ECMO or no ECMO: Do no harm

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Extracorporeal membrane oxygenation (ECMO) has been used in the management of neonates with life-threatening cardiorespiratory diseases since 1982[1]. Several studies have demonstrated that ECMO promotes normal survival in neonates with respiratory failure[2-4]. After decades of discussion, ECMO is now well accepted as a standard of treatment for neonatal respiratory failure refractory to conventional techniques of pulmonary support. The randomized controlled study done by the UK collaborative ECMO trial group[4] has definitely proven the efficacy of ECMO at a time when nowhere in North America this study could have been undertaken. Over the past several years, other therapies such as surfactant replacement, high-frequency oscillatory ventilation (HFOV), and inhaled nitric oxide (iNO) have been introduced and used increasingly in the management of these critically ill infants[5]. Among premature infants with respiratory distress syndrome, surfactant-replacement therapy was shown to reduce mortality[6]. Following an analysis of patients reported to the Extracorporeal Life Support Organization (ELSO) registry[5], it was found that the use of surfactant has been now extended to term or near-term neonates with meconium aspiration syndrome, pneumonia and congenital diaphragmatic hernia. In 1988, no patients had received surfactant prior to ECMO institution. However, in 1997, surfactant administration was reported in 36% of patients. This followed the report by Findlay et al[7] showing that surfactant in term infants with meconium aspiration syndrome decreased air leak, requirement for ECMO, days on oxygen, days on the ventilator and days in hospital. Lotze et al[8] also examined the effect of surfactant in babies with persistent pulmonary hypertension of the newborn (PPHN), meconium aspiration syndrome and sepsis, and found a significant reduction in the need for ECMO.

In a prospective randomized trial, HFOV was successful in 48% of neonatal ECMO candidates whereas continued intermittent positive pressure ventilation (IPPV) only in 26%[9]. Only about 50% of neonates meeting criteria for ECMO required ECMO after a trial of HFOV in another prospective cohort studies[10,11]. These results have been largely supported by clinical experience. Although it is currently not possible to predict which infants will respond to HFOV, it appears appropriate to most clinicians to try HFOV in infants with PPHN who fail conventional ventilation.

NO is produced in vascular endothelial cells and plays an important role in the increase in pulmonary blood flow after birth[12-18]. Exogenously administered, NO causes selective pulmonary vasodilation in newborn lambs (12). In human neonates, iNO was shown to improve oxygenation in 50% of cases[19,20] and furthermore, decreases the need for ECMO[19-21]. However, iNO is ineffective in congenital diaphragmatic hernia[22]. Of interest, when iNO is combined to HFOV, a better response is obtained than when each of the therapy is used alone[23].

Considering that these therapies decrease the need for ECMO[9-11,19,24-26], they will necessarily impact on the type of patients treated with ECMO and may potentially change the general outcome of patients treated with ECMO. In a study done for ELSO, Roy et al[5] showed that the proportion of neonates with congenital diaphragmatic hernia increased from 18% to 26% between the late 80's and the late 90's. This may signify for a particular ECMO center that a greater proportion of the ECMO patients will be more challenging. In this same study, the overall mortality increased from 18% to 22%, but diagnoses-specific mortality rate was unchanged. However, it remains of a particular concern that such therapies may potentially delay the institution of ECMO, the lungs of these neonates may undergo additional barotrauma and neonates may even be excluded from subsequent ECMO if the ventilation period is prolonged. In fact, in a prospective study of 34 neonates of at least 34-week gestation that met ECMO criteria i.e. oxygenation index (OI) greater than 40, 2 patients were denied ECMO because they had undergone already

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14 days of ventilation[27]. Furthermore, in a retrospective study of all patients with meconium aspiration syndrome reported to the ELSO registry for the decade 1989 through 1998, looking at time of institution of ECMO, it was found that delay in institution of ECMO for meconium aspiration syndrome resulted in prolonged ECMO and need for longer post-ECMO ventilation[28]. On the other hand, in a study looking at the demographics and health care practices in neonatal ECMO patients reported to ELSO registry, it was found that the PaO_2/FiO_2 ratio recorded just before initiation of ECMO increased over the years in non-congenital diaphragmatic hernia patients, while the mean peak inspiratory pressure decreased, suggesting that neonatal ECMO patients are healthier[5]. Furthermore, the average age at which ECMO was started had not increased significantly. This may suggest that despite being offered several rescue therapies, if the age at which patients are identified as needing ECMO has not changed, less stringent criteria are applied. However, the group in Boston[29] had a different impression from their data, that is that the patients appeared sicker in the last years. Furthermore, they also speculated that the increased duration of ECMO might, in part, be attributable to the relative increase in patients who traditionally require a longer period on ECMO, i.e. congenital diaphragmatic hernia. They also noted a trend toward increased time on ECMO in their meconium aspiration syndrome, PPHN and sepsis, supporting their hypothesis. Differences may be attributable to local practices.

This conjecture demands that we reevaluate ECMO criteria in the health care era where HFOV, surfactant, and iNO are commonly used to avert the use of ECMO. Historically, criteria for initiation of ECMO had been established before the introduction of HFV, surfactant and iNO[1]. An earlier report in 1992 by Baumgart et al[30] had examined this aspect with respect to high frequency jet ventilation (HFJV) in order to develop criteria for the early initiation of ECMO in neonates who fail to respond to HFJV. They had already suggested that in newborns with a high probability of survival, one should see a rapid decline in the OI, with a level below 20 achieved by 6 hours of treatment. Failure to observe such improvement, especially if there has been an OI greater that 40, should alert the clinician that the child has a high probability of dying. Furthermore, conditions with non-uniform lung disease like meconium aspiration syndrome and congenital diaphragmatic hernia, may be less responsive to HFJV compared with neonates with respiratory distress syndrome or pneumonia. This was later confirmed in neonates treated with high frequency oscillatory ventilation[31]. In that later study, a 6-hour arterial to alveolar oxygen ratio (a/A ratio) of 0.08 or lower yielded the highest sensitivity and specificity in correctly identifying non-congenital diaphragmatic hernia neonates who were treated with ECMO. More recently, a study attempted to identify as early as possible a threshold OI that predicts temporary or persistent improvement with HFOV and iNO in neonatal ECMO candidates[27]. They found in their patients that an OI $\geq$ 25 after 72h of HFOV and iNO predicted unsuccessful HFV/iNO with a sensitivity of 91% and a positive predictive value of 100%. The predictability in this study is obviously great, but most clinicians would want criteria that could help them making a decision earlier than 3 days down in the treatment course. Even though these studies have not succeeded in providing a clear way of determining earlier who are these unresponsive patients, they have at least set some clear questions to be tested in prospective randomized trials. One important point that deserves attention is that one should remember that an OI of 40 does not only reflect the disease severity, but also how hard one is trying to avoid ECMO. If the goal is to avert the use of ECMO, it is important that the outcome of patients avoiding ECMO be determined to ensure that it is done safely and it is not based only on cost issues. Close follow-up through school age is extremely important when one needs to determine which approach is the most appropriate. For example, ECMO for meconium aspiration syndrome with a survival rate of 100%, or other therapies. In a recent study[32] comparing survivors of neonatal ECMO to patients referred for ECMO who improved and did not require ECMO, a similar cognitive and adaptive outcomes at 5 years of age was found. Despite the relative normal IQ values, a significant number in each group were at risk for school failure. Although in general, findings are reassuring in this population, they do indicate that the ECMO patient and those who nearly receive ECMO patient need close follow-up through school age.

The positive side of ECMO being so heavily criticized was that clinicians involved in the care of ECMO patients, became themselves very critical about their own pre-ECMO medical management. The diagnosis of congenital diaphragmatic hernia carries a high mortality rate despite the addition of HFOV, iNO and ECMO to the standard treatment arsenal. Survival rates currently range from 63% to 69% in multicenter studies[33-35] and 53% to 78% in large single-center cohorts[36-38]. The delayed surgical repair has been widespread and avoidance of harmful overventilation has become a great concern[36,39]. In two large studies[36,38], a lower rate of ECMO use is reported (13.3% and 43%) compared to the 46% in multicenter studies[33-35]. This low rate may be attributed partially to overall respiratory care strategy. However, the degree of severity of respiratory failure in their patients was not well defined and it is, then, very difficult to assess the success rate. As a matter of fact, this point was raised by Boloker et al[39], where in their own study, infants treated with gentle ventilation strategy, an OI greater than 20 indicated patients with an increased risk of mortality as opposed to the traditional number of 40. It is therefore important in these

studies, not only to describe the severity of the patients' disease, but also to find a good descriptor.

Although some centers have lowered their gestational criteria to 32 weeks, most centers still only accept for ECMO, infants who are ≥ 34 gestation, with a birth weight greater than 2 kg. This cut off is related to the incidence of intracranial hemorrhage in the less mature ECMO population. Although initially infants with an intracranial hemorrhage (ICH) of any type diagnosed before ECMO were not considered candidates for ECMO, most centers will now consider infants with ICH less than grade II. Most infants are considered for ECMO if there have been fewer than 10 to 14 days of ventilation with high ventilator settings. This decision should be a clinical one, and should be made on a case by case basis. Basically, the disease treated with ECMO has to be reversed in a short period of time. Conversely, older infants with chronic lung disease who have an acute insult, eg, respiratory syncitial virus, can be supported with ECMO for resolution of the acute process, but not to treat the chronic lung disease. Now venovenous (VV) ECMO is used in most centers reporting to ELSO[5], in both congenital diaphragmatic hernia and non-congenital diaphragmatic hernia patients. However, the type of ECMO does not appear to influence the length of ECMO treatment.

Because iNO therapy has become adopted as a standard of care for PPHN, its use has increased in many centers without the capability of providing other rescue therapies, such as ECMO. Although iNO therapy is often effective, 30% to 40% of sick newborns do not have sustained improvement in oxygenation and hemodynamics after initiation of therapy. Prudent integration of functional iNO transport systems within the referring area of an ECMO center has been recommended as a priority[40]. Finally, the use of HFOV and iNO in non-ECMO centers may pose undue risk for infants who subsequently need to be transported. Even under the most skilled care, therapies such as HFOV, surfactant and iNO, patients may not improve rapidly, and if they happen to be at a distant, non-ECMO site, a potentially life-saving therapy may come too late. In fact, an earlier report had stated that up to 10% of patients referred for ECMO might die on transport[41]. Decision should be made in the best interest of the infant. Another important point regarding the dramatic decreasing number of patients per center being supported with ECMO is that there has to be sufficient patients per year to maintain the expertise. It is time to readdress the need for a regional approach to ECMO centers and be innovative in ways to maintain the expertise.

In conclusion, neonatal ECMO has resulted in a significant improvement in survival in neonates with cardiopulmonary failure refractory to maximal medical therapy. Existing criteria to be considered for ECMO were set at a time where medical management of these newborns was quite different and is most likely not appropriate anymore. The current challenge of the clinician is to juggle with all these therapies, including ECMO, and apply them in a timely fashion. Continued evaluation of all therapies in each center is warranted in order to ensure the safety of the patients, not only in term of survival, but also in term of outcome. ECMO is there to stay, at least in the more difficult patients, and for the near-miss ECMO patients, follow-up studies will determine what is best, ECMO or no ECMO.

REFERENCES

1. Bartlett RH. Extracorporeal life support for cardiopulmonary failure. Curr Probl Surg 1990;27:621-705.
2. Bartlett RH, Roloff DW, Cornell RG, Andrews AF, Dillon PW, Zwischenberger JB. Extracorporeal circulation in neonatal respiratory failure: A prospective randomized study. Pediatrics 1985;76:479-87.
3. O'Rourke PP, Crone RK, Vacanti JP, Ware JH, Lillehei CW, Parada RB, et al. Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension: A prospective randomized study. Pediatrics 1989;84:957-63.
4. UK collaborative ECMO Trial Group: UK collaborative randomized trial of neonatal extracorporeal membrane oxygenation. Lancet 1996;348:75-82.
5. 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;106:1334-8.
6. Jobe AH. Pulmonary surfactant therapy. N Engl J Med 1993;328: 861-8.
7. Findlay RD, Taeusch HW, Walther FJ. Surfactant replacement therapy for meconium aspiration syndrome. Pediatrics 1996;97: 48-52.
8. Lotze A, Mitchell BR, Bulas DI, Zola EM, Shalwitz RA, Gunkel JH. Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. J Pediatr 1998;132:40-7.
9. Clark RH, Yoder BA, Sell LL. Prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. J Pediatr 1994;124:427-30.
10. Varnholt V, Lasch P, Suske G, Kachel W, Brands W. High-frequency oscillatory ventilation and extracorporeal membrane oxygenation in severe persistent pulmonary hypertension of the newborn. Eur J Pediatr 1992;151:769-74.
11. Ito Y, Kawano T, Miyasaka K, Katayama M, Sakai H. Alternative treatment may lower the need for use of extracorporeal membrane oxygenation. Acta Pediatr JPN 1994;36:673-7.
12. Abman SH, Chatfield BA, Hall SL, McMurtry IF. Role of endothelium-derived relaxing factor during transition of pulmonary circulation at birth. Am J Physiol 1990;259:H1921-7.
13. Kinsella JP, McQueston JA, Rosenberg AA, Abman SH. Hemodynamic effects of exogenous nitric oxide in ovine transitional pulmonary circulation. Am J Physiol 1992;263:H875-80.
14. Perreault T, De Marte J. Maturational changes in endothelium-derived relaxations in the newborn piglet pulmonary circulation. Am J Physiol 1993;264:H302-9.
15. Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991;43: 109-42.

16. Moncada S, Higgs A. The L-arginine-nitric oxide pathway. N Engl J Med 1993;329:2002-12.

17. Steinhorn RH, Morin FCIII, Fineman JR. Models of persistent pulmonary hypertension of the newborn (PPHN) and the role of cyclic guanosine monophosphate (GMP) in pulmonary vasorelaxation. Semin Perinatol 1997;21:393-408.

18. Berkenbosch JW, Baribeau J, Perreault T. Decreased synthesis and vasodilation to nitric oxide in piglets with hypoxia-induced pulmonary hypertension. Am J Physiol 2000;278:L276-83.

19. Roberts JD Jr, Fineman JR, Morrin FC 3rd, Shaul PW, Rimar S, Schreiber MD, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The inhaled nitric oxide study group. N Engl J Med 1997;336:605-10.

20. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med 1997;336:597-604.

21. 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: 469-74.

22. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. Pediatrics 1997;99:838-45.

23. Kinsella JP, Truog WE, Walsh WF, Goldberg RN, Bancalari E, Mayock DE, 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.

24. De Lemos R, Yoder B, McCurnin D, Kinsella J, Clark R, Null D. The use of high-frequency oscillatory ventilation (HFOV) and extracorporeal membrane oxygenation (ECMO) in the management of the term/near term infant with respiratory failure. Early Hum Dev 1992;29:299-303.

25. Hoffman GM, Ross GA, Day SE, Rice TB, Nelin LD. Inhaled nitric oxide reduces the utilization of extracorporeal membrane oxygenation in persistent pulmonary hypertension of the newborn. Crit Care Med 1997;25:352-9.

26. Muller W, Kachel W, Lasch P, Varnholt V, Konig SA. Inhaled nitric oxide for avoidance of extracorporeal membrane oxygenation in the treatment of severe persistent pulmonary hypertension of the newborn. Intensive Care Med 1996;22:71-6.

27. Kossel H, Bauer K, Kewitz G, Karaca S, Versmold H. Do we need new indications for ECMO in neonates pretreated with high-frequency ventilation and/or inhaled nitric oxide? Intensive Care Med 2000;26:1489-95.

28. Gill BS, Neville HL, Khan AM, Cox CS Jr, Lally KP. Delayed institution of extracorporeal membrane oxygenation is associated with increased mortality rate and prolonged hospital stay. J Pediatr Surg 2002;37:7-10.

29. Wilson JM, Bower LK, Thompson JE, Fauza DO, Fackler JC. ECMO in evolution: The impact of changing patient demographics and alternative therapies on ECMO. J Pediatr Surg 1996;31:1116-22.

30. Baumgart S, Hirschl RB, Butler SZ, Coburn CE, Spitzer AR. Diagnosis-related criteria in the consideration of extracorporeal membrane oxygenation in neonates previously treated with high-frequency jet ventilation. Pediatrics 1992;89:491-4.

31. Paranka MMS, Clark RH, Yoder BA, Null DM Jr. Predictors of failure of high-frequency oscillatory ventilation in term infants with severe respiratory failure. Pediatrics 1995;95:400-4.

32. Rais-Bahrami K, Wagner AE, Coffman C, Glass P, Short BL. Neurodevelopmental outcome in ECMO vs near-miss ECMO patients at 5 years of age. Clin Pediatr 2000;39:145-52.

33. The congenital diaphragmatic hernia study group: Does extracorporeal membrane oxygenation improve survival in neonates with congenital diaphragmatic hernia? J Pediatr Surg 1999;34:720-5.

34. Clark RH, Hardin WD Jr, Hirschl RB, Jaksie T, Lally KP, Langham MR, et al. Current surgical management of congenital diaphragmatic hernia study group. J Pediatr Surg 1998;33: 1004-9.

35. Reickert CA, Hirschl RB, Atkinson JB, Dudell G, Georgeson K, Glick P, et al. Congenital diaphragmatic hernia survival and use of extracorporeal life support at selected level III nurseries with multimodality support. Surgery 1998;123:305-10.

36. Kays DW, Langham MR, Ledbetter DJ, Talbert JL. Detrimental effects of standard medical therapy in congenital diaphragmatic hernia. Ann Surg 1999;230:340-51.

37. Azarow K, Messineo A, Pearl R, Filler R, Barker G, Bohn D. Congenital diaphragmatic hernia – A tale of two cities: The Toronto experience. J Pediatr Surg 1997;32:395-400.

38. Wilson JM, Lund DP, Lillehei CW, Vacanti JP. Congenital diaphragmatic hernia – A tale of two cities: The Boston experience. J Pediatr Surg 1997;32:401-5.

39. Boloker J, Bateman DA, Wung JT, Stolar CJH. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. J Pediatr Surg 2002;37:357-66.

40. Kinsella JP, Griebel J, Schmidt JM, Abman SH. Use of inhaled nitric oxide during interhospital transport of newborns with hypoxemic respiratory failure. Pediatrics 2002;109:158-61.

41. Boedy RF, Howell CG, Kanto WP. Hidden mortality rate associated with extracorporeal membrane oxygenation. J Pediatr 1990;117:462-4.