ARTICLES

Extracorporeal Membrane Oxygenation and Conventional Medical Therapy in Neonates With Persistent Pulmonary Hypertension of the Newborn: A Prospective Randomized Study

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ABSTRACT. Thirty-nine newborn infants with severe persistent pulmonary hypertension and respiratory failure who met criteria for 85% likelihood of dying were enrolled in a randomized trial in which extracorporeal membrane oxygenation (ECMO) therapy was compared with conventional medical therapy (CMT). In phase I, 4 of 10 babies in the CMT group died and 9 of 9 babies in the ECMO group survived. Randomization was halted after the fourth CMT death, as planned before initiating the study, and the next 20 babies were treated with ECMO (phase II). Of the 20, 19 survived. All three treatment groups (CMT and ECMO in phase I and ECMO, phase II) were comparable in severity of illness and mechanical ventilator support. The overall survival of ECMO-treated infants was 97% (28 of 29) compared with 60% (6 of 10) in the CMT group ($P < .05$). *Pediatrics* 1989;84:957–963; *extracorporeal membrane oxygenation, persistent pulmonary hypertension of the newborn.*

ABBREVIATIONS. ECMO, extracorporeal membrane oxygenation; CMT, conventional medical therapy.

Persistent pulmonary hypertension of the newborn is characterized by inappropriate elevation of the pulmonary vascular resistance resulting in right to left shunt through the patent foramen ovale or ductus arteriosus, with resulting systemic hypoxemia.[1] Persistent pulmonary hypertension of the newborn may be idiopathic, but it is most commonly associated with a specific event, such as meconium aspiration, sepsis, pneumonia, or asphyxia.[2]

Conventional therapy for persistent pulmonary hypertension of the newborn includes oxygenation and dilation of the pulmonary vascular bed by vasodilator drug therapy or by increasing pH via hyperventilation and the use of alkalinizing agents.[3,4] Despite advances in this therapy, the mortality rate for infants with persistent pulmonary hypertension continues to be as high as 30%.[5]

Extracorporeal membrane oxygenation (ECMO) has also been used as therapy for persistent pulmonary hypertension of the newborn. The techniques of cardiopulmonary bypass are used, and blood is pumped through a membrane oxygenator and then returned to the body supporting gas exchange independently of pulmonary blood flow.[6] The first successful ECMO support of a neonate with persistent pulmonary hypertension was reported in 1976.[7] Since that time, use of ECMO in the treatment of persistent pulmonary hypertension of the newborn has increased dramatically. In 1988, the Central ECMO Registry reported the use of ECMO support in 715 neonates.[8] These severely ill patients were predicted to have an 80% mortality rate with conventional medical therapy (CMT); with ECMO support, 82% survived. Although these data suggest an improved survival with ECMO, these patients were neither selected nor treated according to a single standardized protocol, and no concurrent control groups were studied.

To date, ECMO and CMT have been compared

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in only one prospective randomized study.[9] The design of the study resulted in assignment of nine patients to ECMO treatment and only one patient to CMT. All ECMO-treated patients lived and the single patient receiving CMT died. The disparity in group size provided little concurrent experience concerning the relative efficacy of the two therapies.[10] In addition, no study has provided information concerning morbidity in comparable concurrent groups of patients treated with ECMO and CMT.

We report the survival data from a prospective randomized study of CMT and ECMO for treatment of neonates with persistent pulmonary hypertension of the newborn.

METHODS

Patient Selection

Patient entry criteria were designed to select a group of infants with similar birth weight, gestational age, and pathophysiologic conditions. All patients were inborn at one of the hospitals of the Joint Program in Neonatology (Brigham and Women's and Beth Israel Hospitals) or were referred to the Children's Hospital. All patients met study criteria while in one of the Joint Program in Neonatology nurseries or the Multidisciplinary Intensive Care Unit.

Infants were eligible for study entry when they met the following criteria: birth weight ≥2.5 kg, gestational age ≥38 weeks, normal cranial ultrasound findings, severe hypoxemia with postductal $Pa_{O_2} \leq 80$ mm Hg while receiving an FI_{O_2} of 1.0, a circulatory pattern of persistent pulmonary hypertension of the newborn with right to left shunting documented by a difference of >10% in pre- and postductal arterial Pa_{O_2} values or documented by echocardiography at either the level of the foramen ovale or the ductus arteriosus, and, finally, an 80% predicted mortality based on a Pa_{O_2}/PA_{O_2} (ratio between arterial and alveolar partial pressure of oxygen) ≤0.15 when two successive arterial blood gases determinations were separated by at least 30 minutes between 12 and 72 hours after birth. Infants were excluded if congenital diaphragmatic hernia, congenital heart disease, or preexisting intracranial hemorrhage were present. No infants were excluded after enrollment.

To characterize infants at high-risk of death, we selected all newborn infants with the diagnosis of persistent pulmonary hypertension of the newborn born at the Brigham and Women's Hospital or transferred to the Children's Hospital, between January 1, 1982, and December 31, 1983. Babies with congenital heart disease, congenital diaphragmatic hernia, gestational age <38 weeks, and birth weight <2.5 kg were excluded.

The charts of all 36 babies with persistent pulmonary hypertension of the newborn and without these exclusion criteria were reviewed for perinatal history, vital signs, ventilator settings, blood gas results, and outcome to identify a simple criterion predictive of mortality in this group. The best criterion was a ratio of the Pa_{O_2} to the PA_{O_2}, where PA_{O_2} is calculated as: PA_{O_2} = atmospheric pressure − water vapor pressure − alveolar partial pressure of CO_2.

A ratio of ≤.15 at 12 to 72 hours of life was highly predictive of early death. Of 13 babies in the high-risk group, 11 (85%) died, whereas only 6 of 21 (29%) in the low-risk group died (Table 1). Two patients who had not been admitted to the Children's Hospital by 12 hours of age were not included in this analysis. Similar results were obtained when patients were classified by the Pa_{O_2}/PA_{O_2} ratio at 24, 36, 48, 60, and 72 hours of age.

Experimental Design

The study was designed to assign approximately equal numbers of patients to each treatment group if the therapies had similar mortality rates and to limit the number of patients receiving the inferior therapy if they did not. Specifically, initial treatment group assignments were determined by 50:50 randomization balanced in blocks of size four (phase I). Randomization was to continue until the fourth death occurred in either group. At that point, randomization would cease and all subsequent patients would be enrolled in the group with less than four deaths (phase II). Enrollment would continue until the fourth death occurred in that group or the number of survivors was significantly larger than the number of survivors in the arm that had been discontinued first. This method of patient assignment implied that part of the study would involve nonrandomized treatment assignments. To avoid selection bias, the randomization strategy was known only to one investigator.

A maximum of four deaths was allowed in either group. This value was determined by a power cal-

TABLE 1. Pa_{O_2}/PA_{O_2} as Predictor of Persistent Pulmonary Hypertension of the Newborn Mortality*

	Pa_{O_2}/PA_{O_2}		
	<.15	>.15	
Alive	2	15	17
Dead	11	6	17

* The probability of death, if Pa_{O_2}/PA_{O_2} is <.15 at 12 hours, is .85 (95% confidence interval 57% to 97%). The probability of survival, if Pa_{O_2}/PA_{O_2} is >.15 at 12 hours is .71 (95% confidence interval 48% to 89%).

culation based on a null hypothesis of 80% mortality rates in both groups and an alternative hypothesis of 80% mortality in the CMT group and a reduction to 20% mortality in the ECMO group. The design based on a maximum of four deaths had power of .74 against this alternative hypothesis using a one-sided testing procedure with type I error of .05. A design based on three deaths would have had power of .55, and one based on five deaths would have had power of .84.

Consent

In this we used the method of randomized consent proposed by Zelen.[11] Consent was sought only from families whose child had been assigned to the ECMO group. This method was chosen in the belief that discussing the possibility of ECMO therapy with families whose child did not ultimately receive ECMO would not benefit those families and would create additional emotional distress. Informed consent for follow-up studies was obtained from parents of all surviving infants enrolled in the study. Informed consent procedures and forms were reviewed and approved by the Institutional Review Boards at both the Brigham and Women's Hospital and the Children's Hospital.

Treatment Groups

Infants randomly assigned to the CMT group remained in their initial neonatal intensive care unit setting at either the Brigham and Women's Hospital or the Children's Hospital. The goals of CMT were to achieve hyperoxemia and a decrease in the pulmonary vascular resistance with therapy including the following: administration of oxygen at an FIO_2 of 1.0; increased mean airway pressure to maximize oxygenation using peak inspiratory pressures up to 40 to 50 cm H_2O with mean airway pressure of 15 to 16 cm H_2O as needed; hyperventilation to achieve hypocarbia with a $PaCO_2$ of 20 to 25 mm Hg; muscle relaxation using pancuronium bromide and analgesia using morphine sulfate or fentanyl; administration of sodium bicarbonate to achieve alkalosis (pH 7.55 to 7.6) in the presence of normocarbia; trials of pharmacologic pulmonary vasodilation with isoproterenol and/or tolazoline; administration of volume expanders, dopamine, and/or dobutamine to maintain systemic blood pressure; and correction of metabolic abnormalities.

ECMO Group

Patients assigned to the ECMO group were transferred to the multidisciplinary intensive care unit except for two patients who remained in the neonatal intensive care unit for their ECMO course because of bed availability. ECMO was instituted immediately after assignment of a patient to the ECMO group.

Venoarterial ECMO was used for all infants. The technology and procedure have been described previously.[6] ECMO flow rates were 100 to 150 mL/kg per minute. The sweep gas was a mixture of oxygen, carbon dioxide, and nitrogen designed to keep the Pa_{O_2} in the range of 70 to 120 mm Hg and the $PaCO_2$ 35 to 45 mm Hg. Heparin administration was adjusted to maintain the activated clotting times between 220 and 260 seconds. The conventional ventilator was set on an FIO_2 of 0.21, rate of four breaths per minute, peak inspiratory pressure of 20 cm H_2O, and positive end-expiratory pressure of 5 cm H_2O. Muscle relaxants were withheld, and the child was sedated with fentanyl and lorazepam. Children were monitored with activated clotting time's hourly, arterial blood gases every 4 hours, a chest radiograph daily, and cranial ultrasounds every other day.

ECMO support was continued until the patient could maintain a $Pa_{O_2} > 60$ mm Hg, a $PaCO_2 < 45$ mm Hg, and a pH >7.30 while being supported with an $FIO_2 \leq .35$, rate ≤30 breaths per minute, and peak inspiratory pressure ≤30 cm H_2O.

Statistical Methods

Most clinical trials are designed to enroll a prespecified number of patients in each treatment group. This study was designed to continue until a fixed number of deaths occurred in each group. This limited the number of deaths that could occur if one or both treatments had high mortality rates. When the number of deaths is fixed by design, the number of survivors follows the negative binomial distribution.[12] Comparison of survival rates was based on the conditional distribution of the number of survivors in the ECMO group given the total number of survivors.[13] *P* values for testing the null hypothesis were derived from this conditional distribution using standard methods. Power calculations were obtained by averaging results of the conditional analysis over the distribution of the total number of survivors under the null and alternative hypotheses.

A modification by Lin and Wei[14] of the method of Wei et al[15] was used to calculate an exact one-sided 95% confidence interval for the difference in survival rates.

Comparisons between groups of the distribution of patient characteristics were based on one-way analysis of variance for group means and exact tests for categorical variables.[16]

As an additional measure of severity of illness, the ECMO entry criteria used at the University of Michigan and those used at The Children's Hospital National Medical Center, Washington, DC, were applied retrospectively to each of the study patients. This was done to compare the degree of disease severity in our patients with that of patients at these institutions with established ECMO programs.

The oxygenation index used at the University of Michigan is calculated by: (FIO_2 × mean airway pressure × 100)/PaO_2.[17] An oxygenation index >40 is predictive of 80% mortality.

The Children's Hospital National Medical Center, Washington, DC, uses a combination of the alveolar-arterial difference in partial pressure of oxygen ($A\text{-}aDO_2$) and the peak inspiratory pressure.[18] Criteria for 80% predicted mortality are an $A\text{-}aDO_2$ >625 mm Hg for >4 hours or an $A\text{-}aDO_2$ >610 mm Hg for >12 hours or for >4 hours with peak inspiratory pressure >38 cm H_2O.

RESULTS

Between February 1986 and July 1988, 45 infants met study criteria. Six infants were not enrolled and were thus not assigned to a treatment group because ECMO was not available, 5 during phase I and 1 during phase II. Three of these patients died; 2 survived with continued conventional therapy; the 1 patient not enrolled during phase II was transferred to another institution for ECMO and survived. Thirty-nine infants were enrolled in the study.

The first 19 patients were randomly assigned to CMT and ECMO therapy (phase I). Nine patients received ECMO, and all survived. Ten patients received CMT. Of these, 6 survived and 4 died (Table 2). After the fourth death, randomization ceased, and the next 20 patients were assigned to ECMO treatment (phase II). Of these, 19 survived, and 1 died. The study was terminated at this point; there had been 4 deaths among 10 infants in the CMT group and 1 death among 29 infants in the ECMO group. Termination was based on the initial study design, which implied that 28 survivors in the ECMO group before the fourth death represented a statistically significant improvement in survival rates relative to the CMT group ($P < .05$).

TABLE 2. Survival Experience of Patients Randomly Assigned to Extracorporeal Membrane Oxygenation Therapy and Conventional Therapy during Phase I, the Randomized Phase of the Trial, and Phase II, the Nonrandomized Phase*

	Phase I		Phase II	
	ECMO	CMT	ECMO	CMT
Lived	9	6	19	0
Died	0	4	1	0

* Abbreviations: ECMO, extracorporeal membrane oxygenation; CMT, conventional medical therapy. Results are numbers of children.

This P value is conservative because it is based on an analysis in which we assumed that the study was continued until the fourth death occurred in the ECMO group. Continued enrollment to the ECMO group could only have increased the number of survivors of ECMO therapy, thereby producing a more extreme P value. This P value is conservative because it was calculated as if the study had been continued until the fourth death occurred in the ECMO group. Fisher's exact test gave a P value of .011 when applied to the 2 × 2 table of outcomes for the 39 patients. Using the sampling plan actually used in the study, we calculated an exact one-sided 95% confidence interval for the difference in survival rates. This interval had a lower limit of .04, indicating that patients receiving ECMO had a survival rate at least 4% greater than that for patients receiving CMT. This small lower limit for the increase in survival rate is consistent with the decision to terminate the trial when the data were just sufficient to establish statistical significance at the .05 level.

Characteristics of phase I CMT- and ECMO- and phase II ECMO-treated patients are compared in Table 3. The only statistically significant difference between ECMO- and CMT-treated patients or between phase I and phase II patients was the later enrollment time of the phase II ECMO-treated patients. This is likely due to the preponderance of outborn patients in phase II (15 of 20 vs 9 of 19 in phase I). Diagnoses are compared in Table 4. The differences among groups were not significant.

There were no serious acute complications in the ECMO group related to bleeding except in the one patient who died in phase II. This baby had the right subclavian vein cannulated at another level III neonatal intensive care unit before transfer to Children's Hospital, and the jugular vein was clotted at the time of cannulation. When the patient had a severe bradycardia, the chest was opened and the right atrium was directly cannulated. Although ECMO support proceeded smoothly for 15 days, internal bleeding prevented successful decannulation, and the patient died on day 16.

The mechanical ventilation and ECMO experience for the babies and the proportion of infants in whom chronic lung disease and intracranial bleeding developed in the two phases of the trial are compared in Table 5.

Thirty-six patients met the criteria used at The Children's Hospital National Medical Center,

TABLE 3. Characteristics of Patients Randomly Assigned to Conventional Therapy and Extracorporeal Membrane Oxygenation Therapy During Phase I and Phase II*

Variable	Treatment Group		
	CMT Phase I (n = 10)	ECMO Phase I (n = 9)	ECMO Phase II (n = 20)
Birth weight (kg)	3.40 ± 0.09	3.62 ± 0.13	3.38 ± 0.13
Gestational age (wk)	39.4 ± 0.5	40.4 ± 0.4	39.8 ± 0.3
Apgar Score			
1 min	5.4 ± 0.8	5.9 ± 0.7	4.8 ± 0.7
5 min	7.4 ± 0.5	7.3 ± 0.7	6.8 ± 0.6
Age at enrollment (h)	26.2 ± 4.5	20.0 ± 2.0	33.9 ± 3.5†
Ventilator settings at time of enrollment			
Inspiratory pressure	44.2 ± 3.9	49.9 ± 4.4	52.4 ± 3.2
Positive end-expiratory pressure	4.9 ± 0.5	5.6 ± 0.7	5.2 ± 0.5
Rate (breaths/min)	93.0 ± 12	80.4 ± 14	84.0 ± 6.0
Mean airway pressure	22.6 ± 2.0	24.0 ± 1.6	24.4 ± 1.6
Arterial blood gases at time of enrollment			
Pao_2 (mm Hg)	38.6 ± 4.5	43.2 ± 4.7	38.9 ± 3.3
$Paco_2$ (mm Hg)	36.6 ± 2.6	42.6 ± 3.2	38.7 ± 4.4
pH	7.49 ± 0.03	7.54 ± 0.04	7.49 ± 0.03
Oxygenation index at time of enrollment‡	69.4 ± 11.7	60.0 ± 6.5	76.1 ± 11.2

* Abbreviations: ECMO, extracorporeal membrane oxygenation; CMT, conventional medical therapy. Results are means ± SEM.
† $P < .022$ for phase I compared with phase II patients.
‡ The use of ratio data results in $FIo_2 > 1.0$.

TABLE 4. Diagnostic Characteristics of Patients Randomly Assigned to Extracorporeal Membrane Oxygenation Therapy and Conventional Medical Therapy in Phase I and Extracorporeal Membrane Oxygenation Treated Patients in Phase II*

Diagnosis	Phase I		Phase II (n = 20)
	CMT (n = 10)	ECMO (n = 9)	
Meconium aspiration syndrome	4 (2)	8	11 (1)
Sepsis: positive blood culture or serum latex fixation	1	1	3
Persistent pulmonary hypertension of the newborn			
Abnormal chest radiographic findings	4 (2)	0	6
Normal chest radiographic findings	1	0	0
Place of Birth			
Outborn	5 (4)	4	15 (1)
Inborn	5	5	5

* Abbreviations: ECMO, extracorporeal membrane oxygenation; CMT, conventional medical therapy. Results are numbers of infants (deaths).

Washington, DC. One patient in the CMT group and two ECMO-treated patients did not meet the $A\text{-}aDo_2$ criterion. Thirty-four patients met the oxygenation index criteria from the University of Michigan. Two patients in the CMT group had an oxygenation index <40 at enrollment (ie, 33 and 35). One patient in the phase I and two in the phase II ECMO groups also had an oxygenation index <40 (ie, 36, 39 and 25). The mean oxygenation index values in the two treatment groups were not significantly different. All 5 patients who failed to meet one or both criteria survived.

DISCUSSION

This prospective clinical trial including a randomized and a nonrandomized phase has shown that ECMO reduces mortality in newborn infants with severe persistent pulmonary hypertension of the newborn. The study was undertaken in 1985 because of the paucity of randomized clinical trial experience with ECMO. Although the Central ECMO Registry had reported results in several hundred babies who had been treated with ECMO, the information from randomized trials was limited to 10 infants, only one of whom had received CMT. The need to rely on historical controls in the evaluation of the registry experience was of concern. Dworitz et al[19] showed that criteria associated with 88% mortality in 1980 to 1981 were associated with 17% mortality in similar infants several years later in the same neonatal intensive care unit. In our institution, a criterion associated with an 85% mor-

TABLE 5. Outcome of Therapy*

	Phase I		ECMO Phase II (n = 19)
	CMT (n = 6)	ECMO (n = 9)	
Duration of ECMO (h)	NA	107.7 ± 10.3	120.6 ± 10.2
Duration of mechanical ventilation (d)	8.2 ± 0.7	8.2 ± 0.6	10.1 ± 0.8
Chronic lung disease (No. of infants)†	0	1	1
Intracranial hemorrhage (No. of infants)	0	0	2‡

* Abbreviations: ECMO, extracorporeal membrane oxygenation; CMT, conventional medical therapy.
† $FIO_2 > .21$ at or beyond 28 days in the presence of an abnormal chest radiographic findings.
‡ One infant with unilateral subependymal hemorrhage and one baby with bilateral grade III intraventricular hemorrhage.

tality rate in 1982 to 1983 resulted in a mortality rate of 40% in 1986 to 1988. Although the 40% and 80% mortality rates are not significantly different because of the small numbers, the striking decrease in the number of deaths illustrates the risks inherent in using historical controls. The need for further examination of the relative effectiveness of ECMO, an invasive therapy that is intensive in its use of resources and personnel, and conventional medical therapy was thought to justify a prospective randomized trial.

Despite that justification, the investigators were concerned about the prospect of randomly assigning infants to two therapies that might prove to have different survival rates. To limit the number of children assigned to what might ultimately prove to be the less effective therapy, we used an adaptive design with both a randomized and a nonrandomized phase. Had the therapies proven to be of equal efficacy, nearly all patients would have been randomly assigned. Because the mortality rates differed substantially, the assignment of patients to conventional medical therapy was halted after the 10th patient, and the nonrandomized phase of the trial began.

Although we rejected a fixed sample size design because of the potential for a large difference in mortality rates, a conventional sample size calculation using the null and alternative hypotheses (described in "Methods") gives a sample size requirement of 10 patients in each group. Had the fixed sample size design been adopted, the first 19 children randomly assigned (that is, phase I) would have been joined by the 20th patient assigned to ECMO, and the survival rates would have been 60% and 100%, a statistically significant difference ($P = .043$).

Having chosen not to use a fixed sample size design, we entered a nonrandomized phase (phase II) in which all patients were assigned to ECMO therapy. This design raises the possibility of selection bias due to either differential ascertainment of cases or differential inclusion in the study in phases I and II. The data suggest that comparability has been successfully achieved both between the two treatment groups in phase I and between the ECMO-treated patients in phases I and II (Table 3). If there is any evidence of differences between patients in phases I and II, it is that phase II patients were enrolled several hours later and were perhaps sicker based on a trend toward higher ventilator settings and poorer blood gas values as evident in the oxygenation index. This probably relates to the higher proportion of outborn patients referred to Children's Hospital as awareness of the trial of ECMO spread through our referral area.

Several features of the study design minimized bias in comparisons between the CMT and ECMO groups. We used a single protocol with a single set of eligibility criteria. The patients were consecutively enrolled. The nonrandomized phase of the trial was limited in time and encompassed approximately 1 year of the study's 2½-year duration. Finally, there were no important changes in either referral practices or clinical practices in the neonatal intensive care unit and multidisciplinary intensive care unit during the time of the study.

Another area of potential concern in the study design is the use of informed consent only in the group randomly assigned or assigned to ECMO. There are two potential problems with this procedure. The first, an ethical one, relates to patients being included in a study without their knowledge. This aspect was discussed at length by the investigators, with consultation from the Institutional Review Boards at each hospital. It was believed that, despite concern about the importance of informing parents, the method of randomized consent was preferable for patient and family welfare. The second potential concern is the scientific issue of whether patients in the ECMO group would refuse to participate in the study. Patients randomly assigned to ECMO treatment but whose parents refused consent would be treated with CMT but

would be included for analysis in the ECMO group to which they were assigned. Even if only a few patients refused, the power of the study could be substantially reduced. In the current study, all 29 patients' parents who were approached concerning ECMO therapy gave their consent. We believe that this is a reflection of the severity of illness of these babies and the difficult situation in which parents were placed by the severity of illness and the availability of a new, if untried, therapy. Pains were taken to ensure that parents were not coerced to give consent to this study, and strict adherence to the written consent form was used. In our judgment, consent was given freely and voluntarily.

Although the survival data from this study are compelling, at least three important questions remain. First, the issue of potential morbidity as a result of ECMO has not been fully addressed at this time. All of the surviving patients have been enrolled in a comprehensive follow-up program, and we hope to report data carrying morbidity in survivors in the two treatment groups. However, at this time the risk to benefit equation in terms of long-term survival remains incomplete. Others[20–22] have reported an increased incidence of right-sided brain lesions and neurologic dysfunction in ECMO survivors so that concerns about long-term outcome in these infants continue. The follow-up portion of this study will have the advantage of providing a group of concurrent, medically treated infants so that the impact of ECMO separate from the initial disease state in these babies may be ascertained.[23,24]

Second, although we defined our routine medical management of babies with persistent pulmonary hypertension of the newborn as CMT, many may find our definition of CMT different from their own.[25] Controversy concerning routine effective therapy is inevitable when outcome remains uncertain. Although CMT may differ from hospital to hospital, our therapy was consistent from baby to baby during the time of the study.

Third, the specific entry criteria for patients enrolled in this study need to be emphasized. Whether ECMO would result in improved survival for babies with different disease states, gestational age, or severity of illness remains unproven.

The findings in this study that ECMO resulted in a significant improvement in survival are encouraging. In two groups of infants chosen with a single group of entry criteria, ECMO resulted in a 97% survival rate, significantly better than the group treated with CMT. The availability of ECMO as a rescue therapy should make it possible to more critically evaluate alternative strategies of CMT as they compare to ECMO and each other.

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