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High survival in adult patients with acute respiratory distress syndrome treated by extracorporeal membrane oxygenation, minimal sedation, and pressure supported ventilation

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Abstract *Objectives*: To evaluate the results of treatment of severe acute respiratory distress syndrome (ARDS) with extracorporeal membrane oxygenation (ECMO), minimal sedation, and pressure supported ventilation.
Design and setting: Observational study in a tertiary referral center, Intensive Care Unit, Astrid Lindgren Children's Hospital at Karolinska Hospital, Stockholm, Sweden.
Subjects and methods: Seventeen adult patients with ARDS were treated with venovenous or venoarterial ECMO after failure of conventional therapy. The Murray score of pulmonary injury averaged 3.5 (3.0–4.0) and the mean PaO_2/FIO_2 ratio was 46 (31–65). A standard ECMO circuit with nonheparinized surfaces was used. The patients were minimally sedated and received pressure-supported ventilation. High inspiratory pressures were avoided and arterial saturation as low as 70 % was accepted on venovenous bypass.
Results: In one patient a stable bypass could not be established.

Among the remaining 16 patients 13 survived (total survival rate 76 %) after 3–52 days (mean 15) on bypass. Major surgical procedures were performed in several patients. The cause of death in the three nonsurvivors was intracranial complications leading to total cerebral infarction.
Conclusion: A high survival rate can be obtained in adult patients with severe ARDS using ECMO and pressure-supported ventilation with minimal sedation. Surgical complications are amenable to surgical treatment during ECMO. Bleeding problems can generally be controlled but require immediate and aggressive approach. It is difficult or impossible to decide when a lung disease is irreversible, and prolonged ECMO treatment may be successful even in the absence of any detectable lung function.

Key words Acute respiratory distress syndrome · Extracorporeal membrane oxygenation · Adult · Lung injury · Mechanical ventilation · Survival rate

Introduction

Acute respiratory distress syndrome (ARDS) is an acute onset of arterial hypoxemia resistant to oxygen therapy alone with diffuse bilateral radiological infiltrates [1]. It is a secondary manifestation of a large number of primary processes of pulmonary (e.g., pneumonia, contusion, aspiration) or extrapulmonary (e.g., sepsis) origin. Mortality remains high in spite of modern conventional therapy including permissive hypercarbia, nitric oxide and prone position [2]. Positive pressure-controlled ventilation with high inspiratory pressures

and a high concentration of inspired oxygen may be mandatory but is harmful to the lungs and may cause further damage [3, 4, 5, 6].

Extracorporeal membrane oxygenation (ECMO) involves gas exchange through an extracorporeal oxygenator and provides oxygenation and carbon dioxide removal without interfering with the lungs. Although initial results were disappointing [7, 8], encouraging reports have recently been published [9, 10, 11].

Our present ECMO program started in 1987 with neonatal patients. Pediatric patients have been accepted since 1988 and in 1995 the program also opened for adult patients (a former program at Karolinska Institutet for adult patients had been closed a few years earlier [12]). The aim of this report was to analyze results from the first 17 adult patients with ARDS treated with ECMO in our center.

Methods and materials

Indications for ECMO

Patients were accepted for ECMO if there was an acute, reversible, life-threatening form of respiratory failure unresponsive to conventional therapy [13]. The criteria for fast entry were: PaO_2/FIO_2 ratio below 60 mmHg and transpulmonary shunt higher than 30 on FIO_2 above 0.9 for 2 h, chest radiography with diffuse infiltrates in all quadrants. Unresponsiveness to prone position, inhaled NO, or high-frequency oscillatory ventilation (since 1998) and persistent hypercapnia were used as slow entry criteria. Exclusion criteria were: age above 60 years, advanced multiple organ failure, underlying severe disease, or severe immune suppression.

ECMO circuit and perfusion

A standard ECMO technique was used [14]. In venoarterial (V-A) ECMO blood was drained from the right atrium via a cannula in the right internal jugular vein and returned to the right common carotid artery, which was ligated cranial to the cannula. In venovenous (V-V) ECMO blood was normally drained from the right atrium and returned to one femoral or external iliac vein, although the opposite direction was used on a few occasions. Normally V-V ECMO was preferred, but if the patient was hemodynamically unstable or was to be transported on bypass, V-A ECMO was used [15]. The blood was pumped with a Stöckert roller pump through two membrane oxygenators (3.5 or 4.5 m^2) and heat exchangers (Avecor) in parallel. Nonheparinized polyvinylchloride tubing was used except for the raceway, where Supertygon was used. The standard ECMO cart was equipped with a battery backup, thus being mobile and useful for transports within the hospital. At the beginning of the series and in all cases of V-A bypass the cannulation was performed as an open surgical cut-down procedure. The last patients in the series on V-V bypass were cannulated using a percutaneous or a semipercutaneous technique. Bypass was maintained at a rate necessary to provide adequate gas exchange or at a rate equal to the maximal venous return.

The membrane lungs were ventilated with oxygen and CO_2 less than 5% at a flow of 5–8 l/min. As soon as the patient was stable on bypass, ventilator settings were reduced to rest settings (approx. FIO_2 0.4, peak inspiratory pressure 25, positive end-expiratory pressure 5–10, rate 10; Siemens 300). ET tubes were avoided in order to decrease the need of sedation. Patients, who were not tracheotomized, received a tracheostoma within a few days on ECMO to facilitate airway management. Initially during the ECMO run when gas exchange over the lungs was minimal, arterial saturations as low as 70% had to be accepted when the patient was on V-V bypass. Patients on V-V bypass were weaned to a flow rate of approx. 1 l/min, after which the sweep gas was decreased and turned off several hours before decannulation. Patients on V-A bypass were weaned to a flow rate of about 0.5 l/min and kept on this low flow for several hours before decannulation. Decannulation was performed with the patients only slightly sedated and under local anesthesia, when the patient had been cannulated by an open surgical procedure. Cannulas inserted percutaneously or semipercutaneously were simply withdrawn without anesthesia and with a gentle pressure applied afterwards. No bridges were used in the circuit. Anticoagulant therapy was kept between 180 and 200 s by a continuous heparin infusion. Apart from standard blood chemistry, coagulation parameters (PK, activated partial thromboplastin time, fibrinogen, d-dimers, antithrombin III, fibrin monomers) were analyzed daily. When there were signs of consumption coagulopathy, intravascular coagulation or fibrinolysis the circuit was changed.

Patient management and monitoring on ECMO

At initiation of ECMO the patients were normally sedated and often paralyzed as well. Muscle relaxation was withdrawn as soon as the patients were on bypass. The degree of sedation was gradually decreased, and by the end of the run the patients were only mildly sedated at night. During the day they were generally awake, able to communicate with the staff and with their family, watching television, etc. $PaCO_2$ was adjusted by adding CO_2 to the sweep gas to stimulate spontaneous breathing in pressure-supported ventilation. Tidal volumes as measured by the Siemens 300 ventilator were recorded on an hourly basis.

Initially most patients were on total parenteral nutrition. This was gradually withdrawn, and enteral feeding was given through a nasogastric tube as soon as possible. Great effort was made to diurese the patients to dry weight. If necessary continuous V-V hemofiltration and/or hemodialysis (CVVHDF) was initiated via the ECMO circuit.

During bypass the hemoglobin was kept higher than 120 g/l and the platelets higher than 100,000/ml. Antibiotics were selected by results from bacterial cultures performed daily from blood and weekly from cannulation sites, urine, and nasopharynx. Examinations for fungus and virus were performed when needed. Corticosteroids were not used routinely. In two patients with ECMO duration exceeding 21 days it was given before decannulation. Chest radiography was performed every 3–4 days, echocardiography weekly for cannula position, and level of pulmonary hypertension and computed tomography of head, thorax, and abdomen when needed.

The patients were monitored and nursed continuously 24 h/day by an ECMO specialist familiar with the principles of ECMO and with detailed knowledge of all the technical equipment and management of patients on ECMO. An ECMO physician or another ECMO specialist was in house 24 h/day during the ECMO run for safety and back-up reasons. The technical monitoring of the patient resembles that of a standard ICU patient.

Table 1 Pre-CMO patient data, including which patients were treated with inhaled NO, HFOV, and prone position (*PIP* peak inspiratory pressure, *PEEP* positive end-expiratory pressure, *HFOV* high-frequency oscillatory ventilation, *Pneu/sept* pneumonia or septicemia, *WG* Wegner's granulomatosis, *over-weight* weight at ECMO start – normal weight, *pre-ECMO PIP/PEEP* the last values before ECMO; *tidal volume* the value obtained from the ventilator also including dead space)

Patient no.	Age (years)	Sex	Cause of ARDS	Duration of pre-ECMO ventilation (days)	Pre-ECMO PIP/PEEP	Pre-ECMO tidal volume	Murray score	PaO_2/FIO_2 ratio	Over-weight (kg)	Inhaled NO	HFOV	Prone
1	39	M	Pneu/sept	5	42/14	533	3.75	48	–	Yes	No	No
2	27	F	Pneu/sept	1	49/0	450	3.00	36	–	Yes	No	Yes
3	37	F	Pneu/sept	13	31/7	460	3.00	51	24	Yes	No	Yes
4	18	F	Embolism	16	38/13	550	3.50	65	–	No	No	Yes
5	17	F	Trauma	1	54/16	947	4.00	35	18	No	No	No
6	51	M	Aspiration	8	42/10	870	3.25	51	4	No	No	Yes
7	42	M	Pneu/sept	8	40/15	560	3.75	54	–2	Yes	No	Yes
8	42	M	Pneu/sept	2	40/15	610	3.50	54	–	No	No	Yes
9	38	F	Pneu/sept	1	44/12	476	3.25	54	–	No	No	No
10	33	M	WG	2	43/6	640	3.25	51	18	No	No	No
11	30	F	Intoxication	9	36/13	578	3.50	31	1	Yes	No	Yes
12	20	F	Pneu/sept	7	40/18	544	3.75	38	10	Yes	No	Yes
13	23	F	Embolism	11	MAP 35	–	3.75	46	15	Yes	Yes	Yes
14	20	M	Trauma	1	35/6	500	3.25	37	6	No	No	No
15	59	M	Pneu/sept	4	46/18	711	3.75	60	9	No	No	Yes
16	39	F	Pneu/sept	5	48/15	563	4.00	45	22	No	Yes[a]	Yes
17	40	M	Pneu/sept	5	40/15	700	3.75	35	16	Yes	No	Yes
Mean				6	43/13	522	3.5	46	12	8/17	2/17	12/17

[a] HFOV was tried in this patient, who, however, was back on conventional ventilation before initiation of ECMO

Interhospital transportation on ECMO

Since 1995 it has been possible for the team to transport patients between hospitals while on ECMO. A special mobile ECMO cart for transportation has been developed. The components are principally the same as described above but include a more powerful battery back-up. A team consisting of one ECMO physician, one ECMO specialist, and one cannulating surgeon initiated ECMO at the referring hospital. The patient is brought back to our institution by ground, helicopter, or fixed-wing craft [16, 17].

Calculations and statistics

Maximal extracorporeal O_2 delivery expressed in ml/min was calculated in each patient according to $ECC \times 1.35 \times (1-S_vO_2) \times Hb$, where ECC is the extracorporeal flow in l/min, S_vO_2 is the mixed venous saturation obtained from the venous return from the patient (before the blood enters the membrane oxygenator) and Hb is the hemoglobin concentration in grams/liter. Data are presented as mean ± SD unless otherwise stated.

Patients

Between December 1995 and October 1999 we have treated 17 adults (8 men, 9 women) aged 17–59 years (mean 34) for ECMO in our institution. Patient data are given in Table 1. They had all been referred to us from other hospitals in Sweden and Norway. Twelve patients had previously been healthy. Among the others there was a history of mild diabetes, obesity, psychiatric disorder, Crohn's disease, or alcohol abuse. ARDS was caused by pneumonia/septicemia in ten, by trauma and postpartum pulmonary embolism in two each, and by Wegner granulomatosis, aspiration, and nortriptylin intoxication in one each.

Before ECMO the patients had been ventilated for 1–16 days (mean 6). Inhaled NO had been tried in 8 patients, and 12 had also been treated in the prone position. The mean P_aO_2/FIO_2 ratio was 46 (31–65). The Murray score [18] was 3.00–4.00 (mean 3.5). Many patients were extremely edematous before the start of ECMO. In 12 of the 17 patients we had access to data on the pre-ECMO weight as well as their normal weight. Their pre-ECMO overweight averaged 12 (–2 to 24) kg.

Results

Of the 17 patients cannulated for ECMO, stable bypass was established in 16. One patient (no. 1), who had unstable hemodynamics by the time of cannulation, rapidly deteriorated with arrythmias and ventricular fibrillation after cannulation. Adequate venous return was never achieved, and in spite of rapid conversion to V-A bypass the patient could not be saved. Autopsy showed massive pulmonary embolism. Data from this patient are excluded in statistical calculations except in calculation of survival. Of the remaining 16 patients 13 survived to hospital discharge. The average length of bypass was 14.6 days (range 3–52; Table 2). There was no significant difference in this respect between survivors (mean 15.3 days, range 3–52) and nonsurvivors (mean 11 days, range 11–12).

Table 2 Data on bypass on the 17 patients treated with ECMO (*G* ground transport, *H* helicopter transport, *F* fixed wing transport *CVVHDF* continuous venovenous hemofiltration or hemodialysis during part of the extracorporeal bypass)

Patient no.	Transport on ECMO	V-A/V-V	Time on ECMO (days)	Maximal extracorporeal flow (l/min)	Maximal extracorporeal O$_2$ delivery (ml/min)	Surgical procedure on ECMO	Volume blood products (liter/day)	CVVHDF	Outcome
1[a]	–	V-V	0	0.6	22	–	–	No	Died
2	–	V-V	12	4.3	137	Cannula[c]	2.0	Yes	Died
3	G	V-A	11	3.5	215	–	0.6	No	Survived
4	–	V-A	13	3.8	260	–	0.3	No	Survived
5	H	V-A	3	2.3	123	–	0.7	No	Survived
6	–	V-V $\to$ V-A[b]	11	4.3	243	–	0.5	No	Died
7	G	V-A	12	4.0	197	–	0.5	Yes	Survived
8	H	V-A	12	5.0	233	Tracheostomy	0.7	No	Survived
9	–	V-V	7	4.2	201	–	0.6	No	Survived
10	–	V-A	8	4.5	122	Tracheostomy	1.1	Yes	Survived
11	–	V-V	11	4.4	238	Tracheostomy, thoracotomy	1.1	No	Died
12	–	V-A	52	5.0	307	Tracheostomy, thoracotomy × 3, cannula[c]	0.9	Yes	Survived
13	F	V-A $\to$ V-V[b]	21	4.8	265	Cannula[c], tracheostomy	0.5	Yes	Survived
14	–	V-V	3	3.5	274	–	1.6	Yes	Survived
15	–	V-V	23	4.7	198	Cannula[c], thoracotomy ×2	0.6	Yes	Survived
16	–	V-V	14	4.5	226	–	0.2	No	Survived
17	–	V-V	23	4.0	251	Tracheostomy	0.6	Yes	Survived

[a]Patient never stable on bypass; data from this patient not included in statistical data
[b]Mode of bypass changed
[c]Position of one or both cannulas adjusted

Eight patients were initially cannulated for V-A bypass and nine for V-V bypass. Of the last nine patients only three were put on V-A bypass. The mode of bypass was changed in two cases. One patient initially on V-V bypass was recannulated for V-A bypass because of substantial increase in pulmonary vascular resistance leading to right heart failure and hepatic malfunction. Another patient treated with V-A bypass for 15 days was electively decannulated after pulmonary improvement, but deteriorated the following hours and was then recannulated for V-V bypass for 6 additional days.

The maximal extracorporeal blood flow during the ECMO run was 4.2 ± 0.68 l/min and the maximal extracorporeal oxygen delivery was 218 ± 53 ml/min, with no significant difference between survivors (220 ± 54) and nonsurvivors (206 ± 60).

Surgical procedures during the ECMO run were performed in one-half of the patients. Four patients needed revision of the cannulation site or adjustment of the position of one or both of the cannulas. Six patients had a tracheostomy performed during bypass. In one case a subsequent revision was necessary because of bleeding. Thoracotomy was performed in three of the patients because of pleural effusion or hemothorax as a complication of insertion of pleural drainage. In one of them (no. 11) the bleeding was controlled after the first procedure. The next (no. 12) required another thoracotomy due to rebleeding after 2 days. After meticulous surgical control of the bleeding, the hemithorax was packed with sponges instilled with ε-aminocaproic acid [19]. The sponges were removed 48 h later and the wound closed. The third patient subjected to a thoracotomy during bypass (no. 15) had the hemithorax packed with sponges in the same way during the first procedure and subsequently removed. The bleeding was then controlled and further surgery in these patients unnecessary.

Two patients had hemopericardium (detected on ECMO day 10 in no. 7 and on day 29 in no. 12), and drainage was inserted and kept in place until decannulation. In patient no. 12 ultrasonography showed a perforation of the venous cannula through the wall of the right atrium. The cannula was withdrawn approximately

2 cm. Eventually the perforation closed spontaneously, and surgical repair was unnecessary.

Eight patients required CVVHDF during a part of the ECMO run due to renal failure. In one patient (no. 12) the renal dysfunction was a side effect of treatment with aprotinin peri- and postoperatively. In all patients the renal function recovered during bypass and dialysis/hemofiltration could be withdrawn before decannulation.

During a total of 233 days of ECMO there were no technical complications. In 24 cases oxygenators or complete circuits were changed due to signs of intravascular (intracircuit) coagulation and/or fibrinolysis. The average duration of one ECMO circuit (oxygenator) was consequently 5.8 days. On 31 occasions patients on ECMO were transported within the hospital for computed tomography.

The total transfusion of packed red cells was 87 l, fresh frozen plasma 44 l, and platelets 42 l during the 233 ECMO days. The mean average daily transfusion packed red cells per patient was 400 ± 282 ml, fresh frozen plasma 203 ± 131 ml, and platelets 193 ± 153 ml. The mean average daily transfusion of blood products was 796 ± 470 ml per patient.

The lowest tidal volume averaged 122 ± 57 ml, which increased to a maximum of 602 ± 252 during the ECMO course. The highest value was higher among survivors (662 ± 202 ml) than among nonsurvivors (345 ± 329 ml). All surviving patients were able to communicate with the staff and their family within 3–7 days after initiation of ECMO.

Three patients developed severe intracranial complications. All of these patients subsequently died. None of the nonsurvivors ever woke up during the ECMO run. One of them (no. 2) had pre-ECMO episodes of hypotension, pronounced hypoxemia, and circulatory arrest. Her pulmonary function improved, but she developed cerebral edema and subsequently a total cerebral infarction 1 day after decannulation. One patient developed a cerebral hemorrhage despite stable coagulation parameters and another a cerebral infarction, both on ECMO. Both lesions increased in extension, and ECMO had to be withdrawn due to total cerebral infarction.

Five of the 17 patients were cannulated in the referring hospital and transported on ECMO by ground, helicopter, or fixed-wing craft (Table 2). The transports were uneventful and all patients transported on ECMO subsequently survived.

Discussion

Successful use of ECMO was first reported in 1972 [20], and this has been followed by other encouraging reports [21, 22, 23]. A multicenter study of adult ECMO sponsored by the National Institutes of Health was completed in 1979, but the results were disappointing as fewer than 10 % of patients in both the ECMO group and the control group survived [7]. A prospective randomized study [8] comparing extracorporeal support and advanced conventional treatment showed a slightly lower (33 %; but not statistically significant) survival in the treatment group than in the control group (42 %). Several other reports have shown a higher survival rate in the treatment of ARDS with extracorporeal support (Table 3). In the two largest recently published series the survival was 66 of 100 patients [24] and 54 of 100 patients [9]. With regard to the Murray score [18] and PaO_2/FIO_2 ratio no difference was detected vs. the patients' pre-ECMO condition (Table 3).

ECMO does not cure the underlying disease of the lungs, but supports the patient and provides gas exchange until the lungs are again capable of this. As a result of this support the lungs can be ventilated at lower inspiratory pressures and with a lower fraction of oxygen and thus further iatrogenic trauma is avoided. Treatment of the primary disease and method of patient care such as mode of ventilation on ECMO may differ between centers and may to some extent explain differences in the results. Furthermore, the extracorporeal life support can be performed in various ways, which also may explain discrepancies in results. Gattinoni et al. [30] focused principally upon CO_2 removal and an almost apnoeic oxygenation, which was also the case in the study by Morris et al. [8]. After initiation of ECMO, however, there is often an increased opacification of the lungs [25] and decreased compliance, resulting in less oxygenation and a demand for higher inspiratory pressures, which again may become harmful to the lungs. With a higher extracorporeal flow the extracorporeal support may also contribute substantially to the oxygenation of the patient. V-A bypass may provide a nearly total extracorporeal gas exchange if the flow is high enough. With V-V bypass a nearly total oxygenation can also be obtained if the cannulas are positioned so that the recirculation is min-

Table 3 No of patients, Murray score, P_aO_2/FIO_2 ratio, and survival in recently published studies of ECMO in adult patients

	n	Murray score	P_aO_2/FIO_2 ratio	Survival (%)
Peek et al. 1998 [24]	100	3.4	66	63
Kolla et al. 1997 [9]	100	4.0	56	54
Morris et al. 1994 [8]	21	–	63	33
Manert et al. 1996 [37]	21	3.2	54	81
Lewandowski et al. 1997 [10]	49	3.4	67	55
Brunet et al. 1993 [38]	23	3.4	84	52
Gattinoni et al. 1986 [30]	43	–	67	49
Wagner et al. 1990 [39]	76	–	–	50
Present series	17	3.5	46	76

imized, and if a slightly lower arterial saturation is accepted than normally.

In the present series 13 of 17 patients survived. Ventilatory "rest settings" were used after stabilization on bypass and high ventilator pressures were avoided in order not to cause further barotrauma to the lungs throughout the entire ECMO runs. Peak inspiratory pressures never exceeded 25 cmH$_2$O during ECMO compared to mean value of 43 cmH$_2$O before ECMO (Table 1). Initially on V-V bypass, when the lungs were unable to contribute to any substantial gas exchange, low arterial saturation values were accepted instead. Great care was taken to sedate the patients minimally and maintain CO$_2$ values at levels so that patients triggered in pressure-supported ventilation [26]. Although not experimentally confirmed, we have gained the impression that pressure-supported spontaneous breaths are superior to intermittent mandatory positive pressure ventilation. This is based mainly on clinical observations when patients on ECMO are subjected to various surgical procedures and require deep anesthesia including muscle relaxation. As soon as spontaneous breaths ceased, gas exchange over the lungs deteriorates, and the patient requires higher extracorporeal flow. When on spontaneous pressure-supported ventilation, the flows can again be decreased.

A randomized multicenter trial [27] has recently shown beneficial effects of ventilation with lower inspiratory pressures and lower tidal volumes than conventional in the treatment of ARDS without ECMO. Mortality was lower among patients ventilated with an initial tidal volume of 6 ml/kg bodyweight than those ventilated with a tidal volume of 12 ml/kg. Inflammatory mediators were more elevated in ARDS patients ventilated with high inspiratory pressures than in patients ventilated with lower pressures in another randomized study [28]. These data together with the present results suggest that a lung protective strategy regarding ventilation is important in the treatment of ARDS.

Four patients in the present series died. In the first patient a stable bypass could never be established. At autopsy massive thrombotic masses were seen in the right atrium and emboli in the pulmonary artery. Although the cannulation may have contributed to pulmonary embolization, the thrombotic masses in the right atrium could hardly be compatible with life for an extended period, an opinion supported by the fact that the circulation was unstable prior to cannulation. The other three patients who succumbed had intracranial complications incompatible with life. They never regained consciousness during ECMO despite withdrawal of sedatives. Computed tomography was therefore performed, and this showed the intracranial complication. Theoretically, cerebral infarction is the only complication that cannot be treated while on ECMO, and a total cerebral infarction is an obvious indication for withdrawal of extracorporeal therapy. Irreversible lung disease has been considered an indication for withdrawal of extracorporeal support [9, 24]. For the same reason, a pre-ECMO ventilatory treatment exceeding 7–10 days is considered a contraindication for ECMO in several centers as the ventilator injury may have caused irreversible lung damage. Seven of the 17 patients in the present series had been ventilated at least 7 days before initiation of ECMO. Two of them subsequently died for the reasons given above. To date, however, we know of no method to determine when the disease is irreversible. Lung biopsy shows only the condition of the tissue being examined, and a diagnosis of irreversibility based on this specimen presupposes that the disease is uniform in all parts of both lungs [29]. The present findings also illustrate that total lack of pulmonary function and pulmonary hypertension does not indicate irreversibility. In 4 of the 17 patients reported the ECMO run time was or exceeded 3 weeks. In all of these patients practically no pulmonary function was demonstrable during the first 2 weeks. In the patient with the longest extracorporeal life support (no. 12), the first signs of any significant gas exchange over the lungs were seen after 46 days on bypass.

Bleeding has been a significant problem during ECMO treatment, with average blood losses up to 1800 ml/day [30], and uncontrolled bleeding has been considered an indication for withdrawal of therapy [8]. Use of heparinized surfaces (Carmeda Bioactive Surface) is also accomplished with a need of substantial blood product transfusions (mean 2.1 U packed red blood cells and 2.5 U fresh frozen plasma) [10]. In another study using nonheparinized equipment the daily need of transfusions averaged 4.6 U red blood cells and 0.5 U fresh frozen plasma (median 3.2 and 0.3, respectively) [31]. Although the exact volume was not given in these reports, the need of transfusion seems to have exceeded 1000 ml/day, suggesting that the volume of an average unit exceeded 250 ml. In the present study the mean daily need for blood products (red blood cells, plasma, and platelets) was only 796 ml. This comparatively low bleeding may be explained by the combination of active surgery and the fact that coagulation parameters were monitored daily, and that the circuits were changed when there were signs of intravascular (intracircuit) coagulation and/or fibrinolysis.

Patient complications demanding surgical intervention were seen in several of the patients. Three patients were subjected to thoracotomies due to hemothorax. Although one patient required reoperation due to continued bleeding, the hemothorax was eventually controlled in all cases, and the surgical procedures well tolerated by all patients. From our experience therefore, fear of bleeding complications should not prevent the patients from having necessary surgical procedures.

In the multicenter study on hospital survival rates in patients with ARDS reported by Vasilyev et al. [2] there

were 152 patients with a PaO_2/FIO_2 ratio of less than 100. Only 29 of these patients survived. Provided that their patient group was similar to ours, the difference in survival between "conventional" treatment according to the different centers' protocols (19.1%) and ECMO treatment according to the protocol described in our present report (13/17, 76%) is highly significant ($p < 0.0001$, χ^2 test). Standardized treatment protocols for ARDS including ECMO have also shown a high survival [10, 32]. A prospective randomized controlled trial similar to that performed in neonates [33] is necessary definitely to evaluate whether ECMO for ARDS in adult patients is life saving and will shortly be initiated [34].

Follow-up investigations regarding pulmonary function, physical performance, and quality of life of the 13 surviving patients in the present material will be performed. Experience reported from other centers, however, indicates that long-term survivors after ECMO have an almost equal quality of life as survivors from ARDS without ECMO and as control patients [35].

ECMO is a highly invasive procedure and should only be used when so-called conventional treatment fails. V-A is more invasive than V-V bypass as it carries the potential risk of infusing arterial emboli. Furthermore, V-A bypass involves ligation of the right common carotid artery in order to infuse to oxygenated blood in the aortic root. Before ligation we normally clamp the artery and measure the pressure above the clamp to ensure an adequate collateral circulation, either through the circle of Willis or via the right external carotid artery. In the present series V-A ECMO was used only in cases of hemodynamic instability or transportation on bypass. In none of the nine patients on V-A bypass were there any neurological complications which could be attributed to the carotid ligation or arterial embolism. The four nonsurvivors in the overall series were all initially on V-V bypass (one was eventually converted to V-A). Bleeding complications are among the most common complications in ECMO [36] but can generally be managed as outlined above. An immediate and aggressive approach is mandatory even if it involves a major surgical procedure. Extracranial bleeding should not be regarded as an indication for withdrawal of ECMO.

In conclusion, it has been shown that a high survival rate, far exceeding that which is expected with conventional therapy, can be obtained in adult patients with severe ARDS using ECMO and spontaneous pressure-supported ventilation with minimal sedation. Surgical complications are amenable for surgical treatment during ECMO, and bleeding problems can generally be controlled. It is difficult or impossible to decide when a lung disease is irreversible, and prolonged ECMO treatment may be successful even in the absence of any detectable lung function.

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