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Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective Randomized Study

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ABSTRACT. A prospective controlled randomized study of the use of extracorporeal membrane oxygenation to treat newborns with respiratory failure was carried out using the "randomized play-the-winner" statistical method. In this method the chance of randomly assigning an infant to one treatment or the other is influenced by the outcome of treatment of each patient in the study. If one treatment is more successful, more patients are randomly assigned to that treatment. A group of 12 infants with birth weight greater than 2 kg met objective criteria for high mortality risk. One patient was randomly assigned to conventional treatment (that patient died); 11 patients were randomly chosen for extracorporeal membrane oxygenation (all survived). Intracerebral hemorrhage occurred in one of 11 surviving children. Extracorporeal membrane oxygenation allows lung rest and improves survival compared to conventional ventilator therapy in newborn infants with severe respiratory failure. *Pediatrics* 1985;76:479–487; *neonatal, respiratory failure, extracorporal circulation, oxygenation.*

Prolonged extracorporeal circulation with a modified heart-lung machine (extracorporeal membrane oxygenation [ECMO]) has been successfully used in several centers to treat infants with severe respiratory failure.[1-4] The technique has been used when infants are judged to be moribund, and unresponsive to optimal ventilator and pharmacologic therapy. These "phase 1" trials of safety and efficacy determined that the technique was safe (the risks of the treatment itself were less than the risks of the disease), and effective (some infants survived who were not expected to recover). Our phase I trial included 55 moribund patients treated in three centers over nine years.[1,4] The birth weight of 40 of these infants was more than 2 kg; 28 survived (70%). The birth weight of 15 infants was less than 2 kg; three survived (20%). With an overall survival of 56% in moribund infants we were ready to proceed to a scientific trial. Therefore, a prospective controlled randomized "phase 2" trial was designed and carried out.

Our group participated in a multicenter National Institutes of Health-sponsored prospective controlled randomized study of ECMO in adult respiratory failure in 1975 to 1979.[5] That study was unique, as a prospective randomized study of an acute life support technique in which death was the end point. In designing the newborn study we sought to avoid the logistic and ethical problems that were identified in the adult study. Specifically, the study design had to insure that: (1) entry into the study or random assignment could not be influ-

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enced by family, treating physicians, or investigators; (2) patient selection criteria must be based on objective physiologic measurements during optimal therapy (ie, treatment intensity should not be decreased simply to achieve arbitrary criteria for study entry); (3) considering the variable nature of a group of infants with respiratory failure, the criteria to include an infant in the study should be to select a group of infants who were as homogeneous as possible with respect to very high mortality risk, optimal respiratory care, and gestational age; (4) the ethical issue of withholding an unproven but potentially lifesaving treatment must be addressed without disrupting the controlled randomized nature of the study.

Using these criteria, we designed and carried out the following study, which was approved by The University of Michigan Medical Center Institutional Review Board.

METHODS

Study Design

Objective criteria were established to select patients with an 80% or greater chance of mortality despite optimal therapy (Fig 1). Two groups of patients were studied: one group whose birth weight was 1 to 2 kg and one group whose birth weight was more than 2 kg. The study of infants weighing 1 to 2 kg is still in progress. This report concerns only the group weighing >2 kg. All patients who met these criteria (and had no contraindications [Fig 1]) were randomly assigned to continuing conventional treatment or ECMO (Fig 2). If the patient was randomly assigned to ECMO, parental consent was obtained, then ECMO was begun. (If parents refused or if the patient died before ECMO was begun, the patient was still to be considered in the ECMO group.) After random assignment, patients were observed until death, lung recovery (defined as extubated 24 hours), or survival (defined as hospital discharge). Survivors were evaluated at regular intervals as outpatients.

The technique was the "randomized play-the-winner" technique of Zelen[6] and Wei and Durham.[7] This method was proposed in 1969, but had not been used for a clinical study. It seemed ideal for our purpose for the following reasons. (1) The outcome of each case is known soon after randomization, making it possible to use. 2) We anticipated that most ECMO patients would survive and most control patients would die, so significance could be reached with a modest number of patients. 3) It was a reasonable approach to the scientific/ethical dilemma. That is, we were compelled to conduct a prospective randomized study, but reluctant to withhold a lifesaving treatment from alternate patients simply to meet conventional random assignment technique.

Eligibility for Randomization

Newborn respiratory failure; >2 kg birth weight.
Optimal/maximal treatment in University of Michigan Newborn Intensive Care Unit (ventilatory, pharmacologic, surgical).
Cranial and cardiac ultrasound studies done.
ECMO available.

Randomization Criteria (Any One of Following Five Categories)

1. Acute deterioration: either Pao_2 <40 mm Hg or pH <7.15 for 2 hours.
2. Unresponsiveness (two of the following three indications for 3 hours): Pao_2 <55 mm Hg; pH <7.4; hypotension.
3. Barotrauma (four of the following seven indications simultaneously):
   Interstitial emphysema;
   Pneumothorax;
   Pneumoperitoneum
   Pneumopericardium
   Subcutaneous emphysema;
   Persistent air leak for 24 hours;
   Mean airway P >15 cm H_2O.
4. Diaphragmatic hernia: Pao_2 <80 on Fio_2 >.8, after honeymoon period.
5. Newborn Pulmonary Insufficiency Index: 80%+ mortality rate at 24 hours of age.

Contraindications:

Intracranial hemorrhage grade II or higher.
More than 7 days of age.
Condition incompatible with normal quality life, including prolonged cardiac arrest and resuscitation.

Fig 1. Study entry criteria. Consideration began only when therapy was considered optimal. Patients who met criteria in at least one category were randomly assigned if there were no contraindications.

In this statistical method the first patient has an equal chance of random assignment to treatment A or B. If treatment A is selected and is successful, the next patient is more likely to be randomly assigned to that treatment. If treatment A fails, the next patient is more likely to be randomly assigned to treatment B. This continues for each successive patient, so that the chance of a patient being randomly assigned to treatment A or B is influenced by the results of all the previous patients in the study. Hence, if there is no difference between treatments A and B the odds of random assignment remain close to 50:50, and the number of patients in each treatment group grows at approximately the same rate. If one treatment is better, then the chance of random assignment to that treatment

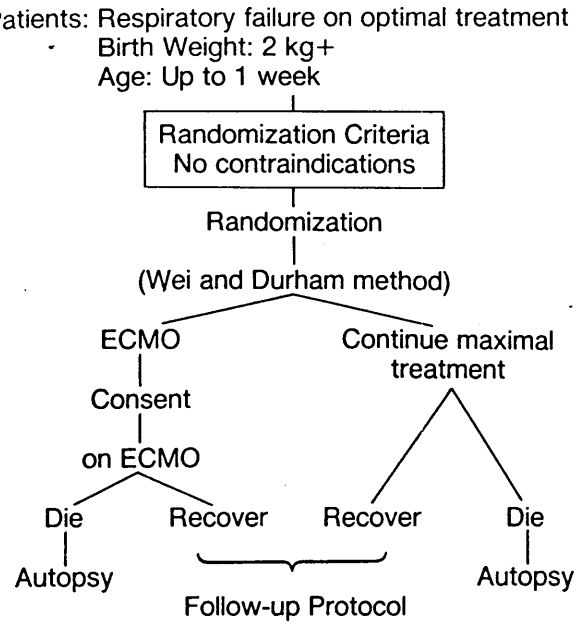

Fig 2. Design of the prospective controlled randomized study. Abbreviation used is: ECMO, extracorporeal membrane oxygenation.

increases and the number of patients in that arm of the study increases as the study grows. In this fashion each patient is truly randomly assigned without prior knowledge of the treatment to be selected, but the probability of a patient being arbitrarily assigned to inferior treatment is decreased.

The Department of Biostatistics prepared random treatment assignments (A or B) in sealed envelopes. The statistician did not know which code designated ECMO. After the outcome (death or lung recovery) of each patient was known, the Department of Biostatistics was notified that treatment A or B had been successful or unsuccessful, and new random assignments were prepared. Multiple envelopes were prepared for each randomization, to be used sequentially if a second patient met criteria before the fate of the first was known. However, this situation did not occur.

Patient Selection

During the 18 months of the study there were 50 infants weighing >2 kg with severe respiratory failure who required intubation and mechanical ventilation and 100% oxygen for 12 hours or more. Three were inborn and 47 were referred from other hospitals. Many were referred from other level III neonatal intensive care centers because of the availability of ECMO in this institution, hence, the overall patient population was skewed to include the highest risk patients from a large geographic area.

Criteria were established to select patients with severe respiratory failure who had a high risk of dying (80% to 100%). These criteria are listed in Fig 1. These criteria were applied only after and despite optimal therapy. For example even if the PaO_2 was less than 40 mm Hg while ventilator settings or drug dosage were being adjusted, consideration of entry criteria did not begin until all treatment was considered optimal by the attending neonatologist. A single Po_2 or pH value above the value defined in Fig 1 "reset" the time clock for study entry. These criteria defined greater than 90% mortality in our Neonatal Intensive Care Unit prior to 1981 (before ECMO was used). They correspond to very high mortality risk in other centers.[2,3,8,9,10] From October 1982 to April 1984, 14 patients whose birth weight was greater than 2 kg met these criteria. Twelve were randomly assigned. (Two patients were not randomly assigned because of conditions considered incompatible with normal quality life. One patient with Down syndrome died of respiratory failure at 12 days of life; another with neonatal sepsis and profound acidosis at the time of referral had a cardiac arrest at 18 hours of life before the investigational team could be mobilized.)

Conventional Treatment

Routine diagnostic studies included serial chest x-rays, cardiac and cranial ultrasound examination,[11] and preductal and postductal arterial blood samples. Arterial blood gases referred to in this report are all postductal umbilical artery catheter samples. Intraaortic catheters were routinely placed via an umbilical artery and Sechrist ventilators were used, using the lowest level of oxygen, pressure, and rate that achieved the desired gas exchange. Pulmonary hypertension with right-to-left shunting (persistent fetal circulation) was almost always present in these infants, either complicating another lung disorder or occurring as a primary event. The treatment of persistent fetal circulation included maintaining full arterial oxyhemoglobin saturation (PaO_2 70 to 150 mm Hg), and hyperventilation with or without bicarbonate infusion to maintain $PaCO_2$ lower than 35 and pH > 7.5. Pharmacologic treatment included paralysis with pancuronium, pulmonary vasodilation with tolazoline or chlorpromazine (systemically or via a pulmonary artery catheter), dopamine if inotropic support was required, and prophylactic antibiotics.

ECMO and Lung Rest

The techniques and details of managing prolonged extracorporeal circulation are described elsewhere[1,4,12] (Fig 3). Venous access was established by cannulating the right atrium via the right

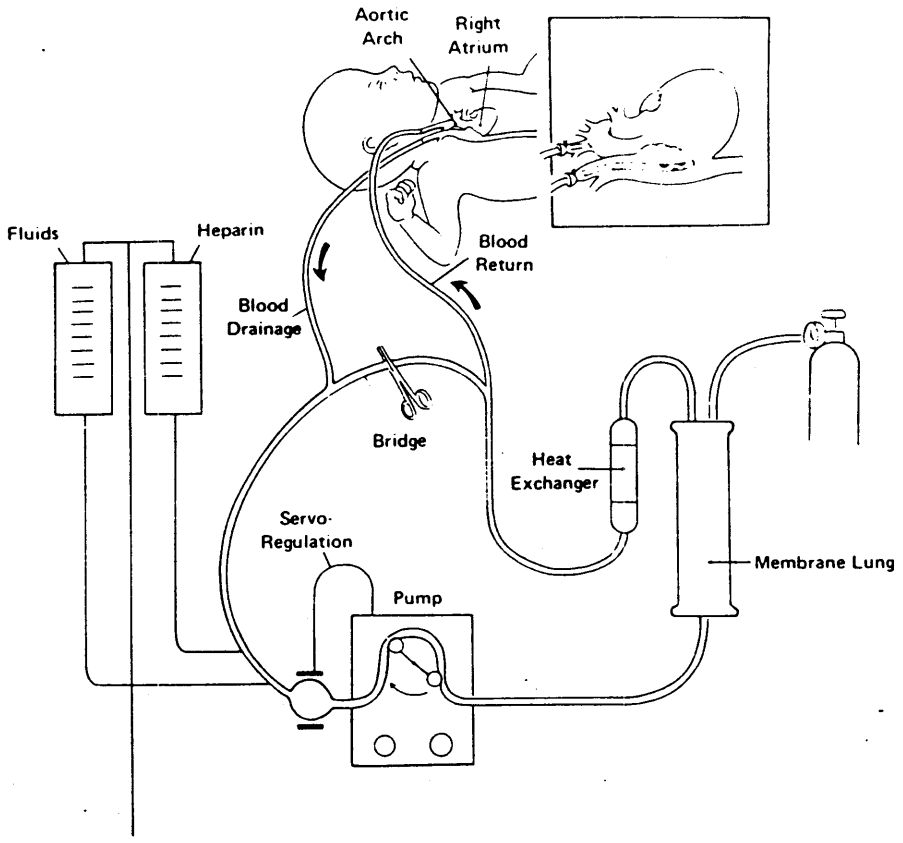

Fig 3. Diagram of venoarterial extracorporeal membrane oxygenation circuit.

internal jugular vein. Cannulation was done under local anesthesia in the Neonatal Intensive Care Unit. Venous blood was drained from the right atrium to a servoregulated roller pump, pumped through a Sci-Med membrane lung, a small heat exchanger, and returned to the patient. Flow was adjusted to maintain Pao_2 60 to 80 mm Hg (typically 120 mL/kg/min). Oxygenated blood was returned to the femoral vein in the case of venovenous bypass[12] and to the aortic arch via the right common carotid artery in the case of venoarterial bypass. In patients with stable hemodynamics, we consider venoarterial and venovenous bypass equally effective for support of gas exchange.[12] Venoarterial bypass was used if there were signs of hemodynamic instability requiring cardiac support. The circuit was primed with blood and the hematocrit maintained at approximately 45%. Anticoagulation was maintained with heparin, titrated to keep the activated clotting time approximately 250 seconds. This required approximately 50 units per kilogram per hour. Platelet transfusions were given to maintain the platelet count greater than 50,000 mm^3. As soon as the patient was stabilized on ECMO, ventilator settings were decreased to "rest" the lung (typically, rate ten per minute, Fio_2 0.3, pressure 20/3 cm H_2O). Lung function (as judged by test periods off bypass) usually decreased for the next 24 hours (usually to the point of no pulmonary gas exchange), then began to improve. As lung function improved, flow through the extracorporeal circuit was decreased. When lung function was adequate to maintain normal gas exchange at low ventilator settings and low ECMO flow rates (15 mL/kg/min), ECMO was terminated and the cannulae were removed. The baby was maintained on low ventilator settings (intermittent mandatory ventilation mode with spontaneous breathing) weaned to constant positive airway pressure, and then extubated.

Follow-up Studies

Before discharge, a cranial ultrasound examination was done, as well as a neurologic evaluation, and height, weight, and head circumference were measured. After discharge, patients were observed by their own pediatrician and in our own follow-up clinic when possible. Follow-up examinations included measurement of height, weight, and head circumference, neurologic and developmental examination and, when possible, Denver Developmental Screening Test, Bayley Scales of Infant Development, EEG, cranial ultrasound, and chest x-ray.

RESULTS

Of the 50 infants with severe respiratory failure as defined above, 36 improved without meeting randomization criteria and survived (two of these infants were treated with ECMO when a moribund condition was reached after seven days of age, outside the age limit for this study). Fourteen met randomization criteria. ECMO was contraindicated for 2 infants (both died), so 12 patients entered the randomized study. Data on the patient group are listed in Table 1.

The first patient was randomly assigned to ECMO and survived. The second patient was randomly assigned to conventional treatment and died. Hence, the odds of the next patient being randomly assigned to ECMO were 3:1. The next patient was randomly assigned to ECMO and survived. This pattern continued until there were ten who had been treated with ECMO or ten control patients who died. This pattern was established in accord with the stopping rule which detected a high probability of selection of the better treatment. Two additional patients who met criteria were assigned to ECMO. Five patients entered the study via the acute deterioration category, five met the nonresponse criteria, and two patients entered via the barotrauma category (Fig 1).

When the study was terminated there was one control patient who had died and 11 ECMO patients, all of whom survived. The results are summarized in Table 2. All parents, informed of potential risks and benefits, gave consent for ECMO. The average time from randomization to institution of ECMO was approximately three hours. During this time the condition of most patients deteriorated. Blood gases prior to ECMO are listed in Table 1. Two patients had a cardiac arrest from hypoxia and hypercarbia before or during the cannulation operation, were supported with external cardiac massage, and were resuscitated only when venoarterial bypass began. ECMO provided total respiratory support in all cases, allowing lung rest. Vasoactive and paralytic drugs were discontinued.

The average time on ECMO was 95 hours. The average stay in the Newborn Intensive Care Unit was 34 days (range, 12 to 79 days). Complications related to ECMO occurred in three patients. The jugular vein tore during cannulation in one patient (O.J.), resulting in moderate blood loss but no further problems. In another patient (K.D.) hemolysis and oxygenator failure occurred which proved to be due to damaged tubing in the roller pump raceway. An intracerebral hemorrhage in the thalamostriatal area occurred in one patient (M.D.) on venovenous bypass, resulting in severe neurologic deficit.

TABLE 1. Characteristics of Patients in Study with Random Assignments*

Patient	Birth Wt (g)	Primary Diagnosis	Entry Category	Ventilator†			Arterial Blood Gases†			A-a D_{O_2}	Age at Which Randomly Assigned	Treatment
				F_{IO_2}	Pressure	Rate	P_{O_2}	P_{CO_2}	pH			
G.M.	4.50	MAS, PFC	Barotrauma	1.0	50/8	70	117	23	7.52	573	133	ECMO
R.M.	2.10	PFC, TAPVD	Nonresponse	1.0	35/5	60	31	41	7.38	641	20	ECMO
M.D.	3.20	MAS, PFC	Barotrauma	1.0	38/4	60	50	22	7.56	641	34	ECMO
D.E.	2.30	RDS, rule out sepsis	Acute deterioration	1.0	34/4	100	38	24	7.52	651	66	ECMO
O.J.	3.03	RDS, PFC	Nonresponse	1.0	50/4	60	41	43	7.36	629	137	ECMO
B.P.	3.33	CDH, PFC	Acute deterioration	1.0	35/5	120	17	51	7.54	645	33	ECMO
R.C.	2.84	MAS, PFC	Acute deterioration	1.0	30/4	80	34	35	7.48	644	10	ECMO
R.S.	3.08	MAS, PFC	Nonresponse	1.0	40/5	60	36	25	7.55	652	18	ECMO
B.G.	3.60	RDS, PFC	Nonresponse	1.0	38/4	60	45	30	7.6	638	79	ECMO
K.K.	3.66	CDH, PFC	CDH nonresponse	1.0	40/3	100	47	31	7.41	635	32	ECMO
K.D.	4.26	MAS, PFC	Acute deterioration	1.0	40/4	60	26	44	7.38	643	15	ECMO
M.J.	2.10	RDS, PFC	Acute deterioration	1.0	45/5	60	22	55	7.31	636	140	Control

* Abbreviations used are: ECMO, extracorporeal membrane oxygenation; MAS, meconium aspiration syndrome; PFC, persistent fetal circulation; TAPVD, total anomalous pulmonary venous drainage; RDS, respiratory distress syndrome; CDH, congenital diaphragmatic hernia.
† Data at time of random assignment.

TABLE 2. Results in Patients Treated with Extracorporeal Membrane Oxygenation*

Patient	Age at Which Patient Was Treated with ECMO	Time on ECMO (h)	Perfusion Mode	Complications	Time to Extubation (h)	Hospital Days
G.M.	135	81	VV	Post-ECMO arrest	167	48
R.M.	23	143	VA	TAPVD, delayed diagnosis	431	46
M.D.	37	58	VV	Intracerebral bleed	42	34
D.E.	70	62	VV	None	40	14
O.J.	141	123	VA	Cannulation problem	498	79
B.P.	36	50	VA	Pre-ECMO arrest	40	28
R.C.	13	104	VA	Pre-ECMO arrest	432	104
R.S.	23	34	VA	None	6	21
B.G.	85	113	VA	None	76	31
K.K.	34	104	VA	None	120	31
K.D.	19	174	VA	Faulty pump tubing	105	31

* Abbreviations used are: ECMO, extracorporeal membrane oxygenation; VV, venovenous; VA, venoarterial; TAPVD, total anomalous pulmonary venous drainage.

The patient who was randomly assigned to conventional treatment entered the study at five days of age via the acute deterioration category. Despite optimal care, he died on day 13 of progressive respiratory failure. Autopsy showed severe bronchopulmonary dysplasia and fibrosis. There was no intracranial bleeding.

DISCUSSION

This study confirms phase 1 studies showing that moribund infants can recover with normal growth and development when treated with ECMO and lung rest.[1–4,13] Furthermore, this study proves that ECMO improves survival when compared to conventional treatment.

When a new treatment is compared to standard optimal treatment in a controlled randomized fashion, consent is required only for the new treatment, hence, consent can be obtained after randomization, as pointed out by Zelen.[14] This principle was used in designing this study. This simplified and improved the logistics for families and providers considerably compared to the adult study of ECMO.[5] That is, if consent is sought before randomization, the distraught family is presented with confusing treatment options which they cannot fully understand, and then asked, in effect, to decide on treatment by accepting or declining the treatment which is subsequently assigned. If the patient dies or sustains brain damage (which can happen with either treatment) the family is guilt-ridden at having selected the "wrong" treatment and angry at the providers for not urging the "right" treatment.

The study design and randomization method met the goals defined at the outset. The "randomized play-the-winner" method was appropriate for this study because the outcome of each case is usually known within a few days after the assigned treatment begins, so that the odds of subsequent random assignment can be adjusted. This method softened the ethical dilemma, although withholding ECMO from the control patient still caused controversy.

Using the balls-in-urn model analogy of Wei and Durham,[7] the randomization procedure consisted of drawing a treatment allocation ball from an urn at random, with replacement. Although the clinicians did not know it, the urn contained one conventional therapy ball and one ECMO ball initially ($\mu = 1$ in Wei and Durham's notation). In retrospect it would have been better to begin with two or three pairs of balls, which probably would have resulted in more than one control patient.[15] The protocol called for the addition of one ECMO ball each time a patient survived on ECMO therapy or failed to survive on conventional therapy. Similarly, it called for the addition of a conventional therapy ball for a survival on conventional therapy or death on ECMO. The stopping rule, determined in advance, was to stop the randomization whenever ten balls of one type were added, and then to continue using only the treatment that gave the better results. This stopping rule was picked because it was the minimum number which met the following criterion a priori: Probability of at least 0.95 of selection of the best treatment for $P_A \geq .8$, $P_A - P_B > .04$, where P_A denotes the probability of survival when the infant receives the better treatment and P_B the

corresponding probability when the infant receives the other treatment. For the probabilities actually thought to hold, namely, $P_A = 0.9$ for ECMO and $P_B = 0.1$ for conventional therapy, the probability of selection of the better treatment after ten patients not only exceeded 0.95 but equaled 1.0. In the study itself, these conditions were met after ten patients were entered and two more were assigned to ECMO and survived. The probability that ECMO is the better treatment is 1.0 (if it is true that the mortality of conventional treatment in patients selected by these criteria is 90%). That is, the probability that ECMO is the better treatment is 1.0 when computed using the observed results under the assumption that the mortality of conventional treatment in patients selected by these criteria is 90% and exceeds that for ECMO by at least 40%. For an exceedance as low as 10% the probability of correct selection still is greater than 0.98.[15]

Selection criteria are the key to the interpretation in this statistical method. Conclusions can be drawn from this study only if the selection criteria really detect a group of patients with high mortality risk. Note that the selection criteria were applied only after optimal and maximal treatment was given. With only one patient randomly assigned to the control group it could be argued that the study entry criteria were not adequately tested. Supporting these entry criteria are the following observations. Patients who met these criteria had a high mortality rate in our own institution prior to the use of ECMO. Two patients who were randomly assigned to ECMO had a hypoxic cardiac arrest during cannulation and would have died if ECMO had not been started immediately. Two patients who met these criteria but were not entered into the randomization for other reasons both died. The patient randomly assigned to control treatment without ECMO died. Similar criteria have been associated with high mortality risk in other major neonatal care centers[2,3,8,9,10] (KD Anderson, personal communication, data review, July 1984). Eleven of 12 patients had an A-a Do_2 over 620 mm Hg, which was associated with 100% mortality in the Richmond study.[2] (This calculation has been used as an indication for ECMO in similar studies.[2] It assumes constants: barometric pressure, 760 mm Hg; temperature, 37°C; and respiratory exchange ratio, 1.0, instead of measured values.)

Finally, since this study was completed (April 1984 to November 1984), ten consecutive additional patients have met the entry criteria in our hospital. Eight were treated with ECMO; all survived. Two infants were not treated with ECMO; both died. In total, then, in 2 years 24 patients met the criteria. All 19 ECMO patients survived; the five others all died. Based on 19 consecutive successes with ECMO, the lower 99% one-sided confidence interval on the probability of survival with ECMO is 78.5. Thus, the null hypothesis that the survival probability is the same for ECMO as for conventional therapy would be rejected in favor of a higher survival probability for ECMO for any specification of a survival probability for conventional therapy less than 78.5. Because this bound is well above the survival rate observed in the past for patients eligible for this trial under conventional therapy, ECMO has a significantly higher survival rate than conventional therapy, at the 1% significance level. This conclusion is based on all the data on ECMO, both before and after the discontinuance of randomization, and on standard confidence interval calculations.

The Newborn Pulmonary Insufficiency Index,[16] which we have used as a measure of high mortality risk in the past, was included as one criterion but was not useful in this group of patients. This is because the Newborn Pulmonary Insufficiency Index is based on the extent of hypoxemia and acidosis during the first 24 hours of life. Since the advent of induced alkalosis as treatment for pulmonary hypertension, the Newborn Pulmonary Insufficiency Index scoring system is not applicable.

Three patients proved to have congenital anomalies which were not diagnosed before ECMO was begun. One child (R.M.) had total anomalous pulmonary venous drainage (which had been missed on cardiac catheterization prior to ECMO). This anomaly was repaired, but complicated by anastomotic stenosis several months later which finally resulted in the death of the infant. One child (R.S.) with meconium aspiration and persistent fetal circulation had a ventricular septal defect, which became obvious after ECMO. One child (R.C.) with severe meconium aspiration syndrome was found to have congenital central nuclear myopathy.[17] This diagnosis was made by muscle biopsy after the patient was taken off ECMO. Although this child was successfully weaned from the ventilator and discharged from the hospital, he ultimately succumbed to the complications of this disease.

Three of the survivors had complications of respiratory failure or its treatment. One patient (O.J.) had radiographic evidence of bronchopulmonary dysplasia at the time he met randomization criteria on the sixth day of life. This patient required prolonged ventilator support and required supplemental oxygen for 10 months after hospital discharge. One child (B.P.) with a right-sided congenital diaphragmatic hernia and persistent fetal circulation required supplemental oxygen for a short time after hospital discharge and required a gastric fundopli-

cation for gastroesophageal reflux at 4 months of age. One child (M.D.) had an episode of intracerebral bleeding in the thalamostriatal area resulting in severe neurologic deficit, and death at 18 months of age.

At least four children (including O.J. and B.P. mentioned above) have evidence of developmental delay or mild neurologic problems. These abnormalities may be due to asphyxia, hypoxia, or ischemia occurring during or after delivery, or to ECMO itself. It is too soon to draw any conclusion regarding the long-term neurologic and developmental status of these children. A detailed follow-up study is under way. There is no evidence of neurologic injury related specifically to carotid ligation. The patient with severe neurologic deficit was treated with venovenous bypass and did not have carotid ligation. In a follow-up study of six ECMO survivors treated in similar fashion, Krummel et al (18) found normal growth and neurologic function in five infants and neurologic deficit in one. Towne et al (19) studied 18 ECMO survivors from our phase I group at 4 to 9 years of age. Thirteen (72%) were basically normal and five (28%) had a neurologic handicap which was severe in two (11%). Whenever critical illness occurs in the neonatal period, the family must be informed that there is a significant chance of permanent brain injury. This is particularly important when a new treatment is likely to be life-saving in a high-risk infant and the family has the option to decline.

In addition to brain injury, the morbidity associated with severe newborn respiratory failure is related to bronchopulmonary dysplasia, systemic sepsis, or necrotizing enterocolitis. Neither sepsis nor necrotizing enterocolitis occurred, despite the invasive nature of this procedure and the possible variations in blood flow to abdominal viscera. Bronchopulmonary dysplasia requiring home oxygen occurred in two patients on ECMO and severe bronchopulmonary dysplasia was found at autopsy in the control patient. We have hypothesized that ECMO and lung rest, instituted early in the course of newborn respiratory failure, would decrease the incidence of intracranial bleeding and bronchopulmonary dysplasia.[1] However, this hypothesis was not tested in this study. Another randomized study to address this question is under way.

Patient G.M. appeared normal neurologically and had been doing well in room air, but he was found apneic and asystolic in his hospital crib on the eighteenth day following venovenous ECMO. No etiology for the cardiopulmonary arrest was found. Following resuscitation he had postasphyxial seizures which were controlled with anticonvulsant medications. A pneumogram done before discharge was normal, and the mother refused home monitoring. This is the only instance of late apnea we have observed in our neonatal ECMO experience.

Extracorporeal circulation provides passive support of the patient (allows "lung rest") and adds the inherent risks of anticoagulation and vascular access. The improved survival must be caused by improving gas exchange and/or diminishing lethal side effects of conventional ventilator management. ECMO improves oxygen delivery slightly, but does not substantially increase the amount of oxygen and CO_2 exchanged. It simply accomplishes gas exchange through a different route. Therefore, the lung rest component of treatment must be a major factor which led to recovery in these patients. In experimental animal models of respiratory distress syndrome (20) and meconium aspiration (21), Kolobow et al have demonstrated that conventional mechanical ventilation is severely damaging to the newborn lung, whereas avoiding overventilation by a short period of ECMO support avoids lung damage. This clinical study strongly supports the thesis of Kobolow et al.

ECMO is now established in several major neonatal centers, and it is appropriate to begin to define the role of ECMO as treatment. It is appropriate treatment for acute, severe, reversible respiratory failure in newborn infants weighing more than 2 kg. It is indicated when other modes of therapy fail, or when other modes of therapy may be damaging to vital organs. The need for the treatment will diminish as perinatal care improves and better pharmacologic and mechanical means of treatment evolve. The technique is invasive and has inherent risks. As in all aspects of neonatal intensive care, there is a possibility that survivors may have neurologic impairment. ECMO should only be used by teams that are familiar with the procedure. When ECMO is applied early in the course of severe respiratory failure, patients will regularly survive who would otherwise have died.

CONCLUSIONS

A prospective controlled randomized study of ECMO in newborn respiratory failure was carried out using the "randomized play-the-winner" statistical method. In this method the chance of randomly assigning a patient to one treatment or the other is influenced by the outcome of each patient in the study. If one treatment is more successful, more patients are randomly assigned to that treatment. A group of 12 infants of greater than 2 kg birth weight met objective criteria for high mortality risk. One patient was randomly assigned to conventional treatment (and died); 11 patients were randomly assigned to ECMO (all survived). Intra-

cerebral hemorrhage occurred in one of 11 surviving children. ECMO allows lung rest and improves survival compared to conventional ventilator therapy in newborn infants with severe respiratory failure.

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