

How Does The Changing Profile of Infants Referred for ECMO Affect the Overall Respiratory Outcome?

Caroline S Beardsmore^a, BSc, PhD, Jennifer Westaway^a, SRN, BSc, Hilliary Killer^b, RN, Richard K Firmin^b, FRCS, Hon. FRCPCH, Hitesh Pandya^a, MD, MRCP

^aDepartment of Infection, Immunity & Inflammation, University of Leicester & Institute of Lung Health, Leicester, UK, ^bDepartment of Respiratory Medicine, Glenfield Hospital, Leicester, UK.

Corresponding Author:

Dr Caroline Beardsmore, BSc PhD

Department of Infection, Immunity and Inflammation (Child Health)

University of Leicester

Robert Kilpatrick Clinical Sciences Building, Leicester Royal Infirmary

PO Box 65, LEICESTER, LE2 7LX UK

Tel: +44 (0)116 252 5811

Fax: +44 (0)116 252 3282

e-mail: csb@le.ac.uk

This study was funded by the Department of Health.

Running Head: ECMO patient profile and respiratory outcome

Word count (text only, excl abstract): 3490

Number of figures: 0

Number of tables: 3

Abstract

Objective: Extracorporeal Membrane Oxygenation (ECMO) has been shown to be effective in full-term neonates with severe but reversible lung disease within the context of randomized controlled trial. Since this trial, ECMO has been open to a wider population of infants in the UK and other treatments have become available. The population referred for ECMO has therefore changed. The aims of this study were (i) to compare respiratory outcomes of infants receiving ECMO in recent years with those from ten years ago, and (ii) to see if respiratory outcome varied with diagnostic group.

Methods: All infants referred to a single ECMO centre below the age of 12 months over a 7-year period were eligible. They attended the laboratory one year after ECMO for measurements of lung volume, airways conductance, maximum expiratory flow, and indices of tidal breathing.

Results: One hundred and six (77% of those eligible) were tested and results compared with 51 infants referred for ECMO as part of the original UK ECMO trial. The groups were of comparable weight and length. Lung volume was not different but there was a strong trend for the infants seen in more recent years to have better forced expiratory flow and specific airway conductance.

Restricting analysis to the major sub-group (Meconium Aspiration) confirmed these findings. When divided into diagnostic subgroups, those infants requiring ECMO for respiratory distress syndrome or who were over 2 weeks when commencing ECMO had a poorer respiratory outcome than others.

Conclusions: The respiratory outcome of infants treated beyond the tightly-regulated criteria of the UK trial remains good and even shows a trend towards improvement. Certain subgroups require ECMO for longer and have poorer pulmonary function when followed up. This is important when providing information to parents and may have implications for workload planning of ECMO units and future healthcare provision.

Keywords: Lung function, meconium aspiration, diagnosis.

Abbreviations

ECMO	Extracorporeal membrane oxygenation
HFOV	High-frequency oscillatory ventilation
iNO	Inhaled nitric oxide
FRC _{pleth}	Functional residual capacity measured by plethysmography
V _{max} FRC	Maximum expiratory flow at functional residual capacity
RDS	Respiratory distress syndrome
TPTEF:te	Time to peak tidal expiratory flow
PPHN	Persistent pulmonary hypertension of the newborn

Introduction

Extracorporeal Membrane Oxygenation (ECMO) has been in use for over 20 years, and has been shown to reduce mortality in paediatric patients with acute respiratory failure (1) and in mature newborns with potentially reversible respiratory disease (2). In addition to improving survival, a randomised controlled trial of ECMO in the treatment of sick newborns resulted in improved respiratory function at 1 year (3). The beneficial influence of an ECMO policy has been shown to extend to these children when studied at 7 years (4).

During the time over which ECMO has been available, other treatments (such as surfactant therapy, inhaled nitric oxide (iNO) and high-frequency oscillatory ventilation (HFOV)) have become available. In some centres ECMO is now used in a smaller proportion of patients in particular diagnostic subgroups than was previously the case (5). There has been an overall fall in the number of neonatal patients treated with ECMO and a fall in the average number treated at each ECMO centre since the early 1990s (6). Trials of iNO in neonates with hypoxemic respiratory failure have shown that it results in a decreased need for ECMO (7,8) and is cost-effective (9,10). Despite the increasing use of iNO, ECMO still remains an essential back-up treatment for some patients such as those with pneumothorax (11). There is less evidence for the effectiveness of iNO specifically for the treatment of infants born at or near term (12), but it would appear to reduce the need for ECMO and be cost-effective (13). The benefits of iNO have been shown in both North America and Europe, but differences in survival rates between the continents suggests that approaches to treatment are not the same and highlights the need for caution when extrapolating findings (13).

Against the background of changes in the population of patients referred for ECMO with regard to their diagnosis, treatment prior to referral, and possible clinical status at the time of initiating ECMO, there is the likelihood of changes in outcome. Diagnosis-specific mortality rates for infants with congenital diaphragmatic hernia, meconium aspiration, respiratory distress syndrome and

sepsis did not alter significantly between 1988 and 1998 (6), but there have been few reports of respiratory morbidity or lung function tests. As the ECMO centre treating the largest number of patients in the UK we are able to report respiratory outcomes in over 100 infants treated after April 1997. Information on almost all infants receiving ECMO in the UK between January 1993 and November 1995 is also available to us, since all such infants were enrolled in a nationwide trial of ECMO (2) and almost 80% of these participated in respiratory follow-up at the age of 1 year (3). The first aim of the current study was, therefore, to compare respiratory outcomes of infants receiving ECMO in recent years with those from 10 years ago. The second aim was to see whether the respiratory outcome varied with diagnostic group, and this was pursued with the more recent data exclusively from our own centre. This could be important when counselling parents of infants receiving ECMO and have implications for workload planning of respiratory centres.

Methods

Subjects

Between 1 April 1997 and 31 March 2003 186 infants below 12 months received ECMO at our centre in Leicester, of whom 137 survived for follow-up 1 year later. One hundred and eight infants came for general and developmental follow-up (not reported here) and 106 of them had assessment of their lung function, which was routine in our center. The percentage of eligible infants in the current study group receiving respiratory follow-up was 77%.

The lung function from this group was compared with that of 51 infants who were studied earlier, as part of the UK ECMO trial (2). This national trial randomized 185 infants to either referral for ECMO at one of 5 centers or to conventional management. One hundred and three survived to discharge, and 99 (62 ECMO) were alive and potentially available for respiratory function testing at one year of age. Seventy-eight infants (51 ECMO) were studied at one of 2 centers (including the

facility testing all the later cohort) involved in the respiratory follow-up (3). The percentage of eligible infants from the UK ECMO study receiving respiratory follow-up was 78%.

The criteria for offering ECMO differed between the two populations. Those infants who entered the UK ECMO trial were term infants of 2kg birth weight or greater. An entry requirement was an oxygenation index of above 40, or PaCO₂ above 12 kPa, and less than 10 days' high-pressure ventilation and age below 28 days at trial entry (2). The criteria for offering ECMO in the time frame for treating the current population were relaxed and 8 of the 106 infants (7.5%) were older than 28 days when ECMO was commenced. Twelve infants (11%) were born preterm (before 37 weeks GA).

The procedure for respiratory function tests common to infants in the UK ECMO trial and those studied later (lung volume, specific conductance, and maximum expiratory flow) were identical (3).

Procedure

Infants attended the laboratory as outpatients. A questionnaire was administered to collect information on symptoms, medication and health care consultations and the infant was given a clinical examination. Parents gave written consent for respiratory function testing, baseline oxygen saturation was recorded from a pulse oximeter (Nellcor) and infants were weighed, measured, and sedated with chloral hydrate (100mg.kg⁻¹ bodyweight, up to a maximum dose of 1g). Once asleep, the pulse oximeter was re-attached to the foot for safety monitoring.

Measurements of lung volume and specific conductance

The infant was placed within the Jaeger whole-body plethysmograph for measurements of lung volume (FRC_{pleth}) and specific conductance during initial inspiration (SGawII) by previously reported methods (3,14). Briefly, the infant breathed through a facemask (Rendell Baker size 2) and

pneumotachograph (Jaeger infant model), which were connected to a valve block that permitted the infant to breathe heated, humidified air for measurement of SGawII, or transient occlusion of the external airway. Signals of mask pressure, flow and plethysmograph pressure were recorded onto a personal computer (Elonex) with specialist software (RASP, Physiologic, Newbury, Berks). After a period of quiet breathing of heated, humidified air the valves were closed and the infant made 2 or 3 respiratory efforts against the occlusion to permit calculation of FRC_{pleth} . Approximately five separate measurements of FRC_{pleth} were made. All recordings were visually inspected and any that the operator judged to be not technically acceptable were discarded. SGawII was calculated as the mean of the best seven individual breaths (selected by the operator on the basis of graphical appearance). The mean of all technically acceptable recordings of FRC_{pleth} was reported.

Measurements of maximum expiratory flow

The infant was wrapped in an inflatable 'squeeze' jacket for measurements of maximum expiratory flow ($V_{max}FRC$). A period of regular breathing of approximately 20 seconds was observed prior to inflating the jacket at the end of a tidal inspiration (15). Measurements of $V_{max}FRC$ were repeated over a range of jacket pressures up to a maximum of 6.5 kPa to obtain the highest values of $V_{max}FRC$ and the pressure at which this was achieved (the optimal pressure) was noted for each infant. Several measurements were obtained at optimal pressure. The highest value of $V_{max}FRC$ was reported, provided that the next highest value was within 10% of this.

Measurements of forced expired volumes by the raised volume technique (RV-RTC)

A bias flow of air was attached to the pneumotachograph using a T-piece attached to an adjustable blow-off valve set at 2.0kPa. Augmented breaths were delivered through the facemask by manually occluding the bias flow at the onset of inspiration so that air was directed into the lungs. At the end of inspiration (when the applied pressure and volume reached plateaux) the occlusion was removed and the infant breathed out passively. A series of four successive augmented inspirations was delivered with passive exhalations, followed by a fifth augmented inspiration, which was accompanied by jacket inflation at end inspiration using the previously-determined optimal jacket pressure. Up to six measurements of RV-RTC were made in each infant.

Measurements of RV-RTC were analysed using specialist software ('Squeeze' version 2.04, Dixon and Stocks, Imperial College, London 1999), using a published technique (16). The largest forced expired volume breathed out in the RV-RTC manoeuvre (FVC_p) was recorded. The forced expired volume in the first 0.4s and 0.5s of expiration ($FEV_{0.4}$ and $FEV_{0.5}$) were measured from the RV-RTC and the highest individual values reported.

Tidal breathing analysis

The time to peak tidal expiratory flow (tPTEF) and the ratio of tPTEF to expiratory time (tPTEF:tE) were measured from periods of quiet breathing recorded prior to $V_{max}FRC$ using specialist software ('Squeeze' version 2.04, Dixon and Stocks, Imperial College, London 1999). The five breaths immediately prior to jacket inflation were taken from each of the first five recordings of $V_{max}FRC$ and mean values of tPTEF:tE were calculated.

Analysis of data

In the first stage of the analysis the demographic data from infants in the current follow-up study were compared with those who were assigned to the ECMO limb of the UK ECMO trial using unpaired t-tests or χ -squared tests. In order to take account of sex- and length-related differences in lung function, measurements of FRC_{pleth} and $V_{max}FRC$ were expressed as SD scores (17,18). The differences of the mean SD scores were calculated and the 95% confidence intervals (95% CI) of the differences of the means were used to compare the two study populations. Measurements of SGawII can be compared directly and so the 95% CI of the difference of the means was used to determine whether there was any difference between the groups.

In the second stage of the analysis infants in the current study were divided into subgroups on the basis of underlying diagnosis. Since all infants in the current study received ECMO at a single center, discharge summaries were readily available. The diagnostic subgroup was based on the discharge summary of each infant, which was reviewed by one of the clinical staff from the ECMO unit. Demographic data and lung function were compared between different subgroups using analysis of variance.

Results

Comparison of current population with those assigned to ECMO in the original trial

One hundred and eighty six infants received ECMO between April 1997 and April 2003, of whom 137 survived beyond one year and 106 attended for respiratory function testing. The main underlying reason for ECMO in the infants who were tested was Meconium Aspiration (MAS), which accounted for 67 (63%) of the infants studied. Neonatal sepsis accounted for the next largest subgroup (11 infants). Ten infants started ECMO when over 2 weeks of age ('older') because of severe bronchiolitis (9 infants) or pertussis. The median age of commencing ECMO in this group was 42 days (range 17-188), and 6 of them had been born preterm. Smaller subgroups received

ECMO for persistent pulmonary hypertension of the newborn (PPHN, 7 infants), or respiratory distress syndrome (RDS, 5 infants). The remaining 6 infants were treated for congenital diaphragmatic hernia, pulmonary haemorrhage, or aspiration of blood following maternal antepartum haemorrhage. The infants who attended for respiratory function tests were not different from those who did not attend with respect to gestational age, birthweight, underlying diagnosis or duration of ECMO (data not shown).

The current study group was initially compared to the 51 infants assigned to ECMO in the original trial (Table 1). There were no overall differences in weight or length but the current population was slightly older. This was mainly because the current population included the subgroup of 10 infants who received ECMO outside the first 2 weeks of life, and were therefore older than the other infants when they were referred to the lab 1-year after ECMO. There were no differences in the proportions of infants on respiratory medications at the time of testing or the frequency of reported symptoms of upper respiratory tract infection since discharge from hospital, but the current population were more likely to come from a smoking household ($p < 0.05$). The measurements of FRC_{pleth} were not different in the two populations and were very close to the predicted value. The mean $V_{max}FRC$ for both populations was within predicted limits but tended to be lower than predicted (18). The mean $V_{max}FRC$ from the current population (seen outside the trial setting) showed a strong trend towards improvement when compared with the infants in the original trial, although this did not reach conventional levels of statistical significance (Table 1). SGaw showed a marked trend towards improvement in the current population (Table 1).

Although there were no statistically significant differences in lung function, there were differences in diagnostic profile that could have confounded the results. The largest subgroup in both populations comprised those with meconium aspiration, so we compared these infants directly to see whether any potential differences in the practice of ECMO might have impacted on the outcome

(Table 2). There were no differences in age, weight or length of these two subgroups. The SD scores for FRC_{pleth} and $V_{max}FRC$ were not different from each other, but there was a strong trend for SGaw to be better in the infants treated more recently than in those who were part of the ECMO trial.

Comparison of different diagnostic subgroups

Data from the current population of infants were divided into diagnostic subgroups and demographic data and lung function were compared (Table 3). There were no differences between the groups with respect to weight or length, but the ‘older’ group had a shorter mean gestational age and tended to be older at the time of test than the other subgroups. The duration of ECMO varied between the subgroups, with those treated for RDS or who started ECMO beyond the first 2 weeks of life needing ECMO for longer. The median duration of ECMO in the ‘older’ group was 7.5 days (range 4-24 days) and for the RDS group the median was 8 days (range 4-12).

Resting lung volume was similar in all subgroups, as shown by the lack of differences in FRC_{pleth} . There were strong trends towards significant variation in airway function, seen in both $V_{max}FRC$ ($p=0.057$) and SGaw ($p=0.076$). This was because the ‘older’ infants and those treated for RDS had worse values than the other subgroups. A similar pattern was seen with data from RV-RTC. There were no differences between the groups in FVC_p , which may be considered as a surrogate for lung volume. The infants treated for RDS had the lowest values of $FEV_{0.4}$ and $FEV_{0.5}$ out of the whole population, although differences between groups failed to reach statistical significance. When these timed volumes were expressed as percentages of FVC_p most subgroups had very similar values (Table 3) but the infants treated for RDS had much poorer function. Infants who were older when treated had intermediate values.

Analysis of tidal breathing ($tPTEF:tE$) did not demonstrate any differences between the subgroups.

Discussion

We have shown that the respiratory outcomes of infants receiving ECMO in more recent years are not statistically different from those seen at the time of the UK ECMO trial. There is a trend for improved outcome, seen in the measurements of airway function ($V_{\max}FRC$, $SGaw$, $FEV_{0.4}$ and $FEV_{0.5}$). When analysis was restricted to infants treated for MAS this pattern was retained. When infants in the current cohort were categorised according to the underlying reason for ECMO, the ‘older’ group and (more particularly) those treated for RDS had similar lung volumes but poorer airway function than the other groups.

The comparison of respiratory function in the two populations may be biased by several factors, including: the inclusion/exclusion criteria for ECMO; differences in treatment between the two populations (including differences in the delivery of ECMO); the survival rates of the two populations; and whether the infants tested were representative of the survivors.

The 1-year survival for infants in the original UK trial who were assigned to ECMO was 68% and in the more recent cohort this had increased to 73%. Although this will reflect changes both in the criteria for offering ECMO and treatment modalities between the two populations, the net effect of improved survival might have been an overall worsening of respiratory morbidity due to increased survival of infants with severely compromised lung function. Our finding of a trend towards improvement in lung function shows that this is not the case. By repeating the analysis and restricting it to those infants with a primary diagnosis of MAS we have shown that there is a marked trend towards improvement in airway function, which strongly suggests ongoing refinement of eligibility criteria and/or management of infants in our ECMO unit. The reported frequency of URTI and the use of respiratory medications were, however, unchanged.

Although the respiratory function one year after treatment is similar in those infants treated recently and those who received ECMO as part of the UK ECMO trial, and shows a trend to improvement in airway function, the heterogeneous nature of the population could mask important differences related to underlying reason for ECMO treatment. Our second aim was to examine respiratory outcome with respect to diagnostic subgroup. With the exception of the MAS subgroup, the small size of the subgroups is a limitation of our study. In addressing our second aim, however, we have shown that infants with RDS or those whose treatment started beyond the first 2 weeks of life had poorer airway function than other subgroups. These two subgroups had required ECMO for longer than the others, suggesting that their underlying condition was worse at the outset and took longer to improve to the point where the lungs could adequately their function of oxygenation. Previous reports of ECMO used to treat infants with bronchiolitis also demonstrated a need for relatively long duration of treatment (19, 20, 21). Our ‘older’ group included one infant with pertussis, and our group have previously reported the poor outcome in terms of survival for such infants when referred for ECMO (22). The remaining 9 infants in the ‘older’ group all had RSV bronchiolitis and 6 of them had been born at or prior to 32 weeks gestational age. Only 2 out of the 10 ‘older’ infants would have met the eligibility criteria for the UK trial in terms of their gestation and age at onset of ECMO, so the requirement of this group for extended time on ECMO is particularly relevant for planning of healthcare provision in future. The cost-effectiveness of ECMO in the context of the UK trial has been reported, and most of the additional costs of ECMO relate mainly to care in the neonatal period (23). The cost-effectiveness of ECMO for other groups of infants should be the basis of future economic research (23).

Our largest subgroup comprised infants with MAS, who had normal values of FRC_{pleth} , $SGaw$ and $V_{max}FRC$. Predicted values of the other indices of lung function are less well established but the MAS infants had the highest measurements of $FEV_{0.4}$ and $FEV_{0.5}$ of any subgroup. Reports of lung function from children who survived MAS indicate airway obstruction, hyperinflation, and an

increase in bronchial reactivity, although these groups did not include patients treated with ECMO (24, 25). A report of lung function in children of school age who received ECMO in the neonatal period found that they were hyperinflated, as shown by an increase in residual volume (26). This study did not report measurements of FRC. In contrast, data from the children in the UK trial who received ECMO had normal values of FRC when compared with healthy matched controls, whereas the infants randomized to conventional management had elevated FRC (27). The role of ECMO in preventing lung injury in infants with MAS needs further research.

The three remaining subgroups in our recent cohort (PPHN, sepsis, and ‘other’) were similar to infants with MAS, in that the mean measurements of FRC_{pleth} and $V_{max}FRC$ were within the predicted ranges. The measurements from RV-RTC and tidal breathing from these subgroups were indistinguishable from the MAS infants.

This study provides the opportunity to examine which indices of respiratory function best identify any differences between groups, although this is limited by the small sizes of some subgroups.

Measurements of lung volume, whether direct (FRC_{pleth}) or indirect (FVC_p) were not indicative of major differences, either between infants in the original UK trial and the current cohort or between different diagnostic subgroups. Predicted ranges are available for FRC_{pleth} (18) and it would appear as if all groups of infants have volumes close to prediction. In contrast, airway function as assessed by $V_{max}FRC$ shows that the infants treated for RDS have mean values below the predicted range and the ‘older’ infants are on the lower limits of prediction. Other indices of airway function that are derived from RV-RTC ($FEV_{0.4}$, $FEV_{0.5}$, $FEV_{0.4}/FVC_p$ and $FEV_{0.5}/FVC_p$) also indicate poorer function in these groups. The measurement derived from tidal breathing ($tPTEF:tE$) failed to discriminate between the subgroups. Low values of $tPTEF:tE$ have been shown to be associated with low forced expiratory flows in infants (28) and this, coupled with the attractiveness of a simple

index that could potentially be measured without the need for sedation or complex equipment, was our reason to apply it in the present study.

In conclusion, this study represents the largest respiratory follow-up of infants receiving ECMO to date. It shows that the respiratory outcome of infants treated subsequent to the UK trial remains good at one year after ECMO, and even shows a trend towards improvement. Certain subgroups of infants, namely those treated for RDS or those treated beyond the first 3 weeks for bronchiolitis or pneumonia, require ECMO for longer and have poorer pulmonary function when followed up 12-months later. The modest size of the subgroups, however, indicates a need for caution in the interpretation of the data. Ongoing respiratory follow-up to include larger numbers of patients with findings extending to later childhood and beyond would be important when providing information to parents of infants being treated and may have implications for workload planning of ECMO units.

Acknowledgements

The follow-up reported in this study was funded by the Department of Health. We thank all staff in the ECMO office at Glenfield Hospital, UHL-NHS Trust for their assistance, and Sarah Clarke for help with data analysis. We acknowledge the consent of Professor Janet Stocks, Institute of Child Health, University of London to include data from infants seen there during the one-year respiratory follow-up in the UK ECMO Trial. We particularly thank all infants and their families for their participation.

References

1. Green TP, Timmons OD, Fackler JC, Moler FW, Thompson AE, Sweeney MF. The impact of extracorporeal membrane oxygenation on survival in pediatric patients with acute respiratory failure. Pediatric Critical Care Study Group. *Crit Care Med.* 1996;24:323-329
2. The UK Collaborative ECMO Trial Group. UK Collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet.* 1996;348:75-82
3. Beardsmore CS, Dundas I, Poole K, Enock K, Stocks J. Respiratory function in survivors of the UK ECMO Trial. *Am J Respir Crit Care Med.* 2000;161:1129-1135
4. McNally H, Bennett CC, Elbourne D and Field DJ for the UK Collaborative ECMO Trial Group. United Kingdom collaborative randomized trial of neonatal extracorporeal membrane oxygenation: Follow-up to Age 7-Years. *Pediatrics.* 2006;117:845-854
5. Hintz SR, Suttner DM, Sheehan AM, Rhine WD, Van Meurs KP. Decreased use of neonatal extracorporeal membrane oxygenation (ECMO): how new treatment modalities have affected ECMO utilization. *Pediatrics.* 2000;106:1339-1343
6. Roy BJ, Rycus P, Conrad SA, Clark RH. The changing demographics of neonatal extracorporeal membrane oxygenation patients reported to the Extracorporeal Life Support Organization (ELSO) Registry. *Pediatrics.* 2000;106:1334-1338
7. Anonymous. Inhaled nitric oxide in term and near-term infants: Neurodevelopmental follow-up of The Neonatal Inhaled Nitric Oxide Study Group (NINOS). *J Pediatrics* 2000;136:611-617

8. Clark RH, Kueser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *N Engl J Med.* 2000;342:469-474
9. Lonnqvist PA. Efficacy and economy of inhaled nitric oxide in neonates accepted for extracorporeal membrane oxygenation. *Acta Physiol Scand.* 1999;167:175-179
10. Angus DC, Clermont G, Watson RS, Linde-Zwirble WT, Clark RH, Roberts MS. Cost-effectiveness of inhaled nitric oxide in the treatment of neonatal respiratory failure in the United States. *Pediatrics* 2003;112:1351-1360
11. Sebald M, Friedlich P, Burns C, Stein J, Noori S, Ramanathan R, Seri I. Risk of need for extracorporeal membrane oxygenation support in neonates with congenital diaphragmatic hernia treated with inhaled nitric oxide. *J Perinatol.* 2004;24:143-146
12. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. *Cochrane Database Syst Rev.* 2001;CD000399
13. Field D, Elbourne D, Hardy P, Fenton AC, Ahluwalia J, Halliday HL et al. Neonatal ventilation with inhaled nitric oxide vs ventilatory support without inhaled nitric oxide for infants with severe respiratory failure born at or near term: The INNOVO multicentre randomised controlled trial. *Neonatology* 2007;91:73-82
14. Dundas I, Beardsmore C, Wellman T, Stocks J. A collaborative study of infant respiratory function testing. *Eur Respir J.* 1998;12:944-953

15. Sly PD, Tepper R, Henschen M, Gappa M, Stocks J on behalf of the ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. Tidal Forced Expirations. *Eur Respir J*. 2000;16:741-748
16. Henschen M, Stocks J, Hoo AF, Dixon P. Analysis of forced expiratory manoeuvres from raised lung volumes in preterm infants. *J Appl Physiol*. 1998; 85:1989-1997
17. Stocks J, Quanjer Ph H. Reference values for residual volume, functional residual capacity and total lung capacity. *Eur Respir J*. 1995;8:492-506
18. Hoo A-F, Dezateux C, Hanrahan JP, Cole TJ, Tepper RS, Stocks J. Sex-specific prediction equations for V_{\max} FRC in infancy: a multicenter collaborative study. *Am J Respir Crit Care Med*. 2002;165:1084-1092
19. Khan JY, Kerr SJ, Tometzki A, Tyszczyk L, West J, Sosnowski A et al. Role of ECMO in the treatment of respiratory syncytial virus bronchiolitis: A collaborative report. *Arch Dis Child Fetal Neonatal Ed*. 1995;73:F91-F94
20. Steinhorn RH, Green TP. Use of extracorporeal membrane oxygenation in the treatment of respiratory syncytial virus bronchiolitis: The national experience, 1983-1988. *J Pediatrics*. 1990;116:338-342
21. Flamant C, Hallalel F, Nolent P, Chevalier J-Y, Renolleau S. Severe respiratory syncytial virus bronchiolitis in children: From short mechanical ventilation to extracorporeal membrane oxygenation. *Eur J Pediatr*. 2005;164:93-98

22. Pooboni S, Roberts N, Westrope C, Jenkins DR, Killer H, Pandya HC, Firmin RK. Extracorporeal life support in pertussis. *Pediatr Pulmonol.* 2003;36:310-315
23. Petrou S, Bischof M, Bennett C, Elbourne D, Field D, McNally H. Cost effectiveness of neonatal extracorporeal membrane oxygenation based on 7-year results from the United Kingdom Collaborative ECMO Trial. *Pediatrics.* 2006;117:1640-1649
24. Macfarlane PI, Heaf DP. Pulmonary function in children after neonatal meconium aspiration syndrome. *Arch Dis Child.* 1988;63:368-372
25. Swaminathan S, Quinn J, Stabile MW, Bader D, Platzker ACG, Keens TG. Long-term pulmonary sequelae of meconium aspiration syndrome. *J Pediatr.* 1989;114:356-361
26. Hamutcu R, Nield TA, Garg M, Keens TG, Platzker AC. Long-term pulmonary sequelae in children who were treated with extracorporeal membrane oxygenation for neonatal respiratory failure. *Pediatrics.* 2004;114:1292-1296
27. Beardsmore C, Lavery A, King C, Jotham D, Paton J, Stocks J. Randomized controlled trial of neonatal ECMO: Seven-year respiratory follow-up. *Am J Respir Crit Care Med.* 2004;169:A379 (Abstract)
28. Clarke JR, Aston H, Silverman M. Evaluation of a tidal expiratory flow index in healthy and diseased infants. *Pediatr Pulmonol.* 1994;17:285-290

Table 1. Comparison of demographics and respiratory function in infants referred for ECMO after the UK ECMO trial and those receiving ECMO within the context of the trial.

		All infants in current study	Infants from ECMO trial	95% CI (Current-ECMO trial)
Number (male)		106(61)	51(31)	
Age (months)		15.2(2.2)	13.6(1.8)	+0.288, +2.79*
Mean Gestational Age (SD) (weeks)		39.2(3.25)	39.3(2.3)	-2.55, +2.37
Mean Weight (SD) (kg)		10.30(1.59)	10.2(1.6)	-0.85, +0.93
Mean Length (SD) (cm)		77.9(4.0)	78.1(3.9)	-5.33, +4.91
Frequency of URTI (%)	Rare	33	27	
	Average	50	51	
	Frequent	17	22	
Number (%) on current resp. medic ⁿ		17(16)	7(14)	
Number (%) from smoking household		47(44)	15(29)*	
V _{max} FRC, mean Z-score		-1.089	-1.497	-0.156, +0.97
FRC _{pleth} , mean Z-score		0.046	-0.065	-0.803, +1.024

SGawII (kPa.s ⁻¹)	2.97	2.18	-0.060, +1.64
-------------------------------	------	------	---------------

Footnote to Table 1: * significant at the 5% level.

Table 2: Comparison of demographics and respiratory function in infants with Meconium Aspiration Syndrome (MAS) referred for ECMO in the current study and those receiving ECMO within the UK ECMO trial.

	Current infants	ECMO trial	95% CI (Current-previous)
Number (male)	67(39)	19(11)	
Mean Age (months)	15.07	14.00	-1.45, +3.61
Mean Weight (kg)	10.38	10.54	-1.227, +0.893
Mean Length(cm)	78.06	78.55	-6.40, +5.42
Number (%) on current respiratory medication	7 (10)	1 (5)	
Number (%) from smoking household	29 (43)	7 (37)	
Frequency of URTI (%)			
rare	20 (33)	7 (37)	
average	36 (59)	8 (42)	
very frequent	6 (9)	4 (21)	
FRC _{pleth} , Z-score	-0.058	0.090	-1.02, +0.72
V _{max} FRC, Z-score	-0.85	-1.18	-0.403, +1.067
Mean SGawII (kPa.s ⁻¹)	2.91	2.18	-0.098, +1.555

Table 3: Comparison of infants according to diagnostic subgroup

	All	MAS	PPHN	Sepsis	RDS	Older	Other	P
Number (male)	106(61)	67(39)	7(2)	11(8)	5(3)	10(5)	6(4)	
Mean Gestation (SD)(wk)	39.2(3.25)	40.5(0.81)	38.6(1.99)	37.6(3.26)	38.6(2.79)	32.8(6.07)	39.8(1.47)	0.0000
Mean Age (SD) (months)	15.2(2.2)	15.1(2.06)	14.9(2.36)	15.0(1.44)	14.5(2.55)	17.2(3.02)	13.7(0.64)	0.052
Mean Weight (SD) (kg)	10.30(1.59)	10.38(1.66)	10.23(1.67)	10.71(1.41)	10.16(2.08)	10.07(1.09)	9.13(0.79)	0.49
Mean Length (SD) (cm)	77.9(4.0)	78.1(4.14)	76.2(3.09)	79.8(2.94)	77.3(6.53)	77.7(3.12)	76.6(3.76)	0.506
Mean No. Days ECMO(SD)	5.6 (3.1)	5.0(2.1)	5.7(4.1)	5.5(2.0)	8.0(3.5)	9.2(5.8)	5.0(2.1)	0.0008
FRC _{pleth} Mean Z-score	0.046	-0.06	-0.03	0.17	0.58	0.33	0.025	0.931
V _{max} FRC _{pleth} Mean Z-score	-1.089	-0.85	-1.02	-1.17	-2.14	-1.96	-0.50	0.057
Mean SGaw (kPa.5 ⁻¹)	2.97	2.91	3.77	4.30	2.76	1.63	3.53	0.076
Mean FVCp (ml)	300 (60)	307	264	286	261	329	297	0.386
Mean FEV _{0.4} (ml)	182 (36)	191	172	176	131	184	184	0.060

Mean FEV _{0.5} (ml)	208 (40)	216	199	203	151	213	208	0.078
Mean FEV _{0.4} /FVCp (%)	62	63.1	65	63	53	56	64	0.281
Mean FEV _{0.5} /FVCp (%)	71	73	75	73	60	65	72	0.162
Mean tPTEF:tE	0.245	0.245	0.310	0.257	0.242	0.221	0.199	0.194