Extracorporeal membrane oxygenation for transport of hypoxaemic patients with severe ARDS

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Summary

Conventional inter-hospital transfer of patients with severe acute respiratory distress syndrome (ARDS) in need of extracorporeal membrane oxygenation (ECMO) may be risky and in severe hypoxaemic patients may be associated with cerebral hypoxia and death. Therefore, we began a phase 1 study to evaluate the feasibility, complications and outcome of inter-hospital transport of these patients using veno-venous ECMO. Eight patients with severe ARDS and a $P_{a,O_2}/F_{I,O_2} < 6.7$ kPa at a PEEP $\geq 10$ cm H$_2$O were placed on a mobile ECMO at the referring hospital. The 495 (SD 123) km inter-hospital transport via a special ground ambulance took 341 (151) min. After transfer, blood-gas tensions were improved in spite of less optimal ventilator settings, compared with data before the start of ECMO. No significant complications occurred. Six patients survived and were discharged from hospital; two patients died because of multiple organ failure. We conclude that initiation of ECMO in hypoxaemic patients before inter-hospital transfer is feasible and enables safe transport to an ECMO centre. (Br. J. Anaesth. 1997; 78: 241–246).

Key words


The acute respiratory distress syndrome (ARDS) is a rapid and severe alteration in lung structure and function characterized by hypoxaemia, reduced respiratory compliance, pulmonary hypertension and diffuse interstitial infiltrates. Since its first description by Ashbaugh and colleagues in 1967, the mortality rate of this syndrome remains greater than 50%, despite extensive clinical and laboratory research efforts. Among other unknown factors, this high mortality may be influenced by the disease itself, in addition to iatrogenic factors such as ventilator settings with high airway pressures, large tidal volume and high inspiratory oxygen concentrations ($F_{I,O_2}$). Therefore, today we aim to reduce peak airway pressure, tidal volume and use lower inspired oxygen concentrations. Conventionally, it is now customary to use pressure- or volume-limited ventilation, or both, with positive end-expiratory pressure (PEEP), body positioning, including prone position, differential lung ventilation, avoidance of fluid overload and acceptance of increased partial pressure of carbon dioxide.

Should these therapeutic measures fail to improve pulmonary gas exchange, extracorporeal lung support has been advocated in the treatment in patients with severe, but potentially reversible, acute respiratory failure. As this technique requires special equipment and knowledge, centres for advanced treatment of ARDS have arisen. However, conventional inter-hospital transfer of patients in need of extracorporeal membrane oxygenation (ECMO) can be risky and in severely hypoxaemic patients ($P_{a,O_2}/P_{I,O_2} < 6.7$ kPa) may be associated with cerebral hypoxia and death. Therefore, we began a phase 1 study to evaluate the feasibility, complications and outcome of inter-hospital transport using ECMO in this group of patients.

Patients and methods

This investigation was performed at the Virchow-Klinikum of the Humboldt-Universität with the approval of the institutional Ethics Committee. Informed consent was obtained from each patient’s family.

Patients were included in the study if they suffered from severe ARDS, that is a Murray score $\geq 2.5$ and fulfilled the modified fast entry criteria of the US National ECMO study ($P_{a,O_2}/P_{I,O_2} < 6.67$ kPa at a PEEP $\geq 10$ cm H$_2$O for $> 2$ h) despite various trials to optimize pulmonary gas exchange. Patients were excluded from the study if they had contraindications to ECMO which include extremely poor prognosis because of the underlying disease (malignancy, unresolvable surgical problems), immunosuppression, assured irreversible damage of the central nervous system, severe chronic pulmonary disease,
primary cardiogenic pulmonary oedema and advanced age (>60 yr). Additional organ failures, such as cardiac, hepatic, renal, CNS, gastrointestinal and haematological failure were assessed using grade II definitions of the score of Goris and colleagues.12

From June 1993 to October 1995, nine patients fulfilling the above criteria were referred to our hospital for extreme respiratory failure unresponsive to conventional treatment. The severity, duration and assumed consequences of hypoxia, and other organ failures were assessed by telephone. As one of the nine patients died within 2 h after the first phone call, there were eight patients (table 1) to be transferred to our intensive care unit (ICU).

TRANSPORT FACILITIES
The ECMO team went to the referring hospital by ground (n = 2) or air (n = 6) transit depending on the distance to the referring hospital. The ECMO team comprised two anaesthetists and one nurse who were experienced with ECMO techniques. A large bus equipped as a mobile ICU was used for inter-hospital transfer of patients from the referring hospital to our hospital. This bus contained a blood-gas, haemoglobin and electrolyte analyser (ABL 505, Radiometer, Copenhagen, Denmark), a monitor system (Siemens Elema, Lund, Sweden), infusion pumps and a bed fitted with a Siemens 300 ventilator (Siemens Elema, Lund, Sweden), an independent power and gas supply, and a portable monitor system (Siemens) with ECG, arterial and pulmonary artery pressures and pulse oximetry (fig. 1).

EXTRACORPOREAL BYPASS AND CANNULATION

TECHNIQUE
After arrival at the referring hospital, the patient’s condition was assessed by the physician, whereas the nurse started immediately to prepare the extracorporeal bypass system. In three patients, a pulmonary artery catheter was introduced and central venous and arterial catheters were changed; in all patients, a short trial was undertaken to improve ventilator settings, which included a test with different PEEP levels and I:E ratios. If $P_{A_{a}}/F_{I_{O_{2}}}$ remained less than 6.7 kPa at a PEEP $\geqslant 10$ cm $H_{2}O$, veno-venous ECMO was initiated. Cannulation was not performed in the operating theatre but in the ICU with the patient in bed. For venous access, 21F cannulae (Biomedicus) were used for adults and 17F cannulae (Biomedicus) for children. Blood was drained via one or—in order to achieve higher extracorporeal blood flows—two spring wire reinforced cannulae introduced percutaneously via the femoral vein, with one cannula placed in the inferior cava and, if possible, a second cannula advanced to the iliac bifurcation. Blood was drained passively into a collapsible reservoir. This reservoir was equipped with a Servo switch to stop the pump if the reservoir collapsed. From here, blood was pumped actively by an almost occlusive roller pump (Stöckert, Germany) through a microporous membrane lung (Medronic Maxima, Anaheim, CA, USA) which was ventilated with oxygen 3–6 litre min$^{-1}$. Oxygenated blood was then returned to a cannula, also introduced percutaneously from the right jugular vein (seven patients) or from the right subclavian vein (one patient) and advanced to the superior cava. All parts of the extracorporeal system were coated with heparin. The extracorporeal flow rate was adjusted to 1.8 litre min$^{-1}$ in children and to 3 litre min$^{-1}$ in adults. Blood temperature was regulated extracorporeally by a heat exchanger and maintained at 36°C. Continuous monitoring of pressure before and after the membrane lung allowed detection of a kink in the tubing, unintended reduced extracorporeal blood flow or disconnection within the extracorporeal bypass circuit. All electrical parts of

Figure 1

Intensive care ground ambulance. The bus is equipped with a blood-gas, haemoglobin and electrolyte analyser (in the back of the bus), monitor system, infusion pumps and a bed fitted with a Siemens 300 ventilator, power pack and gas supply, and a portable monitor system with ECG, arterial and pulmonary artery pressure facilities in addition to pulse oximetry. The patient and mobile ECMO are moved into the bus at the same time via a loading ramp.
Mobile extracorporeal membrane oxygenation

The mobile ECMO unit were attached to a dedicated current powerpack (fig. 2).

The use of surface heparinized equipment reduced the need for heparinization. After an initial bolus injection of heparin 1000–2000 u. immediately before insertion of the cannulae, heparin was infused continuously to maintain the activated clotting time at 120–150 s.

After commencing ECMO, ventilator settings were adjusted for the decreased pulmonary gas exchange needs and to reduce further structural damage produced by high PaO₂, large tidal volumes and/or high peak inspiratory pressures, that is patients’ lungs were ventilated with a pressure controlled mode with a ventilatory frequency limited to ≤10 bpm, i.e. ratio of 1:1, peak inspiratory pressure <35 cm H₂O and a PEEP of 9–16 cm H₂O. PaO₂ was adjusted to maintain PaO₂ at 8–9.3 kPa. At this time inhaled nitric oxide, which was given to three patients by the referring physicians in order to improve arterial oxygenation, was stopped. Infusions of cardiotonic or vasoactive drugs were continued if necessary, whereas parenteral nutrition was always stopped.

TRANSPORT OF PATIENTS ON ECMO

After a stabilization period of 1–2 h, the patient was rearranged in the bed of the mobile ICU and connected to its monitor and respirator. The patient was then moved to the mobile ICU in which the patient, together with the ECMO unit, were placed on a loading ramp. The bed and mobile ECMO unit were anchored in the ICU bus. During inter-hospital transfer, ECG, systemic arterial, pulmonary arterial and central venous pressures, SpO₂, and temperature were monitored continuously. Blood-gas analyses were performed hourly.

On arrival at our hospital, a CT scan of the head and lungs was performed followed by measurement of systemic and pulmonary variables, in addition to arterial and mixed-venous blood-gas tensions. Oxygen contents of arterial, mixed venous and capillary blood were calculated and the venous admixture (Qva/Qt) was derived from the Berggren formula. The quantity of extravascular lung water content (Lung Water Computer 9310, Edwards Laboratories, Irvine, CA, USA) was estimated using the double-indicator dilution technique.

STATISTICAL ANALYSIS

All data are presented as individual values or mean (sd). Differences between values before transport without ECMO and those after inter-hospital transfer with ECMO were analysed using the non-parametric Wilcoxon signed rank test. Changes were considered significant if P<0.05.

Results

Eight patients with a PaO₂/PaO₂ of 6.7 kPa at PEEP ≥5 cm H₂O for >2 h because of severe ARDS (Murray score 3.59 (0.23)) induced by multiple trauma or pneumonia were transferred on ECMO to our hospital. Before the start of ECMO, PaO₂ was 5.7 (0.5) kPa and PaCO₂ was 7.9 (1.5) measured at an FIO₂ of 1.0, peak inspiratory pressure of 37.4 (6.1) cm H₂O and PEEP of 12.6 (2) cm H₂O (table 1).

The interval between the request to transfer a patient and initiating ECMO was 513 (137) min. The 495 (123) km inter-hospital transport took 341 (151) min (table 2). The only complication related to transport which occurred was a breakage of a stopcock on the top of the membrane lung during loading onto the bus. As the conus of the stopcock remained in the membrane lung, the whole membrane lung had to be exchanged. However, the patient survived this event without adverse effects.

After arrival in our ICU, heart rate was 110 (26) beat min⁻¹, mean arterial pressure 83 (19) mm Hg, pulmonary artery pressure 29 (8) mm Hg and cardiac index 3.1 (0.3) litre min⁻¹ (table 3). Extravascular lung water was high with 33.4 (14.2) ml kg⁻¹. Comparing gas exchange variables and ventilator settings before transfer without ECMO with those after transfer with ECMO demonstrated that PaO₂ increased by 3.1 (0.9) kPa (P=0.012), and PaCO₂ decreased by 1.9 (1.4) kPa (P=0.012), R₂O₂ by 0.28 (0.18) (P=0.028), peak inspiratory pressure by 8.3 (7.4) cm H₂O (P=0.036) and ventilatory frequency by 11.4 (3.4) bpm (P=0.012). Total duration of extracorporeal respiratory support was 8 (9) days.

Six patients survived and were discharged from hospital; two patients died as a result of multiple organ failure. In three of the six survivors we observed neurological symptoms after weaning from
the ventilator which were thought to be caused by the hypoxia. All three patients recovered nearly completely during the following months.

**Discussion**

Despite extensive research and increasing knowledge of the pathophysiology of ARDS, newer studies still show an overall mortality rate of more than 50% without ECMO. In our centre, using a combination of advanced therapy and extracorporeal lung support as a last resort therapy the mortality rate was 27%. However, until recently we refused patients who had a $P_{a}/O_2$ of 5.3 kPa in spite of optimization of ventilator settings, because we believed that these patients would not survive conventional interhospital transport. Furthermore, we were anxious to transfer patients with an $P_{a}/O_2$ of 5.5–6.7 kPa as in some of the latter patients transported before the onset of this study, gas exchange deteriorated further during inter-hospital transfer causing periods of arterial oxygen saturation of less than 65%. Boeddy, Howell and Kanto reported a 12% mortality rate for transported infants before ECMO could be initiated. For adults with severe ARDS, no data are available. Therefore, we developed a transport ECMO system to facilitate safe inter-hospital transport of patients with a $P_{a}/O_2$ of 6.7 kPa. This study has demonstrated that ECMO for transport of such patients was feasible with good results and no severe complications.

Some clinicians cast doubt on the benefit of extracorporeal lung support on survival in patients with severe ARDS, especially because two randomized,
controlled studies failed to demonstrate an increase in survival using ECMO or extracorporeal carbon dioxide removal. The US ECMO study was conducted from 1974–1977 and published in 1979. The results showed no differences in survival rates between patients treated by ECMO and patients undergoing mechanical ventilation alone. Patients treated with extracorporeal bypass and mechanical ventilation, and those treated with mechanical ventilation alone, had a high mortality rate (10% vs 8%). However, the ECMO regimen used in the US ECMO study differed markedly from the present method and, in our opinion, is not comparable. The main differences included the use of a high flow veno-arterial bypass potentially inducing insufficient oxygen supply to the lung, non-heparinized systems leading to severe bleeding complications, and mechanical ventilation with high airway pressures and high tidal volumes, possibly further damaging the lung. Moreover, the study was conducted during an influenza epidemic with a high frequency of pneumonia, a cause of ARDS known to be associated with a high mortality rate. Furthermore, the poor results might also have resulted from the study design allowing termination of ECMO if after 5 days of treatment no improvement in lung function could be observed. However, it is well known today that initial improvement in lung function with subsequent survival may occur as late as day 10 to day 20 of treatment.

Similar shortcomings were observed in the second randomized, controlled study conducted from 1987 to 1991 in the pulmonary ICU of the University of Salt Lake City by Morris and colleagues. The purpose of this study was to compare pressure-controlled inverse ratio ventilation (pcCMV-IRV) followed by low frequency positive pressure ventilation with extracorporeal carbon dioxide removal (LFPPV-ECCO2R) with controlled positive pressure ventilation in patients with ARDS. Morris and colleagues found that survival was not significantly different in both groups (33% vs 42%), although overall survival rate had improved significantly compared with survival in the US ECMO study. A possible explanation for why Morris and colleagues did not show benefit from LFPPV-ECCO2R is that they reported 22 bleeding complications in the LFPPV-ECCO2R-treated patients and had to terminate extracorporeal respiratory support in seven of 19 patients because of bleeding problems. In contrast with our routine, Morris and colleagues used extracorporeal bypass with non-heparinized circuits and artificial lungs. The available literature suggests that bleeding remains the most common complication in adult patients with ARDS undergoing extracorporeal lung support, and seems to be related partly to constant heparinization. Another explanation for the poor survival rates of Morris and colleagues in LFPPV-ECCO2R-treated patients may be the relatively low extracorporeal blood flow rates of 2.38 (SEM 0.01) litre min−1. In order to accomplish a significant reduction in intrageneric lung injury caused by mechanical ventilation, higher oxygen transfer rates would have been necessary, requiring a higher extracorporeal blood flow. In our patients extracorporeal blood flow was approximately 50% of cardiac output which makes limitation of peak inspiratory pressure to ≤36 cm H2O and Vp ≥ to < 10 ml kg−1 in our ECMO patients possible; Morris and colleagues had to apply a mean PIP of 49.5 cm H2O during the entire LFPPV-ECCO2R in order to maintain sufficient oxygenation. In our opinion, after commencing pressure- and volume-limited ventilation combined with permissive hypercapnia, the main goal of extracorporeal lung support is to avoid irreversible hypoxic injury. This goal can be achieved using a veno-venous bypass technique with high extracorporeal blood flow and without causing bleeding complications, if heparin-coated systems are used. Obviously, the technique itself cannot heal the lung but allows for sufficient arterial oxygenation in spite of less damaging ventilator settings, as demonstrated in our study. Finally, the extent of practical experience with extracorporeal lung support may also influence the results of clinical studies. Before the start of our study, we had treated more than 35 patients with ECMO, while Morris and colleagues had treated only two patients before they began their randomized clinical study. Although a further prospective, randomized study may be desirable, from our point of view, the positive results in Europe in more than 450 patients with severe ARDS clearly justifies the use of extracorporeal respiratory support as a last resort therapy.

In particular, in the group of patients in this study with an assumed mortality risk of nearly 100%, inter-hospital transport could only be performed without the hazards of hypoxic injury by using ECMO, and six of eight patients survived. Our experience is in accord with that of other groups who consider ECMO to be a feasible alternative to conventional transport for hypoxic neonates or those with an unstable cardiopulmonary system, or for adults. However, to date, transport of patients receiving ECMO is not performed widely because of logistic or technical problems, or both. Using the described technical equipment (mobile ECMO, bed fitted with a ventilator, ICU bus) allowed us to perform all routine intensive care procedures with the exception of x-rays, and therefore this procedure is in accordance with the “Guidelines for the transfer of critically ill patients” provided by the American College of Critical Care Medicine.

Using a ground transport facility for inter-hospital transport of patients led to a mean transfer time of 4.7 h. We are aware that air transport either with fixed-winged aircraft or with a helicopter would have shortened the duration of transport. However, we believe that in patients already receiving ECMO the duration of inter-hospital transfer is less important than adequate space for treatment and full availability of ICU equipment in the ICU bus. The time required for transportation in the ICU bus can be used for further optimization of ventilation and haemodynamic state.

An ECMO transport service is very costly in terms of personnel, vehicles and equipment. Such a service may deprive the ECMO centre of critical care staff for many hours. It would be preferable therefore to...
transport patients in need of advanced treatment of ARDS at a time when the receiving hospital’s ECMO entry criteria are not yet fulfilled. However, four of eight patients transported developed hypoxic respiratory failure and required mechanical ventilation within 2 days of the onset of the disease. Therefore, we believe that there is a need for safe facilities to perform such inter-hospital transport.

References