Extracorporeal Membrane Oxygenation (ECMO) in Neonatal Respiratory Failure

100 Cases

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Extracorporeal membrane oxygenation (ECMO) was used in the treatment of 100 newborn infants with respiratory failure in three phases: Phase I (50 moribund patients to determine safety, efficacy, and risks); Phase II (30 high risk patients to compare ECMO to conventional ventilation); and Phase III (20 moderate to high risk patients, the current protocol). Seventy-two patients survived including 54% in Phase I, 90% in Phase II, and 90% in Phase III. The major complication was intracranial bleeding, which occurred in 89% of premature infants (<35 weeks) and 15% of full-term infants. Best survival results were in persistent fetal circulation (10, 10 survived), followed by congenital diaphragmatic hernia (9, 7 survived), meconium aspiration (44, 37 survived), respiratory distress syndrome (26, 13 survived), and sepsis (8, 3 survived). There were seven late deaths; in follow-up, 63% are normal or near normal, 17% had moderate to severe central nervous system dysfunction, and 8% had severe pulmonary dysfunction. ECMO is now used in several neonatal centers as the treatment of choice for full-term infants with respiratory failure that is unresponsive to conventional management. The success of this technique establishes prolonged extracorporeal circulation as a definitive means of treatment in reversible vital organ failure.

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) is the term used to describe prolonged extracorporeal cardiopulmonary bypass achieved by extra thoracic cannulation under local anesthesia. In this technique a modified heart–lung machine is used to take over part of all of heart and lung function in patients with cardiac or pulmonary failure, allowing the diseased organ to "rest" and recover. The first successful clinical case was reported in 1972,[1] and many clinical trials followed. A multicenter prospective randomized study of ECMO in adult respiratory failure was reported in 1978.[2] Ninety per cent of patients treated with ECMO or conventional ventilation died. However, Gattinoni,[3] using a modified ECMO technique, is currently achieving 50% survival in adult respiratory failure.

Unlike older children and adults, respiratory failure in the newborn is usually caused by immaturity, abnormalities of the airways, or abnormalities of the pulmonary circulation, rather than pulmonary parenchymal disease *per se*. In addition, conventional treatment itself (positive airway pressure and elevated inspired oxygen) is, itself, very damaging to the newborn lung. For these reasons, it was reasonable to expect that ECMO and lung rest could be successful in this group of patients, both as a treatment and a clinical experiment to study life support during vital organ failure. After a series of laboratory studies,[4,5] we began clinical trials of ECMO in 1972, and reported the first successful use of ECMO in newborn respiratory failure in 1975.[6] We continued these trials at the University of California, Irvine, until 1980, and thereafter at the University of Michigan. We reported the results of these trials at regular intervals.[7–9] In this report we review our experience with the first 100 consecutive newborn infants we have treated for respiratory failure with ECMO.

Patients and Methods

We treated 100 newborn infants with ECMO between 1973 and January 1986. During that time, over 3000 infants were treated for respiratory failure in the three neonatal centers where this study was done. Many patients were referred in critical condition specifically for ECMO, including 68 of the 100 patients ultimately treated with ECMO. The management of neonatal respiratory failure

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has changed during this 13-year period but has always included intubation and mechanical ventilation and pharmacologic manipulation of vascular resistance and cardiac output as necessary. Airway pressure and oxygen concentration were maintained at the minimum levels necessary to achieve adequate gas exchange. Pharmacologic paralysis was used if spontaneous breathing or assisted ventilation was not adequate to achieve CO_2 removal. The management of patients was carried out under the direction of the neonatologist investigators and their colleagues. More than two thirds of infants referred from other neonatal centers for ECMO recovered without need of ECMO, following this management protocol.

The technique of ECMO has changed somewhat over this 13-year period but always included cannulation of the right atrium *via* the right internal jugular vein under local anesthesia, venous drainage by siphon to a small collapsible bladder that serves to servoregulate a roller pump, a membrane lung to exchange oxygen and carbon dioxide, small heat exchanger, and return of arterialized blood to the aortic arch *via* the right common carotid artery (for venoarterial bypass) or to the venous circulation (for venovenous bypass). Heparin was given continuously to achieve a whole blood activated clotting time approximately twice normal, and platelets were given as necessary to maintain the platelet count greater than 50,000 m^2. Extracorporeal flow was established to totally support gas exchange (approximately 120 ml/kg/min), and ventilator settings were reduced to "lung rest" conditions (typically FiO_2 0.3, ventilator rate 10, airway pressure 20/4). When lung recovery began, extracorporeal flow was decreased and ECMO was discontinued when gas exchange was adequate on rest ventilator settings. Patients were maintained alert and awake during the ECMO procedure. The full details of the procedure and patient management during ECMO are discussed in detail elsewhere.[10-13]

In this series the indications, case selection, and expectations of treatment evolved in three phases corresponding to the stage of clinical research. Results will be described for these phases and for the series overall (Table 1). During Phase I, ECMO was used when all other therapy had failed and the neonatologist considered the infant moribund. This condition was quantitated by objective methods, particularly the newborn pulmonary insufficiency index (NPPI).[14] The clinical research project was to evaluate the safety and efficacy of the technique. During Phase II, we conducted a prospective controlled randomized study[15] following high mortality risk critieria and used the same criteria as the indication for ECMO in patients who did not qualify for the randomized study. We are currently in Phase III, in which ECMO is used as treatment for all patients if mortality risk is 80% or greater, with the expectation of routine survival. Patients who meet specific criteria are randomized to ECMO or continuing ventilator management when mortality risk is 50%, comparing morbidity and expenses. This entire project has been supported by grants from the National Institutes of Health since 1972.

Results

Extracorporeal flow sufficient for total gas exchange was routinely achieved, providing total respiratory support. During lung rest, air leaks healed, the pulmonary artery pressure decreased, and lung function returned in most patients. Seventy-two patients survived, including 54% in Phase I, 90% in Phase II, and 90% in Phase III. The outcome for each phase is listed in Table 2, and the entire series is summarized, by diagnosis, in Tables 3–6. The pathophysiology of newborn hypoxemia usually includes pulmonary arteriolar spasm, high pulmonary vascular resistance, and right-to-left shunting *via* the ductus arteriosus and foramen ovale (so-called persistent pulmonary hypertension of the newborn or persistent fetal circulation). This occurred as an isolated entity in ten patients and was also present in all patients with congenital diaphragmatic hernia, sepsis, and meconium aspiration, and in many patients with respiratory distress syndrome. During Phase I, it became obvious that intracranial bleeding was rare in full-term infants and common in very premature infants. A summary of the results by gestational age and birth weight is shown in Table 7. Prematurity (<35 weeks gestational age) rather than birth weight was the critical factor associated with intracranial bleeding.

The average time on ECMO was 93.2 hours. Technical procedures and complications are listed in Table 8. None of the technical complications was a direct cause of mortality, but stopping ECMO to change an oxygenator or ruptured tubing often caused physiologic instability.

Patient complications and procedures are listed in Table 9. Because of systemic heparinization, bleeding complications were the most common. Intracranial bleeding occurred primarily in premature infants. Some oozing at the cannulation site occurred in almost all patients; major, life-threatening bleeding occurred in 11. Bleeding was managed by lowering the heparin dose and giving platelets, which may lead to clotting in the circuit, particularly the membrane lung. We did not recognize any episodes of thromboembolism. Seizures can be difficult to diagnose in the newborn; obvious seizures occurred in 24 patients.

When the pulmonary vasospasm relaxes, recovery of lung function begins. Flow through the ductus reverses (becomes left to right), and the ductus usually closes within 24 hours. The ductus remained patent with major left to right shunting in 20 patients. Ductus ligation during ECMO was done in 16, without mortality related to the operation. Other major operations during ECMO included repair of total anomalous pulmonary venous

TABLE 1. *The Three Phases in the Development of Neonatal ECMO Described in This Report*

	I	II	III
Cases	1–50	51–80	81–100
Dates	1/73–2/82	3/82–11/84	12/84–1/86
Case selections	100% mortality Neonatologist NPII	80–100% mortality Specific criteria	50–80% mortality Oxygenation index
Contraindications	<1 kg Bulging fontanelle	<1 kg >10 d ICB 2+	<2 kg >10 d ICB
Mode of bypass	VA	VA + VV	VA + VV
Applied as treatment	Rescue	High risk of dying	High risk of morbidity
Clinical research	Safety Efficacy	Prospective random survival	Prospective random morbidity
Survival	54%	90%	90%

VA = venoarterial; VV = venovenous; ICB = intracranial bleeding.

drainage (TAPVD, 1 patient), pulmonary resection for arteriovenous malformation (1 patient), and thoractomy for control of bleeding (3 patients).

Cannulation is always an emergency and can be difficult, particularly if the operation is rushed because of patient instability. Hypoxic cardiac arrest requiring cardiopulmonary resuscitation occurred during cannulation in four patients. Several other patients had a cardiac arrest before the cannulation operation was begun, and the procedure was aborted (all died). Decannulation was also done at the bedside under local anesthesia. The access vessels were ligated. There were no major complications related to decannulation, or vessel ligation, but it is important that brief paralysis was induced to minimize the chance of air embolism.

Cardiovascular complications included systemic hypertension requiring vasoactive drugs (5), hemopericardium with tamponade (3), and global myocardial dysfunction (1). Renal failure was treated with hemodialysis in six (all died). Continuous hemofiltration[16,17] was done in four patients for renal failure or fluid overload. This procedure was very successful in removing excessive extracellular fluid, and we use it freely now for symptomatic fluid overload.

TABLE 2. *Results of ECMO in 100 Neonatal Respiratory Failure Patients, N (Survivors)*

	I	II	III	Overall
MAS	24 (17)	12 (12)	8 (8)	44 (37)
RDS	16 (6)	7 (5)	3 (2)	26 (13)
PFC	2 (2)	4 (4)	4 (4)	10 (10)
CDH	3 (1)	3 (3)	3 (3)	9 (7)
Sepsis	4 (1)	2 (1)	2 (1)	8 (3)
Other	1 (0)	2 (2)	0 (0)	3 (2)
Overall	50 (27)	30 (27)	20 (18)	100 (72)

MAS = meconium aspiration syndrome; CDH = congenital diaphragmatic hernia; RDS = respiratory distress syndrome; Sepsis = neonatal strep sepsis; PFC = persistent fetal circulation.

Pulmonary recovery during ECMO was incomplete in eight patients, and ECMO was discontinued at high ventilator settings (rate > 60, peak inspiratory pressure > 30, $FiO_2 > 0.6$). These infants had the radiologic and clinical findings of bronchopulmonary dysplasia (BPD), which was evident in most cases before ECMO was begun. The subsequent clinical course was typical for BPD. Three ultimately died and five recovered. On the other hand, since some infants with signs of BPD pre-ECMO recovered lung function quickly, BPD cannot be said to be an absolute contraindication.

Other complications included an episode of sudden unexplained cardiac arrest (SIDS) in one infant just before hospital discharge, femoral thrombosis from an umbilical artery cather, an asymptomatic atrial thrombus diagnosed by echo cardiography, and late onset hydrocephalus (2).

Venovenous bypass is capable of total gas exchange support[18] and has the advantage of avoiding carotid artery ligation. Venovenous bypass was used in 16 patients, 13 jugular to femoral (reported elsewhere[19]) and three with the Kolobow tidal flow system.[20] Although venovenous bypass is feasible, the advantages do not outweigh the disadvantages at the present time.

Follow-up on the 72 survivors ranges from 3 months to 11 years and has been reported in part elsewhere.[21,22] There have been seven late deaths: three due to unresolved BPD or pulmonary hypoplasia, one due to congenital myopathy, one following revision of TAPVD repair, and two with severe irreversible brain damage. Of the 72 infants, 45 (63%) are normal or near normal. Twelve (17%) had major neurologic dysfunction and developmental delay. Eight had pulmonary dysfunction (needed supplemental O_2 at the time of hospital discharge), which resolved in two but not in six (8%). Apparently, poor outcome was

TABLE 3. *Results in Patients with a Primary Diagnosis of Meconium Aspiration Syndrome*

Chron #	Series #	Sex	BW	GA	Age ECMO	Time ECMO	Mode	Complications	Outcome	Comments
1	1	M	4.7	41	40	1	VA	ICB, HE	D	
4	2	M	2.6	42	33	72	VA	0	L	
7	3	M	5.2	45	19	69	VA	ICB, S, Di	D	
8	4	F	3.4	40	22	22	VA	ICB, DI	D	
10	5	M	3.4	43	19	53	VA	0	L	
12	6	F	3.6	40	75	71	VA	S, Ox	L	
15	7	M	3.7	42	10	78	VA	S, Ox, Di, B	D	Brain edema
16	8	M	3.2	42	14	169	VA	Ox, S, B	D	PDA, brain edema
19	9	F	4.2	42	15	23	VA	ICB	D	PDA Lig.
20	10	M	3.9	40	39	67	VA	0	L	
21	11	F	3.8	40	24	43	VA	ICB	D	PDA
22	12	F	3.0	40	21	72	VA	0	L	
24	13	F	3.2	41	45	108	VA	S	L	Arrest pre-ECMO
25	14	F	3.1	42	63	118	VA	S	L	
26	15	F	3.3	40	11	56	VA	ICB, S	L	Late brain cyst, DD
27	16	M	4.0	42	29	87	VA	0	L	
30	17	M	4.1	40	60	45	VA	0	L	
33	18	M	3.7	42	12	92	VA	S	L	
36	19	M	3.6	35	33	67	VA	0	L	
37	20	M	3.7	44	26	58	VA	S	L	
39	21	F	3.6	40	16	83	VA	0	L	PDA Lig.
43	22	M	3.3	40	52	72	VA	B	L	
47	23	M	4.9	40	29	102	VV	S	L	Perinatal asphyxia, CP, DD
49	24	F	3.9	41	24	113	VV	Ox	L	Thoracotomy for bleed
52	25	F	3.0	42	56	107	VV–VA	B	L	
56	26	M	4.5	42	135	81	VV	0	L	Late SIDS, S, CP
59	27	M	3.2	42	37	58	VV	ICB, S	L	Late death, DD
65	28	M	2.8	41	13	104	VA	0	L	Arrest pre-ECMO, congenital myopathy, late death
62	29	M	3.7	42	251	103	VV	Ox, BP	L	
66	30	M	3.1	41	23	34	VA	0	L	
70	31	M	4.3	42	19	174	VA	Ox, S	L	
73	32	M	3.9	40	28	70	VA	BL	L	
74	33	M	3.7	39	18	120	VA	S, BL, Ox	L	PDA Lig., DD
75	34	F	3.6	44	70	127	VV–VA	B, P, Ox	L	L frontal infarct, DD
77	35	F	3.0	44	54	55	VA	BL	L	Arrest pre-ECMO
79	36	M	4.0	40	22	120	VA	0	L	
83	37	M	2.9	40	64	171	VV–VA	Ox	L	
85	38	M	3.2	38	36	91	VA	0	L	
86	39	M	4.0	40	39	53	VA	0	L	
89	40	F	2.3	38	61	191	VA	0	L	
90	41	M	3.8	43	70	91	VA	0	L	
92	42	F	4.2	41	60	44	VA	0	L	
96	43	F	3.4	42	167	190	VA	BP	L	
99	44	F	3.7	41	175	89	VA	0	L	

The following abbreviations apply for Tables 3–10: ICB = intracranial bleeding; Diss = dissection; HE = heat exchanger; S = seizure; Di = dialysis; BL = blood leak; Ox = oxygenator change; Hf = hemofilter; P = pericardial tamponade; Ca = cardiopathy; L = lived; D = died; CP = cerebral palsy; DD = developmental delay; BP = hypertension; BPD = bronchopulmonary dysplasia.

usually caused by events that occurred before ECMO was begun. However, some infants at high risk for brain damage (low Apgar scores, perinatal cardiac arrest, prolonged profound hypoxia, and prolonged fetal distress) have normal mental function; thus, definitive predictors of outcome cannot be determined yet (Table 10).

Discussion

Extracorporeal circulation for newborn respiratory failure was attempted by Rashkind et al.,[23] Dorson et al.,[24] and White et al.,[25] establishing the groundwork for this series. As the Phase I study progressed, the technique was shown to be feasible, then effective (ECMO provided gas exchange, allowing lung rest), then safe (serious complications and death were less common than that of the primary disease). As these results were published, similar studies were carried out with success in Pittsburgh[26] and Richmond,[27] and ECMO is now offered as treatment in at least ten major neonatal centers.[28] The clinical research component of Phase II documented that survival in in-

TABLE 4. *Results in Patients with a Primary Diagnosis of Respiratory Distress Syndrome*

Chron #	Series #	S	BW	GA	Age ECMO	Time ECMO	Mode	Complications	Outcome	Comments
5	1	M	1.8	35	77	70	VA	0	L	
6	2	F	1.6	31	16	8	VA	ICB, Diss	D	
9	3	M	1.1	30	27	90	VA	ICB, Ox, S	D	PDA Lig.
18	4	M	1.9	32	37	53	VA	ICB, S	L	CP
23	5	F	1.9	32	24	106	VA	ICB, Ox, S	D	PDA Lig.
28	6	M	1.9	33	69	40	VA	ICB	D	
29	7	M	1.5	32	174	219	VA	ICB, S, Di	D	PDA Lig. pre-ECMO
31	8	M	1.0	28	17	20	VA	ICB, S, HE	D	
32	9	M	2.4	36	39	101	VA	0	L	PDA Lig.
34	10	F	1.5	34	46	122	VA	S	L	PDA Lig.
38	11	F	2.5	36	18	142	VA-VV-VA	0	L	PDA Lig., late ICB, hydrocephalus
41	12	M	3.3	36	50	100	VA	S, B, Di	D	Renal agenesis
42	13	M	3.3	36	114	61	VA	0	L	
46	14	M	1.2	30	34	24	VA	ICB, S, Ox	D	
48	15	M	1.5	29	204	0	VV	Diss	D	
50	16	M	1.4	33	84	198	VA	ICB	D	
51	17	M	2.7	38	78	45	VV	HE	L	
54	18	M	1.6	32	42	105	VV-VA	Ox, ICB, S	D	
57	19	M	2.1	30	26	146	VA	HE, Di, B, ICB, Ox	D	PDA Lig.
61	20	M	3.0	36	141	123	VA	BP	L	BPD, CP
63	21	M	2.1	33	220	151	VA	ICB	L	BPD, DD, late death
67	22	M	3.6	36	85	113	VA	0	L	
80	23	M	2.6	35	320	265	VA	BL	L	PDA Lig., BPD, late hydrocephalus
81	24	F	2.5	37	156	100	VA	S	L	
87	25	M	2.3	33	40	165	VA	ICB, Ox, HF	D	
95	26	M	2.8	36	51	78	VA	Ox, BL	L	

fants >2 kg is better with ECMO than with conventional ventilation.[15] The statistical method used for that study has generated some interesting controversy.[29,30] The indications and contraindications are fairly well defined, the technique is standardized, and general application is appropriate (Phase III). The clinical research in Phase III addresses the morbidity and cost effectiveness of the procedure.

Patient Selection

In the early stages of Phase I study of a technique with inherent risks, it is appropriate to begin with patients who have failed all conventional treatment. However, this will inevitably lead to a high failure rate, as it did in this study (six of the first ten died); thus, the technique cannot be fully evaluated until patients with a reasonable chance of survival are studied. As more patients survived, it was obvious that the lung lesion in the newborn was often reversible, and we began to enter patients as soon as moribund status was determined (rather than hours or days later). In Phase II we used a specific, rather complex, set of criteria that defined 80% mortality risk.[15] These criteria were developed for the prospective randomized study and were used for all patients. We had hoped to begin ECMO (or randomize) when respiratory failure had progressed to that point, but many patients were referred one or more days after 80% mortality risk had been passed; therefore, the Phase II patient group is best described as 80–100% mortality risk. The same is true of Phase III, although the current clinical research protocol includes only those patients who begin in stable condition and progress to 50% mortality risk under our care. Several methods have been proposed to define mortality risk. We are currently using the oxygenation index[31]: mean airway pressure $\times$ FiO_2 $\times$ 100 $\div$ postductal PaO_2. In our hospital, a value consistently over 25 defines 50% mortality, and over 40 defines 80% mortality.

The patient selection process must detect high risk patients but exclude those with no reasonable chance of recovery or normal life. In Phases I and II we excluded infants less than 1 kg birth weight and those who had congenital abnormalities or conditions incompatible with normal life. Irreversible bronchopulmonary dysplasia or pulmonary hypoplasia in also a contraindication, but "irreversible" is difficult to define.

In Phase III we consider the absence of a "honeymoon period" ($PaO_2 > 60$) to be evidence of hypoplasia in con-

TABLE 5. *Results in Patients with a Primary Diagnosis of Persistent Fetal Circulation and Congenital Diaphragmatic Hernia*

Chron #	Series #	S	BW	GA	Age ECMO	Time ECMO	Mode	Complications	Outcome	Comments
2	1 PFC	F	3.3	40	20	148	VA	0	L	PDA Lig., CP
45	2	F	3.0	37	176	67	VA	0	L	
51	3	M	2.6	36	56	33	VV	0	L	ICB post-ECMO
55	4	M	3.4	38	178	70	VV-VA	0	L	BPD, DD
60	5	F	2.7	36	70	63	VV	0	L	
76	6	M	2.9	41	93	79	VA	BL, B	L	
82	7	M	2.8	40	164	201	VA	Ox, HF	L	PDA Lig., BPD, late death
84	8	F	2.7	37	83	184	VV-VA	P, B, Ox, BL	L	PDA Lig., thoractomy for bleed
93	9	M	2.9	39	168	188	VA	BP, Ca	L	BPD, DD
100	10	M	3.7	39	113	104	VA	0	L	
11	1 CDH	F	2.7	35	26	126	VA	S	D	PDA Lig., ICB after ECMO
13	2	M	2.7	37	46	175	VA	0	L	PDA Lig., BPD, late death
14	3	M	3.9	40	35	7	VA	0	D	PDA, brain edema, arrest pre-ECMO
64	4	M	3.3	38	36	50	VA	Ox	L	Arrest pre-ECMO, DD
69	5	F	3.6	41	35	104	VA	0	L	
71	6	M	2.8	38	14	140	VA	0	L	
88	7	F	2.8	36	131	228	VA	P, HF, B	L	PDA Lig., thoracotomy for bleed, BPD, CP
91	8	F	3.1	37	31	148	VA	Diss	L	
97	9	M	2.8	38	34	156	VA	BP	L	

PFC = persistent fetal circulation; CDH = congenital diaphragmatic hernia.

genital diaphragmatic hernia, hence a contraindication. Similarly, we consider mechanical ventilation over 7 days a relative contraindication and over 10 days an absolute contraindication. Anomalies or conditions incompatible with normal life remain a contraindication. Patient selection based on brain function and intracranial bleeding are discussed below.

Complications

Intracranial bleeding (ICB) is a common complication of respiratory failure in the premature infant and became obvious as a major problem in Phases I and II. The diagnosis of intracranial bleeding pre-ECMO was based on physical examination of the fontanelle for the first 40 pa-

TABLE 6. *Results in Patients with a Primary Diagnosis of Neonatal Sepsis or Other Problems*

Chron #	Series #	S	BW	GA	Age ECMO	Time ECMO	Mode	Complications	Outcome	Comments
3	1	F	3.4	37	44	6	VA	B	D	PDA Lig., bowel Perf, brain edema
35	2	F	2.9	36	10	189	VA	0	L	PDA Lig.
17	3	M	2.2	36	12	19	VA	ICB	D	
40	4	M	1.8	32	10	24	VA	ICB	D	PDA
68	5	F	1.1	27	12	20	VA	ICB	D	
72	6	M	2.2	34	26	38	VA	ICB	L	DD, late death
94	7	F	3.0	36	165	64	VA	Atrial thrombosis	L	
98	8	M	3.6	40	30	78	VA	ICB, HF	D	
44	1	F	1.2	30	11	6	VA	4 anomal, ICB	D	
58	1	F	2.1	35	23	142	VA	TAPVD	L	Late death
78	1	M	4.2	44	29	8	VV	Pulm AVM, OX	L	

TABLE 7. *Results of ECMO in 100 Patients Based on Birth Weight (BW) and Gestational Age (GA)*

GA	BW	N	ICB	Survived
<35 wk	<2 kg	15	13 ICB	1 (DD)
			2 No ICB	1
<35 wk	>2 kg	4	4 ICB	2 (2 DD, 2 late deaths)
35 wk+	<2 kg	1	0	1
35 wk+	>2 kg	80	12* ICB	4 (2 DD, 1 late death)
			68 No ICB	63 (4 late deaths), 1 DD

* Three post-ECMO.

tients, and some infants in that group undoubtedly had small bleeds before ECMO was begun. Cranial ultrasound was used to screen patients in Phase II, and infants with grade 2 or greater hemorrhage were excluded. ICB still occurred, however, in infants under 35-week gestation and/or with grade 1 hemorrhage pre-ECMO. Consequently, in Phase III any evidence of intracranial hemorrhage and gestational age under 35 weeks are currently considered contraindications. (This will be re-evaluated when systemic anticoagulation is not required.) ICB during ECMO is reviewed in detail elsewhere.[32,33]

The incidence of other major bleeding in Phases II and III patients was 12%. We believe that the frequent use of whole blood activated clotting time (specifically the BaSon method[34]) is essential to monitor heparin effect and titrate the continuous infusion. Methods using other activators can be misleading. If bleeding persists when the ACT is under 200 seconds and the platelet count is >50,000, aggressive operative management is appropriate. In this series, thoracotomy was required in three patients for bleeding, with successful results. ECMO without systemic anticoagulation has been successful in the laboratory[35] and should be ready for clinical use soon.

Technical Considerations

ECMO differs from operating room cardiopulmonary bypass in the cannulation site, the absence of a reservoir and direct gas interfaces, the method of anticoagulation, and the temperature. The fact that near-total bypass can be carried out for days at a time provides some lessons for the cardiac surgeon. Cannulation *via* the neck vessels before anesthesia is induced in the newborn avoids hemodynamic instability and is recommended for operating room use in these small patients.[36] The patients' venous circulation is used as the reservoir, eliminating the most thrombogenic component of the heart–lung machine. The reservoir is primarily a safety measure, and necessary in the operating room, but the gas interface should be excluded for long bypass runs. Infinite anticoagulation is needed for stagnant blood in the heart and lung during total bypass, but this can be achieved with local heparin irrigation. Systemic heparin dose could be much lower than that usually used. Hypothermia is standard practice for several reasons, but it contributes to cellular injury and coagulopathy and is not necessary. Some of the best results in cardiac surgery come from centers where hypothermia has never been used.[37]

TABLE 8. *Technical Complications and Procedures, N (Died)*

	I	II	III	Overall
Oxygenator failure	7 (5)	8 (3)	5 (0)	20 (8)
Blood leak		4 (0)	3 (0)	7 (0)
Heat exchanger	2 (2)	2 (1)		4 (3)
Dialysis	5 (5)	1 (1)		6 (6)
Hemofilter		1 (1)	3 (0)	4 (1)
Venovenous	4 (1)	10 (1)	2 (0)	16 (2)

Considering the total of 12½ months of cumulative ECMO time in these 100 patients, the incidence of technical complications is very low. When malfunction occurs, however, it is always life threatening and requires immediate repair; thus, the patient is continuously attended by an ECMO technical specialist thoroughly trained in the procedure. This is not a technique to be undertaken on the spur of the moment by an unprepared team. The next step in technical development will be simplification, more servoregulation and automatic monitoring, so that a single nurse, with appropriate technical training and support, can care for both the baby and the circuit (as is currently done with ventilators, for example).

Venovenous circulation is theoretically ideal for support of gas exchange in the patient with a normal heart and worked well in several of our patients. It avoids ligation of the carotid artery, which, although safe, is certainly a psychological deterent to ECMO. However, the occasional need for better support and the extra complexity of the system leads us to favor venoarterial bypass at present. The use of a double-lumen venovenous catheter has been proven feasible in the laboratory[38] and will soon be tested clinically. As we treat patients earlier in the course of respiratory failure, the need for total support will be less (some gas exchange will persist in the native lung), and venovenous bypass will probably become the method of choice for most newborn patients, as it is in Gattinoni's experience in the adult.[3]

Newborn Respiratory Failure

From the experience in this series and other centers,[28] it is clear that almost all respiratory failure in infants over 34 weeks' gestation is reversible, and the same is probably true for premature infants, were it not for intracranial

TABLE 9. *Patient Complications Procedures, N (Died)*

	I	II	III	Overall
Intracranial bleed	19 (17)	8 (4)	2 (1)	29 (22)
Seizures	19 (10)	4 (1)	1 (0)	24 (13)
Other bleeding	5 (4)	4 (1)	2 (0)	11 (5)
PDA	15 (10)	2 (1)	3 (0)	20 (11)
PDA ligation	11 (6)	2 (1)	3 (0)	16 (7)
Hypertension		2 (0)	3 (1)	5 (1)
Cardiac arrest	1 (0)	3 (0)		4 (0)
Cannulation problems	2 (2)		1 (0)	3 (2)
Pericardial tamponade		1 (0)	2 (0)	3 (0)
Cardiac failure			1 (0)	1 (0)

bleeding. Moreover, the quality of survival is the same or better than that reported for conventional respiratory care,[39] and the cost may be less. Hence, although the technique is radical and invasive, it must be considered the treatment of choice in infants over 34 weeks who have reached a high mortality risk with conventional treatment. From this experience we have learned that pulmonary hypertension is the underlying mechanism of respiratory failure in full-term infants, and it is always transient (functional rather than structural). Pulmonary hypertension is reversed by changing the mode of ventilation (since ECMO provides only passive support); therefore, it is exacerbated to the point of lethality by some aspect(s) of conventional ventilator management. This supports the laboratory work of Kolobow[40,41] and the clinical report of Wung,[42] emphasizing the damaging effects of mechanical ventilation in newborn respiratory failure. Hence the major benefit of the ECMO experience will probably be the demonstration of these phenomena, leading to better methods of ventilation or better mediators of pulmonary vascular resistance that may eventually eliminate the need for ECMO in newborn patients.

Another observation from this experience is the establishment of prolonged extracorporeal circulation as a definitive means of life support in vital organ failure. The establishment of a stable technology in several centers in this specific group of patients should support continuing clinical investigation of extracorporeal support in other patients with respiratory or cardiac failure.

TABLE 10. *Follow-up Results of 100 Neonatal ECMO Patients*

	I	II	III	Total
Survivors	27	27	18	72
Late death	1	6	0	7
Current age	5–11 yr	1–5 yr	3 mo–1 yr	3 mo–11 yr
Normal, near normal	18	13	14	45
Major developmental delay	5	6	1	12**
Major pulmonary problems	1	2	3	6***
Other		TAPVD re-op* Congenital myopathy*		2**
Incomplete follow-up	3	5	2	10

* = 1 death.
** = 2 deaths.
*** = 3 deaths.

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Discussion

DR. ROBERT M. FILLER (Toronto, Ontario): I would like to congratulate Dr. Bartlett and his associates for their very fine presentation and the beautiful demonstration that indicates that this very sophisticated and complex method of life support can be applied to the very small infant with a minimum of complications. Dr. Bartlett's work over the past 10 years has been extraordinary and, I think, very well recognized around the world.

However, there is an issue that remains to be solved, and that deals with the conclusion that ECMO is the procedure of choice when standard ventilatory support fails. This has not been completely accepted in many neonatal centers. The main issue appears to be whether infants treated by ECMO could have been salvaged by other means.

All agree that Dr. Bartlett and his associates have selected only desperately ill neonates for treatment, but reports from other centers that do not use ECMO and employ more conventional means of respiratory support indicate equivalent survival data in what appear to be equally ill infants.

For example, I was supplied data by our neonatal intensive care head at the Hospital for Sick Children, in which we use high frequency oscillation, a ventilation method originally designed by Dr. Bryan at our institution. This has been used for infants with severe respiratory failure. For those of you who are unfamiliar with it, it is basically a technique in which a piston pump is attached to an endotracheal tube and oscillates gases at a frequency of 900 cycles per minute.

Since 1983 there were 31 neonates with severe respiratory failure from a variety of causes, similar to those treated by Dr. Bartlett and his group. This excludes infants with diaphragmatic hernia, however. The 31 patients have been treated in the past 3 years. The indications have been similar to Dr. Bartlett's, in that arterial alveolar oxygen gradients have been greater than 600 mm, with high mean airway pressures or hypercarbia with PCO_2s greater than 50, with peak airway pressures greater than 30 cm H_2O. Twenty-five of the 31 infants treated have survived, and three of the five deaths were unrelated to acute respiratory failure, results very similar to what we see with ECMO.

I am very interested in hearing Dr. Bartlett's comments on this controversial area. This remains the one part of the system that I think we need to know a little more about.

DR. LAZAR J. GREENFIELD (Richmond, Virginia): I want to express sincere appreciation and indebtedness to Dr. Bartlett not only for his excellent presentation and the opportunity to review his manuscript, but primarily for the leadership he has shown in this important area and his willingness to share his expertise.