Reprinted from ASAIO, January-March 1988
Vol. 11, No. 1

Extracorporeal Circulation in Adult Respiratory Failure

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Adult Respiratory Distress Syndrome (ARDS) is still a significant problem in the ICU. It has been estimated that approximately 50,000 deaths per year occur due to the syndrome in the European Economic Community.[1] In spite of the many new techniques and improvements in management, mortality remains high,[2] ranging from 20 to 90% depending upon series and source.

Severe hypoxemia is the major pathophysiologic trait of the condition, and mechanical ventilation with positive end expiratory pressure has emerged as the standard treatment. Following the discouraging results of the US Extracorporeal Membrane Oxygenation (ECMO) study,[3] we began treating the most severe cases of ARDS with extracorporeal CO_2 removal ($ECCO_2R$).[4] In this article we will summarize the rationale for its use and the clinical experience in 55 patients treated from July 1979 to December 1986.

Goals of ARDS Therapy

Because ARDS invariably complicates various disease processes, effective treatment of the syndrome requires the resolution of the original underlying disease. Survival, however, depends upon supportive measures aimed at providing adequate gas exchange while avoiding further damage to the lungs and other organ systems.[5] Mechanical ventilation in its various forms is presently the most common treatment for ARDS, but mechanical ventilators are not "oxygenators," but simply pumps that move air in and out of the patient's lungs; hence, they mainly control CO_2 elimination rather than oxygenation. Airway pressure and FiO_2 are indeed the main determinants of oxygenation[6]; mechanical ventilation can be seen as a rather indirect approach to the problem of ARDS hypoxemia.

Nonhomogeneity of Lung Tissue in ARDS: Therapeutic Implications

Pathophysiologic studies indicate that ARDS stems from an initial diffuse lung injury, manifested at first as an increased permeability leading to interstitial edema.

In full blown ARDS, however, available evidence suggests an evolution towards a nonhomogeneous pattern in which different kinds of lesions occur concomitantly in the same lung (e.g., fibrosis, alveolar and/or interstitial edema, vascular occlusion, focal (secondary) sepsis). Computerized tomographic studies[7] show the presence of relatively "normal" areas interspersed with well defined lung densities, mainly localized in the dependent lung fields.[8]

Gas exchange studies also support the concepts of "dense" nonventilated regions (true shunt)[9,10] coexisting with normal gas exchanging zones (high or normal ventilation/perfusion ratio). The mechanical ventilator will then preferentially hyperventilate the healthier and more compliant lung regions and very high tidal volumes and pressures will have to be used, since both the overall gas exchange efficiency and compliance will be decreased by the reduced size of the efficient parenchyma. The side effects of mechanical ventilation may, however, be very unfavourable; experimental work has shown that high airway pressures impair lung function[11] and cause lung edema[12] and atelectasis, resulting in respiratory failure. Even high volume ventilation without the use of positive pressure has been proven to cause severe lung damage.[13] Mechanical ventilation, therefore, can hardly be thought of as the ideal supportive measure for ARDS; the side effects may well offset the possible gas exchange benefit. Indeed, the effects of the original disease process cannot be separated from the ones of ventilatory support.[14]

Rationale for $ECCO_2R$

In 1977 Kolobow and Gattinoni introduced the concept of Extracorporeal CO_2 removal ($ECCO_2R$) as opposed to extracorporeal oxygenation.[15] Since $PaCO_2$ could then be controlled at will by the extracorporeal lung, ventilation could be set at any desired combination of tidal volume and frequency, down to complete apnea.[16]

A clinical protocol to evaluate the clinical feasibility of $ECCO_2R$ in severe ARDS patients was started in Milan. The goal was to reduce the motion of the diseased lung to a minimum; ventilation was almost completely avoided, although 3 to 5 "sighs" per minute were provided to maintain lung volume (low frequency positive pressure ventilation, LFPPV).

Patients and Methods

We elected to admit to the study only those patients with a higher than 90% chance of dying. The entry criteria were basically the same as those used in the NIH ECMO study ($PaO_2 < 50$ mmHg at FiO_2 0.6, PEEP 5 cm H_2O or higher)[17];

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Supported in part by the National Research Council (CNR-Rome, Italy) Grants n 84.02098.57 and n 85.01487.57.

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Table 1. Hemodynamic Parameters Before Bypass

	Survivors	vs.	Nonsurvivors
CI (L/min/m)	4.32 ± 1.2	(n.s.)	4.61 ± 1.14
PAP (mmHg)	31.12 ± 11.05	(n.s.)	31.52 ± 9.45
WP (mmHg)	10.08 ± 6.25	(n.s.)	11.04 ± 4.34
PVR (dyne/cm^{-5}/sec)	281.32 ± 190.46	(n.s.)	249.43 ± 129.94
PVC (mmHg)	9.33 ± 6.61	(n.s.)	7.97 ± 4.31
SVR (dyne/cm^{-5}/sec)	1072.1 ± 489.85	(n.s.)	882.63 ± 337.66
SAP (mmHg)	87.02 ± 17.54	(n.s.)	81.48 ± 18.54

Mean ± SD; t-test for unpaired data.
n.s. = not significant.

in adjunct a total static lung compliance lower than 30 ml/cm H_2O was required. A detailed description of the admission and exclusion criteria has recently been reported.[18]

Each patient was evaluated for the presence or absence of six major risk factors, defined herein as "organ system dysfunction," according to the following criteria: liver dysfunction (bilirubin level > 2 mg/dl and/or serum transaminase levels 3 times normal); renal dysfunction (blood creatinine > 2 mg/dl); CNS dysfunction (coma); coagulation disorders; host defense failure (sepsis with positive blood cultures); cardiovascular failure (when vasoactive drugs were required to support systemic perfusion).

Technique

Extracorporeal CO_2 removal

Veno-venous bypass was instituted. As a rule blood was drained into a collapsible reservoir, pumped by a roller pump through two SCI-MED KOLOBOW membrane lungs (ML) mounted in series (total surface area 7–9 m^2), and then returned to the patient's venous system. A humidified air-oxygen mixture was aspirated through the ML gas compartment at flow rates up to 40 L/min.$^{-1}$

Vascular Access

In 14 cases we used femoro-jugular bypass that required two separate cutdowns and additional distal cannulation of both the internal jugular and femoral veins. Later, a double lumen catheter was designed that provided vascular access through single cannulation of the femoral vein (12 cases). Of late (23 cases), we have resorted to a sapheno-saphenous cannulation, thereby minimizing surgical trauma and cannulation time, and eliminating distal drainage of the venous system of the leg. Six miscellaneous vascular accesses were used in those cases in which the anatomy of the patient did not allow for any of the standard cannulation techniques.

Table 2. Respiratory Parameters Before Bypass

	Survivors	vs.	Nonsurvivors
VE (ml/kg/min)	236.15 ± 75.35	(n.s.)	233.65 ± 64.87
FiO_2	0.74 ± 0.21	(n.s.)	0.83 ± 0.14
PEEP (cm H_2O)	10.38 ± 5.79	(n.s.)	12.39 ± 3.71
PaO_2 (mmHg)	58.84 ± 19.6	(n.s.)	60.24 ± 18.31
$PaCO_2$ (mmHg)	43.29 ± 7.86	(*)	55.10 ± 16.43
Qva/Q	49.81 ± 13.05	(n.s.)	52.02 ± 11.15
TSLC (ml/cm H_2O)	26.74 ± 11.79	(n.s.)	24.11 ± 8.83

Mean ± SD; t = test for unpaired data.
n.s. = not significant, * = $P < 0.01$.

Airway Management

The patients were intubated, sedated, and paralyzed throughout the procedure. PEEP ranging between 15 and 25 cm H_2O was applied to keep the lungs inflated between the mechanically delivered "sighs." The ventilator was set in the intermittent mandatory ventilation (IMV) mode, at a mandatory frequency of 3 to 5 breaths per minute; airway peak pressure was limited to between 35 and 45 cm H_2O. Because oxygen was consumed (apneic diffusion) during the long expiratory time, a constant oxygen flow at a rate sufficient to compensate for oxygen consumption and airway leaks was provided via a small catheter advanced through a side port connector to the level of the carina.

Anticoagulation

Immediately before insertion of the catheters, a bolus of 100 U/kg of heparin was given. The circuit priming solution was heparinized with 2–4 U/ml. A continuous infusion of heparin subsequently maintained the activated clotting time (measured either with RACT or Hemocron tubes)[19] at 1.5 to 2 times the normal value.

Disconnection from Bypass

During the procedure our aim was to maintain gas exchange with the lowest FiO_2 and airway pressure tolerated. After consistent improvement occurred, muscle relaxation was suspended and trials of CPAP were started. $ECCO_2R$ was progressively reduced by decreasing the gas flow ventilating the ML, and bypass was disconnected when the patient was able to tolerate either CPAP or IMV for at least 6 hours.

Results

Of the 55 patients enrolled in this study whose expected mortality rate was higher than 90%, 26 survived. The prognostic value of the ECMO entry criteria has recently been reconfirmed.[20]

Some relevant data obtained immediately before bypass are shown in **Tables 1** and **2;** of these, only $PaCO_2$ showed a significant difference between survivors and nonsurvivors. The average length of time on bypass was 192 hours (range 9–766 hrs), at an average blood flow of 1.5–2.0 L/min, corresponding to 25 to 30% of the cardiac output.

The target anticoagulation level was achieved by the use of 15–30 U/kg/hr. The platelet count showed a progressive decrease during the procedure, dropping to approximately 50% of the baseline value after the first 24 hours and then tapering over one week's time to approximately 30%.[21]

Tables 3 and **4** indicate selected hemodynamic and respi-

Table 3. Time Course of Hemodynamic Parameters During Bypass

		Baseline	20%	40%	60%	80%
Survivors	(n = 24)	4.33 ± 1.23	3.70 ± 1.14	3.88 ± 0.98	3.94 ± 0.95	4.19 ± 1.17
CI ($L/min^{-1}/m^{-2}$)		(n.s.)	(n.s.)	(n.s.)	(n.s.)	(n.s.)
Nonsurvivors	(n = 28)	4.66 ± 1.12	4.30 ± 1.11	4.33 ± 0.91	3.94 ± 1.16	3.87 ± 1.11
Survivors	(n = 25)	31.12 ± 11.05	27.44 ± 6.13	27.52 ± 7.02	24.84 ± 7.05	24.84 ± 6.76
PAP (mmHg)		(n.s.)	(n.s.)	(*)	(†)	(†)
Nonsurvivors	(n = 29)	31.52 ± 9.45	29 34 ± 9.08	32.21 ± 9.18	33.10 ± 7.23	33.45 ± 9.49
Survivors	(n = 26)	87.02 ± 17.54	89.04 ± 18.49	89.65 ± 16.05	88.42 ± 12.03	88.00 ± 9.91
SAP (mmHg)		(n.s.)	(n.s.)	(n.s.)	(n.s.)	(†)
Nonsurvivors	(n = 29)	81.48 ± 18.54	87.62 ± 16.63	92.86 ± 20.57	80.52 ± 17.32	73.52 ± 15.33
Survivors	(n = 17)	229.94 ± 94.86	233.22 ± 110.94	238.94 ± 109.28	191.83 ± 89.30	204.24 ± 75.85
PVR ($dyne/s/cm^5$)		(n.s.)	(n.s.)	(n.s.)	(n.s.)	(n.s.)
Nonsurvivors	(n = 16)	246.49 ± 142.51	247.66 ± 183.84	252.09 ± 135.64	233.63 ± 81.70	263.27 ± 107.18
Survivors	(n = 17)	1093.2 ± 528.1	1449.9 ± 748.7	1214.5 ± 540.8	1214.6 ± 367.1	1147.0 ± 534.9
SVR ($dyne/s/cm^5$)		(n.s.)	(*)	(n.s.)	(*)	(n.s.)
Nonsurvivors	(n = 27)	863.8 ± 327.6	1037.1 ± 509.1	1067.5 ± 402.7	950.7 ± 387.8	901.2 ± 383.6

Mean ± SD; t = test for unpaired data.
* $P < 0.05$; † $P \ll 0.01$.
CI = cardiac index; PAP = mean pulmonary artery pressure; SAP = mean systemic arterial pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; n.s. = not significant.

ratory parameters at various times during the bypass. By and large, the hemodynamic parameters tended toward normal during the procedure, with a reduction of the pulmonary artery pressure in the survivor group.

Gas exchange data improved consistently in the survivor group, while remaining fairly unchanged in the nonsurvivor group. The ratio of oxygen transfer of the natural lung/total body oxygen consumption (VO_2 nat %) provides the proportion of the body's oxygen need provided by the patient's own lungs, the rest being taken care of by the artificial extracorporeal membrane lung.

At all considered times VO_2 nat % was higher in survivors than in nonsurvivors.

Complications

We did not incur any technical complication dictating the interruption of bypass with the present technique in over 10,500 hours of bypass.

Figure 1 shows the incidence of individual organ system dysfunction before and during bypass, which indicates a tendency toward an increase in concomitant organ dysfunction in extrapulmonary systems.

Table 4. Time Course of Respiratory Parameters During Bypass

		Basal	20%	40%	60%	80%
Survivors	(n = 26)	0.74 ± 0.21	0.56 ± 0.18	0.48 ± 0.14	0.43 ± 0.16	0.44 ± 0.14
FiO_2		(n.s.)	(n.s.)	(*)	(*)	(‡)
Nonsurvivors	(n = 29)	0.83 ± 0.14	0.57 ± 0.17	0.59 ± 0.22	0.57 ± 0.23	0.63 ± 0.23
Survivors	(n = 23)	10.83 ± 5.47	17.17 ± 4.95	18.02 ± 5.35	17.26 ± 4.62	15.91 ± 5.58
PEEP (cm H2O)		(*)	(*)	(*)	(†)	(†)
Nonsurvivors	(n = 28)	12.39 ± 3.71	19.43 ± 4.98	20.46 ± 5.57	21.41 ± 3.94	20.96 ± 5.44
Survivors	(n = 25)	58.56 ± 19.95	94.00 ± 34.48	116.75 ± 52.10	123.36 ± 56.41	112.01 ± 30.25
PaO_2 (mmHg)		(n.s.)	(*)		(‡)	(‡)
Nonsurvivors	(n = 29)	60.24 ± 18.31	77.57 ± 43.59	76.38 ± 30.76	71.34 ± 27.32	73.99 ± 37.30
Survivors	(n = 24)	0.50 ± 0.13	0.40 ± 0.18	0.32 ± 0.17	0.25 ± 0.14	0.25 ± 0.15
Qva/Q		(n.s.)	(*)	(*)	(‡)	(‡)
Nonsurvivors	(n = 29)	0.52 ± 0.11	0.51 ± 0.19	0.50 ± 0.26	0.51 ± 0.24	0.55 ± 0.25
Survivors	(n = 7)		71.53 ± 13.21	76.57 ± .44	82.24 ± 7.33	77.09 ± 11.97
VO_2 nat %				(*)	(*)	(*)
Nonsurvivors	(n = 14)		57.77 ± 17.08	51.19 ± 41.06	54.77 ± 23.09	48.08 ± 33.33

Mean ± SD; t = test for unpaired data.
* $P < 0.05$; † $P < 0.01$; ‡ $P \ll 0.01$.
FiO2 = inspired oxygen fraction; PEEP = positive end expiratory pressure; PaO_2 = arterial partial oxygen pressure; Qva/Q = venous admixture; VO_2 nat % = (oxygen transfer of the natural lung)/(total body oxygen consumption) ×100 (see the result section for details); n.s. = not significant.

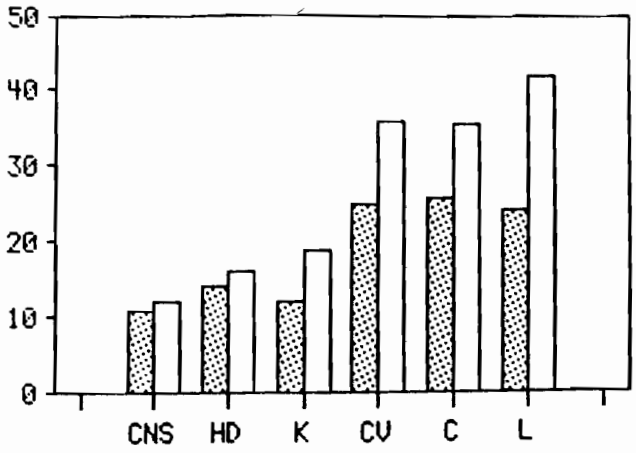

Figure 1. Incidence of individual "organ system dysfunction" (in addition to pulmonary failure) in the patients studied before (dotted bars) and during bypass (solid white). CNS = central nervous system; HD = host defense failure; K = kidney dysfunction; CV = cardiovascular dysfunction; C = coagulation disorders; L = liver dysfunction.

Complications related to bleeding were the most important. The average blood loss (as judged by the amount of transfused blood required to maintain an hematocrit of approximately 35% amounted to 1.37 ± 1.36 L/day (range 0–12.25). Blood sampling, however, represented some 300 ml/day, with bleeding uniformly minor during the first 2 days of bypass, rarely exceeding 1 L/day. With time, bleeding tended to increase, due on most occasions to surgical or other traumatic maneuvers (the most common being the positioning of chest drainage tubes). We performed a thoracotomy during the bypass in eight patients, either to control chest bleeding or a major air leak. In this "surgical" group mean blood loss during the 24 perioperative hours amounted to 6 L. Only one patient of this group survived.

Discussion

With LFPPV-$ECCO_2R$ we achieved a 47% survival rate in a population with an expected mortality rate higher than 90%. Moreover, the technique proved able to maintain a viable gas exchange in all subjects for up to 32 days. When present, the occurrence of major bleeding during the procedure represented a very dangerous complication.

Taking into account that $ECCO_2R$ was always offered as a last resort procedure after CPPV and other nonconventional forms of respiratory support had failed, this result indicates that the use of the technique is advantageous at least in the treatment of the most severely compromised ARDS patients.

Table 5 summarizes most of the worldwide experience with $ECCO_2R$, which totals 89 patients, with an overall survival rate comparable to the one we report here.

To improve patient selection and decrease the overall cost/benefit ratio of the procedure we believe two strategies are possible: 1) Identifying a subgroup of "responder" patients within those who meet the ECMO criteria; and 2) expand the application to a less severe class of patient who meets criteria for an expected mortality rate of approximately 50%.

In an attempt to identify survivors beforehand in those patients meeting ECMO criteria, we compared baseline data (*i.e.*, before bypass) between survivors and nonsurvivors. $PaCO_2$ was the only parameter showing a significant difference and impaired efficiency in CO_2 clearance has already been suggested as an indicator of very advanced disease.[22] In spite of the fact that the survivor and nonsurvivor groups were basically indistinguishable before bypass except for the $PaCO_2$ level, the behavior of gas exchange during the early phase of the procedure (first 24–48 hrs) might be of importance in predicting the final patient outcome. Intrapulmonary shunting and VO_2 nat % show a significant difference between survivors and nonsurvivors at a very early stage of treatment (from 20% of total bypass time on).

Those patients in which CPPV lasted for 7 days or less and in which $PaCO_2$ was still lower than 55 mmHg before bypass comprised 19 of the 26 survivors, while only nine of the 29 nonsurvivors could be classified in this group.

In conclusion, our experience indicates that the possibility of achieving an improved selection criteria for those requiring ECMO, based upon both the length of previous treatment and the $PaCO_2$ obtained during maximal mechanical ventilation, exists.

Research is ongoing in various directions to expand the use of and indications for extracorporeal respiratory support. The novel technology of heparinized circuits[23] could avoid the risk of bleeding and justify the application of a partial $ECCO_2R$ technique (PECOR)[24] to patients unable to sustain spontaneous breathing (CPAP) or low rate intermittent mandatory ventilation (IMV). In doing so we will entirely avoid mechanical ventilation and its related damage. On the other hand, decompensated Chronic Obstructive Pulmonary Disease patients might possibly benefit from the application of low flow extracorporeal support.[25]

Table 5. $ECCO_2R$: Clinical Experience in Different Centers

Center	Country	Number of Cases	Survivors
Milan	Italy	55	26
Marburg[26]	W. Germany	25	13
Dusseldorf[27]	W. Germany	3	1
Paris[28]	France	1	1
Geneva[29]	Switzerland	2	0
Stockolm	Sweden	1	1
Salt Lake[30]	USA	1	1
Christchurch[31]	New Zealand	1	0

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