Zeitschrift EJ ej884
DOI 10.1055/s-2006-924751
Satzbetrieb Ziegler + Müller
Verlag Thieme/Mündel
Datum 06.11.2006

F. Morini[1]
A. Goldman[2]
A. Pierro[1]

Extracorporeal Membrane Oxygenation in Infants with Congenital Diaphragmatic Hernia: A Systematic Review of the Evidence

Original Article

Abstract

Aim: The aim of this study was to evaluate the evidence supporting the use of extracorporeal membrane oxygenation (ECMO) in infants with congenital diaphragmatic hernia (CDH) and severe respiratory failure. **Methods:** Medline, Embase, ISI Current Contents and Biosis databases were searched using a defined strategy. Case reports and opinion articles were excluded. We performed: 1) a systematic review of non randomised studies comparing mortality when ECMO was not available with a period when ECMO was available. Mortality was classified as "early" (before hospital discharge) and "late" (after discharge). Patients were classified as "ECMO" and "non-ECMO" candidates according to criteria reported by the authors; 2) a meta-analysis of randomised controlled trials (RCTs) comparing ECMO and conventional mechanical ventilation (CMV). Differences in mortality are reported as relative risk (RR) and 95% confidence intervals. **Results:** *A) Systematic review:* 658 studies and 21 (2043 patients) fulfilled the entry criteria. Both early (RR 0.60 [0.51 – 0.70]; $p < 0.001$) and late mortality (RR 0.63 [0.53 – 0.73]; $p < 0.001$) were significantly lower when ECMO was available than when ECMO was unavailable. This difference in mortality was observed in "ECMO candidates" (RR 0.46 [0.32 – 0.68]; $p < 0.001$) but not in "non-ECMO candidates" (RR 0.80 [0.58 – 1.10]; $p = 0.17$). *B) Meta-Analysis:* 3 trials comparing ECMO and conventional ventilation were identified which included 39 infants with CDH. The early mortality was significantly lower with ECMO compared to CMV (RR 0.73 [95% CI 0.55 – 0.99]; $p < 0.04$), however, late mortality was similar in the two groups (RR 0.83 [0.66 – 1.05]; $p = 0.12$). **Conclusions:** Non randomised studies suggest a reduction in mortality with ECMO. However, differences in the indications for ECMO and improvements in other treatment modalities may contribute to this reduction. The meta-analysis of RCTs indicates a reduction in early mortality with ECMO but no long-term benefit. A large RCT in infants with CDH and severe respiratory failure is warranted.

Key words
Congenital diaphragmatic hernia · ECMO · extracorporeal life support · extracorporeal membrane oxygenation

Introduction

Congenital diaphragmatic hernia (CDH) is a common cause of respiratory failure, and is still associated with a high mortality rate, ranging from 8 to nearly 80% [7,16,20,58]. Its incidence is estimated to be between 1 in 2000 and 1 in 5000 live births, although in addition, 30% of affected foetuses are stillborn. CDH is characterised by herniation of bowel loops and liver to the thorax. This in turn leads to compression of the lungs, mediastinal shift and hypoplasia of both the ipsilateral and contralateral lungs. At birth, pulmonary hypertension due to hypoxia, hypercapnea, respiratory acidosis and hypothermia lead to persistent foetal circulation with pulmonary hypertension, patent ductus arteriosus and right-left shunting. The current treatment consists of endotracheal intubation, mechanical ventilation and fluid resuscitation. In addition, high-frequency oscillatory ventila-

Affiliation
[1] Department of Paediatric Surgery, Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, London, UK
[2] Cardiac Intensive Care Unit, Great Ormond Street Hospital for Children NHS Trust, London, UK

Correspondence
Prof. Agostino Pierro · UCL Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust · 30 Guilford Street · London WC1N 1EH · United Kingdom · E-mail: pierro.sec@ich.ucl.ac.uk

Received: ■ · Accepted after Revision: ■

Bibliography
Eur J Pediatr Surg 2006; 16: 1 – 7 © Georg Thieme Verlag KG Stuttgart · New York ·
DOI 10.1055/s-2006-924751 ·
ISSN 0939-7248

Zeitschrift EJ ej884 Satzbetrieb Ziegler + Müller
DOI 10.1055/s-2006-924751 Verlag Thieme/Mündel
Datum 06.11.2006

tion and/or inhaled nitric oxide are frequently used to provide a more gentle ventilation and to correct the pulmonary hypertension. In some centres, extracorporeal membrane oxygenation (ECMO) is also used in selected patients that do not respond to the ventilatory strategies listed above.

Extracorporeal membrane oxygenation (ECMO) is a complex technique that allows the blood to be oxygenated outside the body, obviating the need for gas exchange in the lungs. It is a last resort therapy in those patients who do not respond to maximal conventional therapy. In 1974, Bartlett reported the first newborn with respiratory failure successfully treated by ECMO [2]. Since then, this technique has gained more popularity and over 19000 newborns have been treated with ECMO worldwide and registered in the Extracorporeal Life Support Organization registry [15]. ECMO provides effective but short-term support for the respiratory failure associated with CDH. The use of ECMO provides additional time in which to reverse the persistent pulmonary hypertension which would otherwise be lethal [4,31]. In addition, the use of ECMO avoids high volume and/or pressure ventilation which is traumatic for the lungs. The reported overall survival rate after ECMO for severe respiratory failure is 77% in neonates with a predicted mortality exceeding 80% [15].

The use of ECMO in patients with CDH is receiving growing attention, as testified by the fact that, in 2005 alone, three reviews on this specific issue were published in peer reviewed journals [19,27,42]. However, no conclusive data are available in favour or against the use of ECMO in infants with CDH and respiratory failure. Therefore, in an attempt to define whether ECMO has a role to play in the treatment of infants with severe respiratory failure associated to CDH, we performed a systematic review of published articles comparing ECMO with conventional treatment in infants with CDH. A meta-analysis of both non randomised studies and randomised controlled trials (RCTs) was performed, to compare early and late mortality in the two intervention groups as outcomes.

Methods

Search strategy and data collection

Studies were identified by searching Medline (1966 – 2004), Embase (1978 – 2004), Biosis (1985 – 2004), ISI Current Contents, and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2005) databases, using the terms "extracorporeal" and "diaphragmatic hernia". These databases encompass most of the available literature, including medical congress proceedings and scientific journals. In addition, the references of the identified studies were reviewed and included where appropriate.

All studies reporting patients with CDH treated with ECMO were considered. Case reports and opinion articles (editorials, review papers, and letters to the editor) were excluded. Studies reporting the outcome with ECMO alone, or comparing the mortality rates with ECMO with that expected on the basis of mathematical formulas, were also excluded. Studies reporting the outcome of infants with CDH treated when ECMO was available compared with a period when ECMO was not available and RCTs comparing ECMO with conventional ventilation were included.

Data on early mortality (before hospital discharge) and late mortality (after hospital discharge) were extracted. In non randomised studies, the patients were classified into ECMO candidates and non-ECMO candidates according to the severity criteria reported by the authors, and mortality was extracted for each subgroup. In non randomised studies patients with lethal congenital or chromosomal anomalies, or those fulfilling ECMO exclusion criteria, were excluded. Data from different studies reporting results from the same centre were pooled as appropriate.

Data analysis

Analysis was performed using the Comprehensive Meta-Analysis software, version 1.0.23 (Biostat Inc., Englewood, NJ, USA). Risk ratios (= relative risks, RR) with 95% confidence intervals (CI) were calculated for each study. In non randomised studies, we used a random effects model (DerSimonian-Laird method) to pool the treatment effects estimated in each study, because non randomised studies have a high degree of inter-study variability, due to both clinical and methodological diversity. In RCTs, we used a fixed effects model (inverse variance method), provided no significant heterogeneity between the studies was found. If significant heterogeneity was found ($p < 0.1$), the DerSimonian and Laird method was used. Pooled results are expressed as RR and 95% CI.

Results

Our search strategy resulted in 658 papers, seven of which reported the results of RCTs of ECMO versus conventional ventilation in infants. Thirty-four papers (24 studies) had data directly comparing ECMO with conventional ventilation in infants with CDH, either retrospectively or prospectively (RCTs) [1,3,5,6,8,12 – 14,16,21,22,24 – 26,30,32,33,35,36,39,44 – 48,50 – 56].

Description of studies

Non randomised studies

Twenty-one retrospective studies were identified, reporting the outcome of a total of 2043 patients [1,6,8,12 – 14,16,21,22,24 – 26,30,32,33,35,36,39,45 – 48,52 – 56]. Of these, 67 patients were excluded because of reported associated anomalies or ECMO exclusion criteria. There was a high variability in both inclusion (Table **1**) and, to a lesser extent, exclusion criteria for ECMO.

Randomised controlled trials

In addition, we identified three RCTs comparing ECMO with conventional ventilation in infants with severe respiratory failure and which included data on CDH patients [3,5,44,50,51]. Two trials were carried out in Ann Arbor [4,44]; the data of these two trials were pooled together and analysed by intention-to-treat. In the first trial [4], patients were randomised using the Zelen's "play the winner" technique, [59], in which the first patient has the same probabilities to fall into each of the trial arms, but subsequent assignments are based on the results for previous patients, so that patients will have higher probabilities to be randomised into the arm with the treatment doing better. Parental consent was requested only for those patients allocated

Zeitschrift EJ ej884 Satzbetrieb Ziegler + Müller
DOI 10.1055/s-2006-924751 Verlag Thieme/Mündel
Datum 06.11.2006

Table **1** Indication criteria for ECMO in the retrospective studies included in the meta-analysis

Indication criteria	*Studies (see references)*
OI > 40	[1, 8, 12, 13, 16, 21, 22, 26, 32, 33, 35, 36, 45 – 47, 56]
PaO_2 < 30 mmHg	[8, 25]
PaO_2 < 40 mmHg for > 2 hours	[6, 12, 16, 21, 22, 26, 35, 36, 46, 47]
PaO_2 < 50 mmHg for > 4 hours	[6, 56]
$PaCO_2$ > 40 mmHg	[56]
$PaCO_2$ > 60 mmHg	[8]
$PaCO_2$ > 100 mmHg for > 2 hours	[35, 36]
$AaDO_2$ > 600	[39]
$AaDO_2$ > 610	[6, 35, 36]
MAP > 15 cmH_2O for > 12 hours or MAP > 12 cmH_2O for > 24 hours	[35, 36]
Cardiac failure (aystolic blood pressure < 40 mmHg; pulse rate > 180 bpm; ejection fraction < 30 %) for > 8 hours	[35, 36]
Mean blood pressure < 20 mmHg	[8]
Progressive barotrauma	[21, 35, 36, 45]
FiO_2 > 0.9 for > 24 hours	[35, 36]
pH < 7.15 for > 2 hours	[6, 21, 45]
Lactate level > 3 mmol/L	[26]
Failure to stabilise with conventional therapy	[8, 13, 16, 30, 32, 33, 39, 52, 54, 55]

to ECMO. Randomisation would have been stopped if 10 patients died in either arm of the trial. The trial was stopped when there were 12 randomised patients, one to conventional ventilation (second patient) who died and 11 to ECMO who all survived [3]. Two of these 12 patients had CDH and were both allocated to ECMO treatment. The second randomised controlled trial aimed at a cost-benefit analysis of ECMO [44]. In this trial, an oxygenation index persistently over 25 was an inclusion criteria, instead of over 40 like in the first trial. Patients allocated to conventional ventilation ■?which oxygenation index raised to 40? ■ were switched to ECMO. Each patient was randomised using an unknown block length design and sealed opaque envelopes into either the ECMO or conventional ventilation arm. In this trial, out of 41 randomised infants, two with CDH were allocated into the conventional management arm and were subsequently switched to ECMO due to failure of conventional ventilation.

The third RCT was from the UK Collaborative ECMO Trial Group [5, 50, 51]. In this trial, patients with severe respiratory failure were considered for ECMO if they had an oxygenation index > 40. After the parents agreed to trial entry, the infant was randomly allocated to treatment by a computerised minimisation algorithm taking into account primary diagnosis, severity, and referral hospital and ECMO centre. This trial was stopped early on by the trial steering committee after 185 patients were enrolled, because the data accumulated showed a clear advantage with ECMO. Patients were analysed by intention-to-treat. Among the 185 enrolled infants, 35 had CDH and were randomised, 18 to ECMO and 17 to conventional ventilation.

Meta-analysis

Non randomised studies

Nineteen studies (1810 patients) reported data on early mortality [1, 6, 8, 12 – 14, 16, 21, 22, 25, 26, 30, 32, 33, 35, 36, 39, 45 – 48, 52 – 56]. The meta-analysis of these studies (Fig. **1 a**) showed that early mortality was significantly lower when ECMO was available compared with a period when ECMO was not available (RR 0.60 [95 % CI 0.51 – 0.70]; p < 0.001).

Late mortality was reported in eight studies (352 patients) [12, 21, 22, 33, 35, 39, 45 – 48, 53, 54]. As for early mortality, ECMO was associated with a lower late mortality compared with the period when ECMO was not available (Fig. **1 b**) (RR 0.63 [95 % CI 0.53 – 0.73]; p < 0.001).

Seven studies allowed the subdivision of patients in ECMO candidates (184 patients) and non-ECMO candidates (90 patients) [1, 6, 21, 24, 30, 45, 52, 54]. ECMO candidates (Fig. **2 a**) had a reduced mortality with ECMO available than when ECMO was unavailable (RR 0.46 [95 % CI 0.31 – 0.68]; p < 0.001). Conversely, for non-ECMO candidates (Fig. **2 b**) mortality was similar in the two time periods (RR 0.80 [95 % CI 0.58 – 1.10]; p = 0.17].

Randomised studies

Both studies reported early and late mortality. The use of ECMO was associated with a significant benefit for early mortality (RR 0.73 [95 % CI 0.55 – 0.99]; p < 0.04) (Fig. **3 a**). However, late mortality was similar in patients treated with ECMO compared to those treated with conventional ventilation (RR 0.83 [95 % CI 0.67 – 1.05]; p = 0.12) (Fig. **3 b**).

Discussion

Our meta-analysis of non randomised, retrospective studies on the role of ECMO in patients with CDH suggests a significant reduction in mortality with the use of ECMO, both in the short and the long term. Conversely, the analysis of RCTs comparing ECMO and conventional ventilation in infants with CDH and severe respiratory failure indicates an improvement only in short-term survival.

Meta-analysis of retrospective studies

The meta-analysis of retrospective studies suggests that the introduction of ECMO led to an improvement of survival in infants with CDH. In fact, both early and late mortality were 20% higher when ECMO was not available compared with a period when ECMO was available. In particular, with the introduction of ECMO short-term mortality fell from 53.2% to 34.5% (p < 0.001), and long-term mortality from 56.6% to 35.5% (p < 0.001), with a major benefit for those patients considered ECMO candidates and therefore more severely affected.

The use of ECMO in the treatment of infants with CDH was introduced in the late 1970s [17], and since then, the management of infants with CDH has greatly changed. As the studies analysed in this part of the meta-analysis cover a long time span, it is possible that the introduction of other treatment modalities, such as delayed surgery, gentle ventilation with permissive hypercapnea, high frequency ventilation, and inhaled nitric oxide may

Zeitschrift EJ ej884 Satzbetrieb Ziegler + Müller
DOI 10.1055/s-2006-924751 Verlag Thieme/Mündel
Datum 06.11.2006

a- Short term mortality

Study	ECMO	No ECMO	RR	95% CI	NTotal	PValue
Ann Arbor	39 / 109	8 / 16	0.716	0.413 - 1.241	125	0.273
Bergamo	4 / 29	4 / 12	0.414	0.123 - 1.390	41	0.151
Birmingham	9 / 20	12 / 15	0.562	0.326 - 0-972	35	0.036
Boston	81 / 176	11 / 20	0.837	0.546 - 1.283	196	0.446
Charlottesville	14 / 42	10 / 19	0.633	0.346 - 1.159	61	0.153
Detroit	36 / 75	16 / 24	0.720	0.498 - 1.040	99	0.111
Gainesville	13 / 67	10 / 12	0.233	0.134 - 0.403	79	<0.001
Houston	10 / 32	21 / 62	0.923	0.496 - 1.716	94	0.798
Indianapolis	15 / 46	37 / 65	0.573	0.359 - 0.913	111	0.011
Kasugai	7 / 33	9 / 21	0.495	0.217 - 1.126	54	0.089
Lille	28 / 85	40 / 52	0.428	0.305 - 0.600	137	<0.001
Los Angeles	9 / 31	30 / 58	0.561	0.307 - 1.027	89	0.040
Nijmegen	16 / 37	12 / 18	0.649	0.396 - 1.062	55	0.103
Philadelphia	11 / 30	22 / 32	0.533	0.315 - 0.902	62	0.011
Pittsburg	14 / 31	24 / 62	1.167	0.709 - 1.921	93	0.551
San Diego	13 / 33	22 / 45	0.806	0.480 - 1.353	78	0.405
Shizuoka	6 / 34	12 / 26	0.382	0.166 - 0.883	60	0.017
St Louis	38 / 101	59 / 102	0.650	0.481 - 0.879	203	0.004
Stockolm	11 / 73	27 / 65	0.363	0.196 - 0.672	138	0.001
Combined (19)	**374 / 1084**	**386 / 726**	**0.596**	**0.505 - 0.703**	**1810**	**<0.001**
b- Long term mortality						
Ann Arbor	9 / 34	8 / 16	0.529	0.252 - 1.114	50	0.101
Bergamo	4 / 29	4 / 12	0.414	0.123 - 1.390	41	0.151
Charlottesville	17 / 42	10 / 19	0.769	0.438 - 1.350	61	0.376
Indianapolis	18 / 46	37 / 65	0.687	0.453 - 1.044	111	0.065
Kasugai	6 / 21	9 / 21	0.667	0.289 - 1.540	42	0.334
Lille	34 / 85	40 / 52	0.520	0.385 - 0.702	137	<0.001
Newcastle upon tyne	17 / 48	41 / 81	0.700	0.451 - 1.085	129	0.093
St Louis	39 / 101	59 / 102	0.668	0.496 - 0.898	203	0.006
Combined (8)	**144 / 406**	**208 / 368**	**0.625**	**0.534 - 0.731**	**774**	**<0.001**

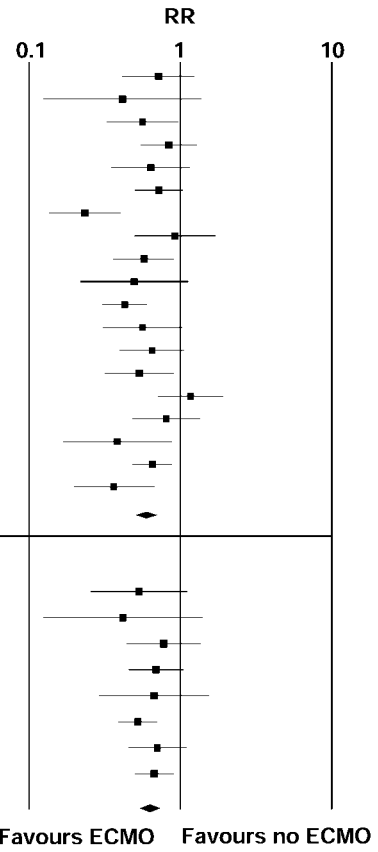

Fig. **1 a** and **b** Meta-analysis of retrospective studies: short-term (**a**) and long-term (**b**) mortality of CDH patients when ECMO was available compared with a period when ECMO was not available. Relative risk (RR) and 95% confidence intervals (CI) of each study and DerSimonian-Laird combined RR and 95% CI estimate.

a- ECMO candidates

Study	ECMO	No ECMO	RR	95% CI	N Total	P Value
Akita	2 / 3	8 / 8	0.662	0.305 - 1.437	11	0.141
Ann Arbor	2 / 15	3 / 3	0.179	0.054 - 0.591	18	0.005
Birmingham	9 / 13	11 / 13	0.818	0.532 - 1.258	26	0.352
Detroit	14 / 27	12 / 13	0.562	0.378 - 0.835	40	0.012
Indianapolis	2 / 13	14 / 16	0.176	0.048 - 0.638	29	<0.001
Los Angeles	4 / 13	18 / 19	0.325	0.143 - 0.739	32	<0.001
Nijmegen	7 / 19	9 / 9	0.395	0.220 - 0.707	28	0.003
Combined (7)	**40 / 103**	**75 / 81**	**0.463**	**0.316 - 0.680**	**184**	**<0.001**
b- non-ECMO candidates						
Ann Arbor	6 / 19	5 / 13	0.821	0.316 - 2.132	32	0.687
Birmingham	0 / 7	1 / 2	0.125	0.007 - 2.301	9	0.094
Detroit	22 / 48	12 / 20	0.764	0.477 - 1.224	68	0.287
Indianapolis	13 / 33	23 / 49	0.839	0.500 - 1.408	82	0.500
Los Angeles	2 / 15	3 / 27	1.200	0.225 - 6.401	42	0.831
Nijmegen	2 / 11	1 / 7	1.273	0.140 - 11.550	18	0.829
Combined (6)	**45 / 133**	**45 / 118**	**0.802**	**0.584 - 1.100**	**251**	**0.171**

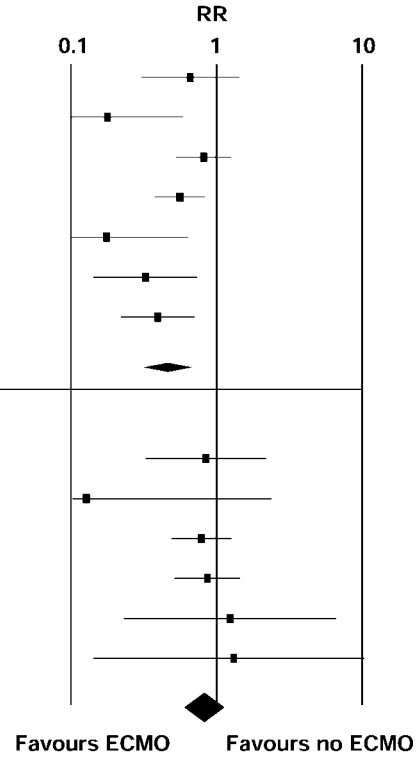

Fig. **2 a** and **b** Meta-analysis of retrospective studies: mortality of CDH patients when ECMO was available compared with a period when ECMO was not available for ECMO candidates (**a**) and non-ECMO candidates (**b**). Relative risk (RR) and 95% confidence intervals (CI) of each study and DerSimonian-Laird combined RR and 95% CI estimate.

Zeitschrift EJ ej884 Satzbetrieb Ziegler + Müller
DOI 10.1055/s-2006-924751 Verlag Thieme/Mündel
Datum 06.11.2006

a- Short term mortality

Study	ECMO	CMV	RR	95% CI	N Total	P Value
Ann Arbor RCT	0 / 2	0 / 2	1.000	0.20 - 28.08	4	1.000
UK Collaborative Trial	13 / 18	17 / 17	0.731	0.54 - 0.98	35	0.031
Combined (2)	**13 / 20**	**17 / 19**	**0.732**	**0.54 - 0.98**	**39**	**0.039**
b- Long term mortality						
Ann Arbor RCT	0 / 2	1 / 2	0.333	0.015 – 4.232	4	0.386
UK Collaborative Trial	15 / 18	17 / 17	0.839	0.668 - 1.053	35	0.126
Combined (2)	**15 / 20**	**18 / 19**	**0.834**	**0.664 – 1.045**	**39**	**0.116**

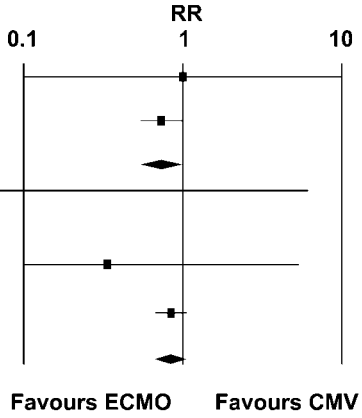

Fig. **3a** and **b** Meta-analysis of RCTs: short-term (**a**) and long-term (**b**) mortality of CDH patients treated with ECMO compared with conventional mechanical ventilation (CMV). Relative risk (RR) and 95% confidence intervals (CI) of each study and combined (inverse variance method) RR and 95% CI estimate.

have influenced the outcome in terms of survival. Until the 1990s, CDH was considered a surgical emergency. However, surgical repair is followed by deterioration of respiratory compliance [43], and preoperative stabilisation improves the outcome [37]. For these reasons most centres repair neonatal CDH after preoperative stabilisation. However, both two small randomised trials [10,38] and a recent Cochrane Systematic Review [34] on early versus delayed surgical repair of CDH failed to reveal a clear evidence favouring either early or delayed repair. Also ventilatory strategies have changed over time. Persistent pulmonary hypertension of the newborn was treated with aggressive hyperventilation (frequently achieved with extremely high peak inspiratory pressures, ventilatory rates, and oxygen concentrations) to alkalinise the patient and to maintain post-ductal oxygen saturations above 90%. However, with this ventilatory strategy, many infants deteriorated and survival was often complicated by iatrogenic lung disease. In 1985 [57], Wung showed that minimizing iatrogenic barotrauma, avoiding harmful overdistension and tolerating relatively high $PaCO_2$ may have the potential to improve the outcome of infants with persistent pulmonary hypertension, and later reported that this strategy proved beneficial also in infants with CDH [58]. High frequency ventilation is the ventilation modality currently used in order to reduce hyperventilation-related lung injury. However, controversy surrounds its use in infants with CDH and severe respiratory failure. Although some studies reported encouraging results [11,40], others have demonstrated no benefit with this ventilation modality [23,29]. Last but not least, in the last decade inhaled nitric oxide has been introduced in the treatment of infants with CDH and severe hypoxemic respiratory failure. Nitric oxide is a potent and selective pulmonary vasodilator which was shown to improve oxygenation in infants with persistent pulmonary hypertension of the newborn [28,41]. However, infants with CDH and severe hypoxemic respiratory failure do not demonstrate a sustained beneficial response to inhaled nitric oxide [49]. The lack of improvement with inhaled nitric oxide in infants with CDH may be due to the fact that in these patients, hypoxemic respiratory failure is secondary not only to persistent pulmonary hypertension of the newborn but also to associated severe lung hypoplasia. Therefore, based on the lack of definitive evidence, it is not possible to conclude that any of the ventilation strategies discussed above taken singularly is able to change the prognosis of infants with CDH, although a combined effect cannot be excluded.

In an attempt to elucidate the effect of ECMO on survival, we performed a subgroup analysis of the non randomised studies by dividing the patients into ECMO candidates and non-ECMO candidates. From the meta-analysis of these studies, it appears that when ECMO became available, survival improved only for ECMO candidates, whose mortality fell from 83.5% when ECMO was not available to 38.3% when ECMO became available ($p < 0.001$). Conversely, for non-ECMO candidates mortality did not change significantly (38.1% to 33.9%; $p = 0.17$). Therefore, the changes in treatment modalities over time (including ECMO) have especially influenced the survival of the most severely affected patients. It is possible that the improvement in survival seen over time could be attributed, at least in part, to the introduction of ECMO.

Meta-analysis of RCTs

A potential source of bias when analysing the results of the retrospective part of the meta-analysis is related to the intrinsic inter-study heterogeneity of retrospective studies and potential biases. This is demonstrated by the variability in the indications for ECMO among the analysed studies, which led to the use of ECMO in patients with markedly different degrees of respiratory failure (Table **1**). In order to overcome this problem, we performed a meta-analysis of RCTs comparing ECMO and conventional ventilation in infants with CDH and severe respiratory failure. We found only three RCTs comparing ECMO and conventional ventilation in 39 patients with CDH and severe hypoxemic respiratory failure. Two RCTs from the same centre included in the meta-analysis [3,44] had infants with CDH (2 infants each) in only one arm of the trial. In addition, in one of these two trials [44], infants with CDH were initially allocated to the conventional ventilation arm and subsequently shifted to the ECMO arm of the trial due to lack of improvement with conventional ventilation. We pooled together the patients from these two trials and analysed them by intention-to-treat.

Zeitschrift EJ ej884 Satzbetrieb Ziegler + Müller
DOI 10.1055/s-2006-924751 Verlag Thieme/Mündel
Datum 06.11.2006

The meta-analysis of RCTs suggests that in infants with CDH and severe respiratory failure, ECMO heralds a benefit in terms of short-term mortality compared to conventional ventilation. This benefit is lost at longer term follow-up. However, it should be noted that in the UK Collaborative ECMO Trial [5,50,51], which accounts for 90% of patients included in our meta-analysis, long-term survivors were found only in the ECMO arm of the trial, suggesting a possible effect of ECMO on long-term survival.

The meta-analysis of RCTs included 20 infants treated with ECMO and 19 treated with conventional ventilation. This small number of patients does not allow us to draw any firm conclusion in favour or against the use of ECMO in infants with CDH and severe hypoxemic respiratory failure.

Conclusions

In infants with CDH, ECMO may contribute to improve survival. However, the available data from both retrospective studies and RCTs, are insufficient to draw firm conclusions with respect to either supporting or discouraging its use. In addition, the use of ECMO in very severe CDH patients may lead to long-term disability [9,18]. Therefore, a large RCT with long-term follow-up is much needed to establish whether ECMO plays a role in infants with CDH and if its use is associated with ominous long-term sequelae.

References

[1] Atkinson JB, Poon MW. ECMO and the management of congenital diaphragmatic hernia with large diaphragmatic defects requiring a prosthetic patch. J Pediatr Surg 1992; 27: 754 – 756
[2] Bartlett RH, Gazzaniga AB, Jefferies MR et al. Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. Trans Am Soc Artif Intern Organs 1976; 22: 80 – 93
[3] Bartlett RH, Roloff DW, Cornell RG et al. Extracorporeal circulation in neonatal respiratory failure: a prospective randomized study. Pediatrics 1985; 76: 479 – 487
[4] Bartlett RH, Gazzaniga AB, Toomasian J et al. Extracorporeal membrane oxygenation (ECMO) in neonatal respiratory failure. 100 cases. Ann Surg 1986; 204: 236 – 245
[5] Bennett CC, Johnson A, Field DJ et al. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation: follow-up to age 4 years. Lancet 2001; 357: 1094 – 1096
[6] Breaux CW Jr, Rouse TM, Cain WS et al. Improvement in survival of patients with congenital diaphragmatic hernia utilizing a strategy of delayed repair after medical and/or extracorporeal membrane oxygenation stabilization. J Pediatr Surg 1991; 26: 333 – 336
[7] Chan DK, Ho LY, Joseph VT. Mortality among infants with high-risk congenital diaphragmatic hernia in Singapore. J Pediatr Surg 1997; 32: 95 – 98
[8] D'Agostino JA, Bernbaum JC, Gerdes M et al. Outcome for infants with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation: the first year. J Pediatr Surg 1995; 30: 10 – 15
[9] Davis PJ, Firmin RK, Manktelow B et al. Long-term outcome following extracorporeal membrane oxygenation for congenital diaphragmatic hernia: the UK experience. J Pediatr 2004; 144: 309 – 315
[10] de la Hunt MN, Madden N, Scott JE et al. Is delayed surgery really better for congenital diaphragmatic hernia? A prospective randomized clinical trial. J Pediatr Surg 1996; 31: 1554 – 1556
[11] Desfrere L, Jarreau PH, Dommergues M et al. Impact of delayed repair and elective high-frequency oscillatory ventilation on survival of antenatally diagnosed congenital diaphragmatic hernia: first application of these strategies in the more "severe" subgroup of antenatally diagnosed newborns. J Intens Care Med 2000; 26: 924 – 941
[12] Dubois A, Storme L, Jaillard S et al. Congenital hernia of the diaphragm. A retrospective study of 123 cases recorded in the Neonatal Medicine Department, URHC in Lille between 1985 and 1996. Arch Pediatr 2000; 7: 132 – 142
[13] Ehren H, Frenckner B, Palmer K. Diaphragmatic hernia in infancy and childhood – 20 years experience. Eur J Pediatr Surg 1992; 2: 327 – 331
[14] Evans M, Dudell G. Congenital diaphragmatic hernia: can ECMO save them all? Pediatr Res 1991; 29: 213A
[15] Extracorporeal Life Support Organization. ECMO Registry of the Extracorporeal Life Support Organization (ELSO), Ann Arbor, Michigan, January 2005
[16] Frenckner B, Ehren H, Granholm T et al. Improved results in patients who have congenital diaphragmatic hernia using preoperative stabilization, extracorporeal membrane oxygenation, and delayed surgery. J Pediatr Surg 1997; 32: 1185 – 1189
[17] German JC, Gazzaniga AB, Amlie R et al. Management of pulmonary insufficiency in diaphragmatic hernia using extracorporeal circulation with a membrane oxygenator (ECMO). J Pediatr Surg 1977; 12: 905 – 912
[18] Hamutcu R, Nield TA, Garg M et al. Long-term pulmonary sequelae in children who were treated with extracorporeal membrane oxygenation for neonatal respiratory failure. Pediatrics 2004; 114: 1292 – 1296
[19] Harrington KP, Goldman AP. The role of extracorporeal membrane oxygenation in congenital diaphragmatic hernia. Semin Pediatr Surg 2005; 14: 72 – 76
[20] Harrison MR, Adzick NS, Estes JM et al. A prospective study of the outcome for fetuses with diaphragmatic hernia. JAMA 1994; 271: 382 – 384
[21] Heiss K, Manning P, Oldham KT et al. Reversal of mortality for congenital diaphragmatic hernia with ECMO. Ann Surg 1989; 209: 225 – 230
[22] Jaillard SM, Pierrat V, Dubois A et al. Outcome at 2 years of infants with congenital diaphragmatic hernia: a population-based study. Ann Thorac Surg 2003; 75: 250 – 256
[23] Kamata S, Usui N, Ishikawa S et al. Prolonged preoperative stabilization using high-frequency oscillatory ventilation does not improve the outcome in neonates with congenital diaphragmatic hernia. Pediatr Surg Int 1998; 13: 542 – 546
[24] Kato T, Yoshino H, Hebiguchi T et al. Therapeutic strategy and clinical outcome in congenital diaphragmatic hernia. Nippon Geka Gakkai Zasshi 1997; 98: 1001 – 1007
[25] Kays DW, Langham MR Jr, Ledbetter DJ et al. Detrimental effects of standard medical therapy in congenital diaphragmatic hernia. Ann Surg 1999; 230: 340 – 348
[26] Keshen TH, Gursoy M, Shew SB et al. Does extracorporeal membrane oxygenation benefit neonates with congenital diaphragmatic hernia? Application of a predictive equation. J Pediatr Surg 1997; 32: 818 – 822
[27] Khan AM, Lally KP. The role of extracorporeal membrane oxygenation in the management of infants with congenital diaphragmatic hernia. Semin Perinatol 2005; 29: 118 – 122
[28] Kinsella JP, Neish SR, Shaffer E et al. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992; 340: 819 – 820
[29] Kinsella JP, Truog WE, Walsh WF et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. J Pediatr 1997; 131: 55 – 62
[30] Lessin MS, Thompson IM, Deprez MF et al. Congenital diaphragmatic hernia with or without extracorporeal membrane oxygenation: are we making progress? J Am Coll Surg 1995; 181: 65 – 71
[31] Lyrenne RK, Phillips JB. Control of pulmonary vascular resistance in the fetus and newborn. Clin Perinatol 1984; 11: 561 – 584
[32] Mallik K, Rodgers BM, McGahren ED. Congenital diaphragmatic hernia: experience in a single institution from 1978 through 1994. Ann Thorac Surg 1995; 60: 1331 – 1335
[33] McGahren ED, Mallik K, Rodgers BM. Neurological outcome is diminished in survivors of congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation. J Pediatr Surg 1997; 32: 1216 – 1220
[34] Moyer V, Moya F, Tibboel R et al. Late versus early surgical correction for congenital diaphragmatic hernia in newborn infants. Cochrane Database Syst Rev 3: CD001695, 2003

Zeitschrift EJ ej884 Satzbetrieb Ziegler + Müller
DOI 10.1055/s-2006-924751 Verlag Thieme/Mündel
Datum 06.11.2006

[35] Nagaya M, Tsuda M, Murahashi O et al. Management of congenital diaphragmatic hernia by extracorporeal membrane oxygenation (ECMO). Eur J Pediatr Surg 1991; 1: 10 – 14
[36] Nagaya M, Tsuda M, Hiraiwa K et al. Extracorporeal membrane oxygenation (ECMO): applications and results in patients with congenital diaphragmatic hernia. Pediatr Surg Int 1993; 8: 294 – 297
[37] Nakayama DK, Motoyama EK, Tagge EM. Effect of preoperative stabilization on respiratory system compliance and outcome in newborn infants with congenital diaphragmatic hernia. J Pediatr 1991; 118: 793 – 799
[38] Nio M, Haase G, Kennaugh J et al. A prospective randomized trial of delayed versus immediate repair of congenital diaphragmatic hernia. J Pediatr Surg 1994; 29: 618 – 621
[39] Okazaki T, Kohno S, Hasegawa S et al. Congenital diaphragmatic hernia: efficacy of ultrasound examination in its management. Pediatr Surg Int 2003; 19: 176 – 179
[40] Reyes C, Chang LK, Waffarn F et al. Delayed repair of congenital diaphragmatic hernia with early high-frequency oscillatory ventilation during preoperative stabilization. J Pediatr Surg 1998; 33: 1010 – 1014
[41] Roberts JD, Polaner DM, Lang P et al. Inhaled nitric oxide in persistent pulmonary hypetrension of the newborn. Lancet 1992; 340: 818 – 819
[42] Rothenbach P, Lange P, Powell D. The use of extracorporeal membrane oxygenation in infants with congenital diaphragmatic hernia. Semin Perinatol 2005; 29: 40 – 44
[43] Sakai H, Tamura M, Hosokawa Y et al. Effect of surgical repair on respiratory mechanics in congenital diaphragmatic hernia. J Pediatr 1987; 111: 432 – 438
[44] Schumacher RE, Roloff DW, Chapman R et al. Extracorporeal membrane oxygenation in term newborns. A prospective cost-benefit analysis. ASAIO J 1993; 39: 873 – 879
[45] Shanley CJ, Hirschl RB, Schumacher RE et al. Extracorporeal life support for neonatal respiratory failure. A 20-year experience. Ann Surg 1994; 220: 269 – 280
[46] Somaschini M, D'Alessio A, Bellan C et al. Congenital diaphragmatic hernia: increase of survival using advanced ventilation techniques and preoperative stabilization. Ital J Pediatr 1998; 24: 128 – 132
[47] Somaschini M, Locatelli G, Salvoni L et al. Impact of new treatments for respiratory failure on outcome of infants with congenital diaphragmatic hernia. Eur J Pediatr 1999; 158: 780 – 784
[48] Stege G, Fenton A, Jaffray B. Nihilism in the 1990s: the true mortality of congenital diaphragmatic hernia. Pediatrics 2003; 112: 532 – 535
[49] The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. Pediatrics 1997; 99: 838 – 845
[50] UK Collaborative ECMO Trial Group. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. UK Collaborative ECMO Trial Group. Lancet 1996; 348: 75 – 82
[51] UK Collaborative ECMO Trial Group. The collaborative UK ECMO (Extracorporeal Membrane Oxygenation) trial: follow-up to 1 year of age. Pediatrics 1998; 101: E1
[52] vd Staak FH, de Haan AF, Geven WB et al. Improving survival for patients with high-risk congenital diaphragmatic hernia by using extracorporeal membrane oxygenation. J Pediatr Surg 1995; 30: 1463 – 1467
[53] Weber TR, Kountzman B, Dillon PA et al. Improved survival in congenital diaphragmatic hernia with evolving therapeutic strategies. Arch Surg 1998; 133: 498 – 502
[54] West KW, Bengston K, Rescorla FJ et al. Delayed surgical repair and ECMO improves survival in congenital diaphragmatic hernia. Ann Surg 1992; 216: 454 – 460
[55] Wiener ES. Congenital posterolateral diaphragmatic hernia: new dimensions in management. Surgery 1982; 92: 670 – 681
[56] Wilson JM, Lund DP, Lillehei CW et al. Congenital diaphragmatic hernia – a tale of two cities: the Boston experience. J Pediatr Surg 1997; 32: 401 – 405
[57] Wung JT, James LS, Kilchevsky E et al. Management of infants with severe respiratory failure and persistence of the fetal circulation without hyperventilation. Pediatrics 1985; 76: 488 – 494
[58] Wung JT, Sahni R, Moffitt ST et al. Congenital diaphragmatic hernia: survival treated with very delayed surgery, spontaneous respiration, and no chest tube. J Pediatr Surg 1995; 30: 406 – 409
[59] Zelen M. Play the winner rule and the controlled clinical trial. J Am Stat Assoc 1969; 64: 131 – 146