrapulmonary gas exchange system perfused by the heart. The effective gas exchange surface area amounts to 1,3 m^2. An oxygen supply (10 – 12 l/min) to the membrane results in an effective carbon dioxide elimination and a modest improvement in arterial oxygenation. Contraindication for the application of the system is the hemodynamic instability of cardiac origin, since an average driving pressure difference of 60 – 80 mm Hg (femoral artery – femoral vein), a mean arterial pressure of 70 mm Hg, respectively, are mandatory to produce a flow rate of approximately 1 – 2 l/min through the gas exchange membrane. The iLA is suitable for patients with potentially reversible respiratory failure, for example trauma, pneumonia, aspiration, pancreatitis and sepsis.

Clinical experience and scientific results

At the University Hospital Regensburg, between November 1996 and December 2006, a total of 150 patients were treated with iLA for ≥ 24 hrs. The diagnoses leading to ARDS were pneumonia, multiple trauma, pancreatitis, peritonitis, sepsis, postoperative, brain injury and aspiration or drowning. In patients who were at risk for life-threatening hypoxemia and/or excessive hypercapnia, iLA was implemented when the combined use of advanced optimised therapeutic strategies had failed and a sufficient oxygenation (PaO_2/

FIO_2 > 70 mmHg) and/or a sufficient carbon dioxide elimination ($PaCO_2$ < 60 mmHg and pH > 7,25) was not achieved. In most patients, iLA induced a prompt carbon dioxide removal that resulted in a reduction of hypercapnia and consequently in the possibility of less "aggressive" ventilation. Furthermore, a moderate increase in arterial oxygenation was observed (10). On the other hand, we recorded a marked frequency of complications, predominantly due to bleeding during the cannulation procedure and due to ischemia of a lower limb after arterial cannulation. During the initial period (1996-2000) we used large arterial cannulae (17 – 19 Fr). Meanwhile - as an import consequence of the experience of ischemic complications - the insertion of smaller cannulae (15 Fr) that allow improved distal perfusion while maintaining adequate blood flow through iLA is routinely performed. Since 2001, the incidence of ischemic complications has dropped markedly.

In 2009, we reported our experience with iLA in 51 patients suffering from severe ARDS prospectively (11) and we demonstrated an acute and impressive CO_2-removal after implementation of iLA and a moderate oxygenation improvement. We were able to modify the ventilation variables towards a "lung protective concept" after initiation of iLA and hospital the mortality rate was 49 %. Adverse events occurred in 6 patients (11,9 %).

An actual modification of the indication for iLA might allow clinicians to prioritise lung protection in patients suffering from ARDS with severe hypercapnia. Such a concept aims at providing adequate gas exchange realising a strict lung protective strategy by the help of the extracorporeal lung assist while exerting a most effective carbon dioxide elimination. By the use of smaller arterial cannulae (15 Fr) and accepting a moderate blood flow through the gas exchange membrane (ca. 1,5 l/min), ischemic complications may be reduced. This concept has to be proven by a prospective randomized multicentre study, which has been started.

Extracorporeal lung assist in severe lung failure: current recommendations and clinical perspectives

Although the concept of a pumpless extracorporeal lung assist represents a new and attractive therapeutic option due to easy handling properties and low cost, a precise knowledge of limitations and complications and of accurate indications for initiation of the iLA are required - as well as for the implementation of ECMO. In patients with severe persistent hypoxemia (PaO_2/FIO_2 < 70 mmHg), ECMO still has its indications, since the capability of pump-driven veno-venous ECMO is superior to that of iLA. On the other hand, iLA will find a place in the scenario of acute ARDS management as

an extracorporeal assist to support ventilation with low tidal volume and reduced inspiratory pressures.

Furthermore, iLA was found to be a promising alternative for patients with ARDS and acute brain injury (12). In these patients, hypercapnia might exert detrimental effects on intracranial pressure and cerebral outcome. Due to extended systemic anticoagulation, ECMO is contraindicated in patients suffering from acute cerebral lesions and we found that iLA has minor restrictions, limitations and side effects. Additionally, we used iLA sucessfully for the interhospital transportation of patients with severe lung failure from tertiary hospitals to our centre by air our ground (13). In these patients we implemented the system at the referring hospital and we observed no severe complications during transport.

In summary, the technique of a pumpless extracorporeal lung assist using arteriovenous bypass is a new and promising strategy for patients with severe acute lung failure allowing a de-escalation of invasive ventilation mode. In the near future, a multicenter prospective randomized study will start, but meanwhile the routine use of iLA is restricted to several specialised centres, in which precise indications and a careful implementation technique are used.

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