CLINICAL STUDY

# Extracorporeal membrane oxygenation in lung transplantation

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**Abstract**

**Lung transplantation has become an accepted surgical modality. As the primary pulmonary graft failure accounts for almost one third of early deaths, new possibilities to positively influence this life-threatening complication had been searched for.**
**extracorporeal membrane oxygenation (ECMO) offers an unique advantage to overcome the demanding peri- and postoperative period.**
**The authors present the advantage of ECMO use, introduce a review of experience with its application in lung transplantation.** ***(Fig. 2, Ref. 36.)***
**Key words: extracorporeal membrane oxygenation, lung transplantation, primary graft failure.**

**Definition of the ECMO technique, historical overview, technical description**

Extracorporeal membrane oxygenation (ECMO) is a technique, which allows oxygenation of the blood outside the body and which does away with the need for gas exchange inside the lungs. (Berger, 1998). Now it has become a kind of a standard therapy for patients unresponsive to conventional ventilation and pharmacological support (Klein and Whittlesey, 1994).

This device was clinically introduced more than 20 years ago, and had been proved to provide effective treatment for neonatal respiratory failure, myocardial failure in postoperative pediatric cardiac surgery (Stolar et al, 1991).

Since that time progress has been made in improvement of the extracorporeal devices in terms of bio-compatibility: less traumatizing oxygenators and pumps were developed.

Each ECMO apparatus must contain the following basic constant parts: a hollow-fiber oxygenator, a bio-centrifugal pump, a flow probe, a tubing system.

Some companies supply those tubing systems already heparin-bounded. All of these together with the possibility of transcutane application make this system less invasive and more biocompatible.

As it can be seen from the above mentioned, the most important two elements are the oxygenator and the bio-centrifugal blood pump.

The hollow-fiber oxygenator allows the flow from 1 to 7 liters, contains integrated warm exchanger and is heparin bounded, as all the other elements.

In 1974 Medtronic Company introduced to the market its new Bio-Medicus Bio-pump Centrifugal Blood Pump. This pump is composed of nested, smooth cones that rotate using viscous drag. This results in a smooth, gentle pumping action that minimizes damage to the blood (Fig. 1, 2).

In comparison with the conventional roller pumps, which transfer low volumes at high pressures leading to creation of turbulence in blood, the centrifugal ones transfer high volumes at a low pressure thus minimizing the damage of blood elements.

The clinical advantages of this Bio-pump are evident and can be summarize into the following points:

- the hospital stay for patients perfused with the Bio-Pump is shorter than for patients perfused with a roller pump (Beki et al, 1992; DeBois et al, 1995; Green et al, 1991),
- patients experienced less 24-hour weight gain post-opera-

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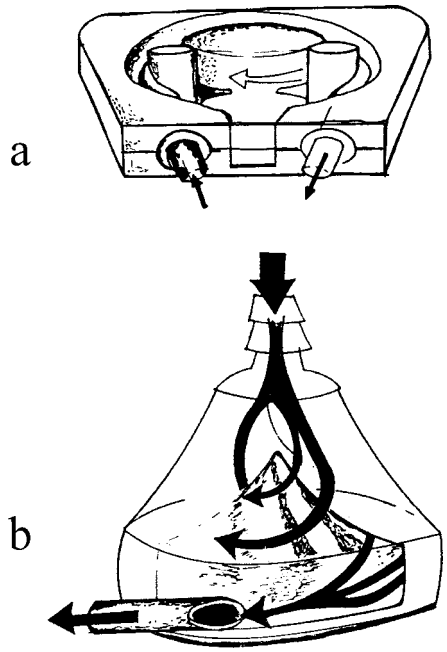


**Fig. 1. Perfusion pump technologies: a) Roller Pump: rollers push the blood along. Leading and trailing edges of rollers create turbulence in the blood, b) Centrifugal Pump: smooth, rotating cones use viscous drag. Pumping action is smooth and gentle. The blood does its own pumping.**

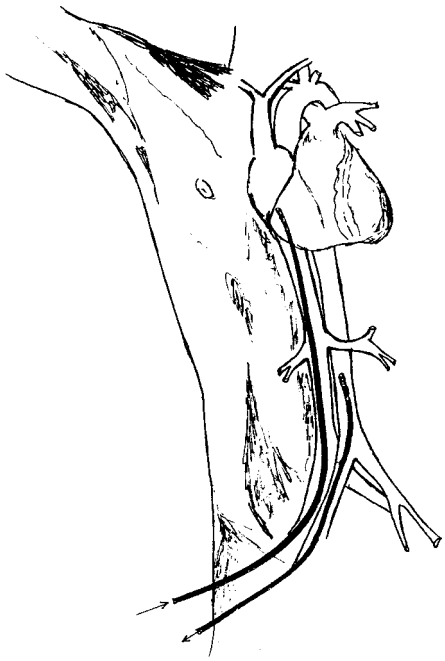

**Fig. 2. Application of ECMO via femoral veno-arterial approach.**

tively when perfused with the Bio-Pump (Bludszuwit, 1995)
- the overall cost was reduced for patients perfused with the Bio-Pump (Berki et al, 1992; Bludszuwit, 1995; DeBois et al, 1995),
- less replacement blood products were required for Bio-Pump patients (Berki et al, 1992; Colon et al, 1987; Green et al, 1991),
- less hemolysis occurred with the Bio-Pump (Clark et al, 1996; Curtis et al, 1996; El-Banayosy et al, 1995),
- better preservation of platelet number and function with the Bio-Pump (Curtis et al, 1996; El-Banayosy et al, 1995),
- less postoperative chest drainage occurred with the Bio-Pump (El-Banayosy et al, 1995),
- reduced betathromboglobulins for Bio-Pump patients (Green et al, 1991)
- less blood loss postoperatively with the Bio-Pump (Green et al, 1991).

## ECMO and lung transplantation

The successful and advantageous application of ECMO in neonatal and pediatric medicine was already described (Stolar et al, 1991; Green et al, 1991; Klein and Whittlesey, 1994). Due to the similar indication — therapy for respiratory failures in patients unresponsive to conventional ventilatory and pharmacological support — ECMO began to be also applied in adults. Alas, the results with the adults are not so encouraging as with the children. According to authors Strueber and Haverich the overall survival in adult patients was reported to be about 40 % (Strueber and Haverich, 1999).

Nowadays, in contrary, more and more reports evidence the successful use of ECMO in lung transplantation (e.g. in graft failure after lung transplantation or in bridging to lung transplantation) (Slaughter et al, 1993; Glassman et al, 1995; Macha M et al, 1996; Vlassellaers et al, 2000; Meyers et al, 2000; Nguyen et al, 2000).

The following chapters will be devoted to this topic.

## Scientific reasoning of ECMO use

*Pulmonary graft re-perfusion injury*

Primary pulmonary graft failure accounts for almost one third of early deaths (30 days), and it is associated with approximately 15 % of death within 3 months after lung transplantation (Hosenpud et al, 1999). Lung preservation and its attendant ischemia-reperfusion injury is a complex phenomenon that begins with lung injury that may be present in the donor before any preservation intervention. From this moment forward the ischemia injury begins and increases during the phase of organ storage (Unruh, 1995). With re-perfusion, another phase of lung injury begins as the ischemic lung is overloaded with oxygen and oxygen free radicals are generated.

*Endothel injury and leukocyte depletion*

Ischemia-reperfusion lung injury is mediated by free-radical production in the endothelium, which triggers polymorphonucle-

ar leukocyte and complement activation. So, the leukocytes have been found to be a major mediator of reperfusion injury in various organs (Unruh, 1995; Halldorsson et al, 1998; Grach, 1994; Breda et al, 1985). These activated leukocytes adhere to the injured endothelium (Unruh, 1995; Boyle et al, 1997). Once bound, the activated leukocyte releases a variety of mediators, such as oxygen free radicals and proteases, that ultimately cause cell injury or death (Unruh, 1995; Halldorsson et al, 1998; Boyle et al, 1997).

*Re-perfusion injury and mechanical shear stress*

The mechanism, by which low pressure exerts this protective effect, is not precisely known. There is no doubt that simple hydrostatic pressure plays a role, and mechanical forces (shear stress) have also been implicated (Bhabra et al, 1996; Okamoto et al, 1986). Recent experimental studies showed that pressure can independently activate endothelial cells, which increase white cell adherence resulting in pulmonary injury (Grosso et al, 1989). The injury of endothelium causes activation of the above-described factors leading to definite organ failure.

*Time of controlled re-perfusion*

Bhabra and colleagues, proved, that by reducing the pressure during the first 10 minutes of re-perfusion, the pulmonary re-perfusion injury was significantly reduced (Bhabra et al, 1996). Another work assessed that 20 minutes of controlled re-perfusion is superior to 10 minutes in organ ischemia (Allen et al, 1986). Therefore, nowadays the length of time and the pressure of re-perfusion is an active area of investigation.

Routine clinical approaches of controlling the re-perfusion period is to compress the pulmonary artery for about 10 minutes after removal of vascular clamps during re-perfusion, or performing the procedure under Cardiopulmonary Bypass (CPB) (Halldorsson et al, 1998, 1998; Aeba et al, 1994).

*Experimental settings and recommendations for controlling re-perfusion*

Several studies demonstrated that after different periods of cold lung ischemia severe pulmonary re-perfusion injury occurs with uncontrolled re-perfusion using unmodified blood (Halldorsson et al, 1998, 1998; Bhabra et al, 1996). To avoid this injury a setting with isolated lung perfusion using modified reperfusate (leukocyte filtered, crystalloid and different substrate-enriched blood) and special equipment (heaters, filters and roller pump) were tested and recommended (Halldorsson et al, 1998, 1998; Bhabra et al, 1996).

## International statistics

Several cases of ECMO as an adjunct to adult lung transplantation have been reported (Slaughter et al, 1993; Glassman et al, 1995). Recently Vlasselaers and his colleagues reported about a patient with severe re-perfusion injury after bilateral lung transplantation successfully treated with 50h of ECMO therapy (Vlasselaers et al, 2000). Meyers and co-workers reviewed 12 patients and also found that ECMO provides effective therapy for acute post-transplantation lung dysfunction (Meyers et al, 2000). Similar results have been reported by Zenati and co-workers reviewed the experience of the University of Pittsburgh with ECMO for primary severe allograft dysfunction in 8 patients after lung transplantation (Zenati et al, 1996). They reported an 87 % rate of successful weaning from ECMO with a low incidence of complications. Ko and co-workers also reported their 5 patients experience of using ECMO instead of the conventional CPB in single lung transplantation for primary pulmonary hypertension (PPH) and extending its use into the early postoperative period (Zenati et al, 1996; Ko et al, 1999).

Advantage of ECMO and its prolonged application is, that the hemodynamically unstable perioperative and postoperative course can be fully controlled.

Since ECMO is an approved and routinely applied modality in most centers all over the world, it should be preferred to any experimental device.

Furthermore, the ECMO support is not expected to effect cytokines release, as well as leukocyte, complement and coagulation activation because of superior ECMO bio-compatibility due to heparin coated circuits and intraoperative blood aspiration into the cell saver system. Blood aspirated from the operative field contains large amounts of thrombin and plasmin. Exclusion of this blood from the perfusate decreases postoperative blood loss, and this is why this exclusion is probably as important as using the coated circuits.

As it is described, ECMO in lung transplantology seems to find broad realisation, and the future will surely authorises this technique.

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