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ORIGINAL ARTICLE

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Oxygenation index for extracorporeal membrane oxygenation: is there predictive significance?

Abstract Although extracorporeal membrane oxygenation (ECMO) is known to improve survival in neonates with respiratory failure, there has been a significant decrease in the use of ECMO in recent years. Alternative modalities such as high-frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), and surfactant therapy are associated with this decline. The criteria for the initiation of ECMO, developed about 20 years ago, are likely no longer relevant. We examined the predictive significance of the oxygenation index (OI) as a patient entry criterion for ECMO use. We sought a critical OI level predicting death or chronic lung disease (CLD) with and without ECMO use. We also examined whether patients with certain OIs are more likely to have worse outcomes. One hundred and seventy-four term-newborn admissions between 1995 and 2000 requiring mechanical ventilation were enrolled in the study. Receiver operating curve analysis was performed to find a cutoff value of OI for ECMO initiation. Mortality rates and CLD probability were compared to the worst OIs. Our 6-year ECMO administration experience showed that an OI of 33.2 is a suitable cutoff value for ECMO initiation with high sensitivity and specificity as a predictive criterion. The critical OI value associated with the CLD risk when ECMO is not used is in the 40s. OI is a good predictor of CLD; the probability of CLD increases with higher OIs. Our data support the trend toward the use of new interventions over ECMO, especially for patients with OI scores of less than 33.2. Only when the probability of ventilator-associated lung injury becomes significant is it better to consider ECMO than conventional modalities.

Key words Extracorporeal membrane oxygenation · Lung disease · Mortality · Oxygenation index

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Introduction

Extracorporeal membrane oxygenation (ECMO) has been used for treatment of respiratory failure since the 1970s.[1] ECMO adapted conventional cardiopulmonary bypass technology to provide prolonged respiratory or cardiorespiratory support for patients who failed to respond to conventional intensive care management. With the use of ECMO specifically for newborns with persistent fetal circulation, the overall survival rate increased to 84%–100% for patients with an anticipated mortality rate (based on criteria from the early 1980s) of 80%–85%.[2] Several studies have demonstrated that ECMO promotes normal survival in neonates with respiratory failure.[3,4] However, a significant decrease has been shown in the total number of ECMO cases recently.[5–7] This decline in ECMO use is presumed to be a result of the emergence of alternate modalities such as high-frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), and surfactant therapy.[5,6] As such, the 25-year-old entry criteria derived from the original randomized trials can no longer be considered relevant.[8] Further, consideration is given to the use of ECMO to reduce morbidity.[7,8] The oxygenation index (OI) has been proposed as an entry criterion for ECMO administration.[9] The objective of this study was to analyze the predictive significance of OI as a patient entry criterion for ECMO use and to investigate the outcomes of patients with various OI values.

Patients and methods

We identified term newborns admitted to our hospital from 1995 to 2000 who required mechanical ventilation. A total

of 174 patients [59 with meconium aspiration syndrome (MAS), 26 with primary pulmonary hypertension (PPH), 18 with congenital diaphragmatic hernia (CDH), 16 with congenital heart disease (CHD), and 55 with other diagnoses] were identified. ECMO was used in 81 of these patients, whereas 44 patients underwent other treatment modalities such as surfactant therapy, HFOV, and/or iNO. The remaining 49 newborns received conventional ventilation only. An infant was considered to have chronic lung disease (CLD) if this diagnosis was recorded in the chart or the need for supplemental oxygen was documented. Mortality rates and CLD incidence were compared with regard to the worst oxygenation indexes (oxygenation index = mean airway pressure $\times F_iO_2 \times 100/PaO_2$). Receiver operating curve (ROC) analysis was performed to demonstrate a cutoff OI value for ECMO initiation. ROC refers to a method of quantifying how accurately experimental subjects, professional diagnosticians, and prognosticators perform when they are required to make a series of fine discriminations or to say which of two conditions or states of nature, confusable at the moment of decision, exists or will exist.[10] Other statistical analyses used were the Mann–Whitney *U* test and the chi-squared test for comparison between groups (ECMO vs non-ECMO group and OI ≤ 33.2 vs OI > 33.2 group), Kruskal–Wallis was used for comparison among diagnostic groups (MAS, PPH, CDH, CHD, and others), and logistic regression analysis was used for risk calculations.

During the entire 6-year period of data review, the ECMO team was run by a small group of ECMO specialists drawn largely from respiratory therapists. All ECMO was done in a single critical care unit and nursing was mostly done by senior staff nurses. Medical direction was provided by the critical care attending. Occlusive roller-head pumps were used throughout this 6-year period. Mid way through the study period, the pumps were transitioned from Cobe to Stockert–Shiley.

The decision to use ECMO was made jointly by the neonatal and the pediatric critical care attendings. The general pediatric surgical and cardiothoracic surgical attendings were also decision makers for neonates with CDH and CHD respectively. In general, ECMO was considered in term neonates (estimated gestation age more than 36 weeks) with reversible cardio- and/or respiratory failure. Head ultrasounds documented no large hemorrhages and cardiac echocardiograms showed no structural lesions (except for neonates with CHD). All neonates failed to respond to medical therapies. The severity of illness was estimated using the OI and generally an OI of 40 was considered worrisome.

Results

In order to reveal the OI scores which represent our institutional inclination for ECMO application over the past 6 years, we performed ROC analysis. ROC analysis demonstrated an OI cutoff value of 33.2 for ECMO administration with 84.8% specificity and 86.5% sensitivity (area under curve: 0.92 ± 0.023, $P = 0.0001$) (Fig. 1).

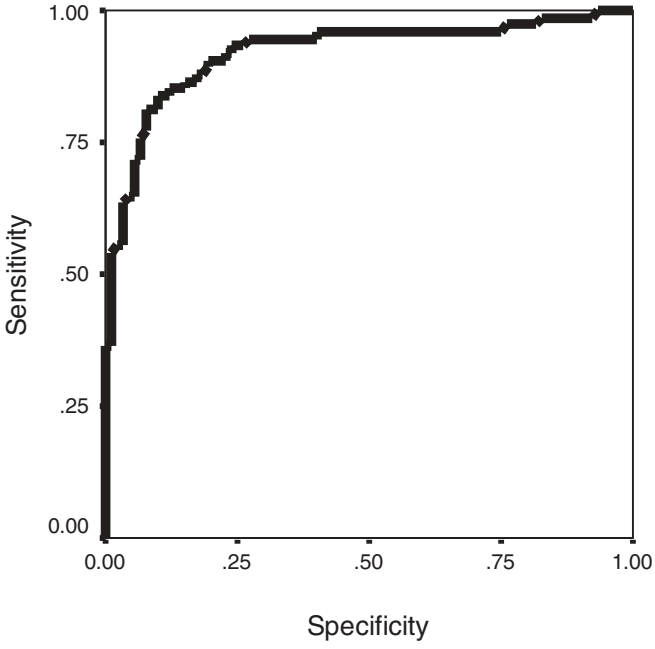

Fig. 1. Receiver operating curve representing an oxydation index (OI) of 33.2 as a cutoff value for extracorporeal membrane oxygenation (ECMO) administration. This cutoff value has 84.8% specificity and 86.5% sensitivity (area under curve: 0.92 ± 0.023, $P = 0.0001$). A cutoff level of 33.2 represents our institutional inclination for OI levels for ECMO preference over the past 6 years

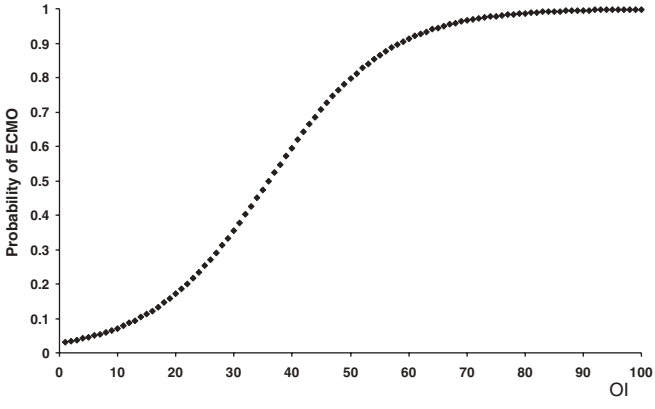

Fig. 2. Probability of ECMO application for different levels of oxygenation index (*OI*)

Median OI values were significantly higher in ECMO-treated patients (64 vs 17) ($P = 0.0001$). A one unit increase in OI increased the probability of ECMO administration by 10.96% ($P = 0.0001$). For the group with OI > 33.2, the ECMO initiation probability was found to be 35 times higher on bivariant logistic regression analysis ($P = 0.0001$). The relationship between the probability of ECMO applications and OI is demonstrated in Fig. 2.

The mortality risk was 2.7 times higher for patients with OI > 33.2. A one unit increase in OI elevated the mortality risk by 1% ($P = 0.1157$). Figure 3 represents the rising risk of mortality on increasing OI.

The ECMO group had a higher mortality rate (12.3% vs 3.3%) ($P = 0.024$). The mortality risk was elevated four

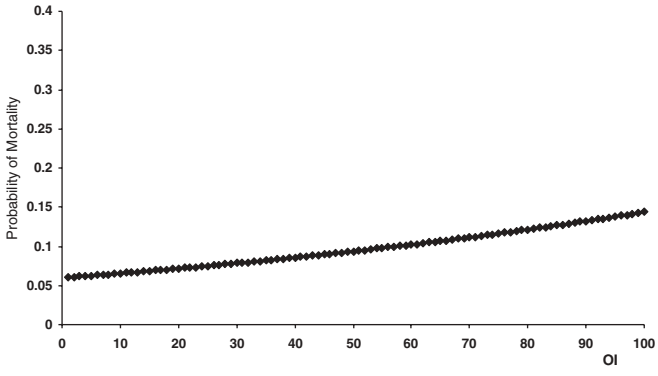

Fig. 3. Risk of mortality for different levels of OI

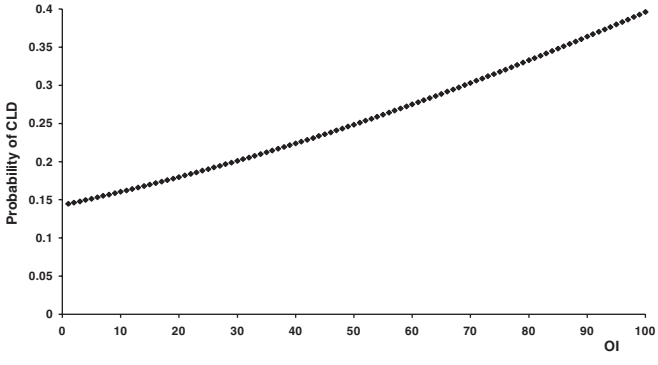

Fig. 4. Risk of chronic lung disease (*CLD*) for different levels of OI

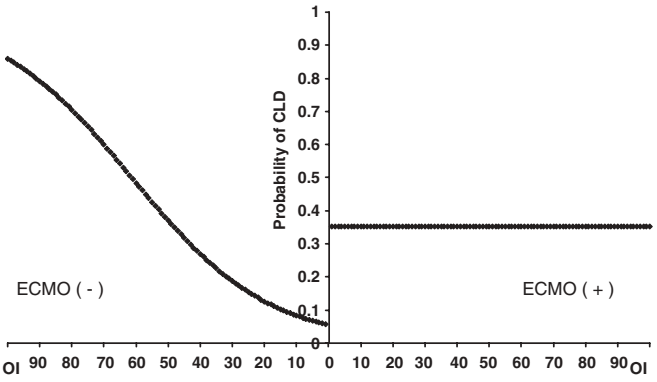

Fig. 5. Probability of CLD for different levels of OI for ECMO and non-ECMO patients. The probability of CLD is constant for ECMO-treated patients, but it has a direct relationship with increases in OI for non-ECMO patients. The data gathered from the logistic regression analysis for CLD risk is used in this figure to display its relation with OI. For non-ECMO patients, CLD risk is less than that for ECMO patients until OI exceeds 49. For OI values greater than 49, the CLD risk for non-ECMO patients exceeds the CLD risk for ECMO patients

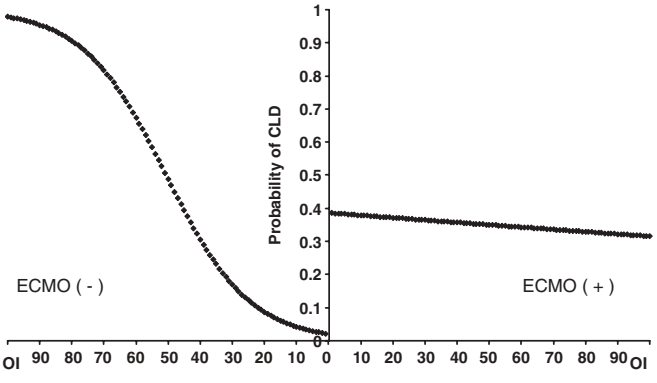

Fig. 6. Probability of CLD for different levels of OI for meconium aspiration syndrome (MAS) patients with or without ECMO. The high-risk OI level for MAS patients is 44, which is critical for CLD developement if ECMO is not performed

times in ECMO patients (P = 0.0347), and was higher for those with OI > 33.2 (P = 0.094). CLD incidence was also higher in ECMO-treated patients (40.8% vs 12%) (P = 0.000). CLD risk was increased five fold in the ECMO group (P = 0.0001). The probability of CLD development increased on OI elevation (Fig. 4).

High OI was not a significant predictor of mortality (P = 0.176) but was a good predictor for the development of CLD (P = 0.001). CLD was related with higher OI levels because patients with chronic pulmonary disease had significantly higher OI levels than others (median 44.2 vs 21.8) (P = 0.001). A one unit increase in OI increased the CLD risk by 1.46% (P = 0.0077). CLD risk was significantly increased for OI > 33.2 (P = 0.0003). Patients with an OI > 33.2 had a 3.2 times greater CLD risk. As shown in Fig. 5, the probability of CLD is constant for ECMO-treated patients, but it shows a direct relationship with OI values for other patients. The data gathered from logistic regression analysis for CLD risk is used in this figure to display its relation with OI. For non-ECMO patients, the CLD risk is lower than that for ECMO-treated patients until OI exceeds 49. With OI values greater than 49, the CLD risk in the non-ECMO group exceeds the CLD risk in the ECMO group (Fig. 5).

The mortality rate was higher in CHD (25%) and CDH (22.2%) patients, whereas the incidence of CLD was higher in CDH (50%) and MAS (31%) patients. For CDH the patients, mortality risk and CLD incidence were significantly increased in the ECMO-treated group, and 80% of these newborns had an OI > 33.2.

MAS patients formed the largest group treated by ECMO. Approximately half the MAS group (52.6% P = 0.001) were treated with ECMO and the OI was > 33.2 in 75.4%. The OI was significantly higher in MAS patients than in other patients (median 48.5, P = 0.001), and 75% of MAS patients had IO values greater than 33.2 (P = 0.000). A one unit increase in OI for the MAS group was associated with an increase in ECMO use of 10% (P = 0.0006). The graph of CLD probability for the MAS group is very similar to that for all patients (Fig. 6). The high risk OI level for MAS patients is 44, which is critical for CLD developement if ECMO is not performed.

Discussion

The criteria for ECMO institution require both reversible cardiorespiratory failure and a high likelihood of mortality. The evolution of neonatal intensive care over the past 20 years, particularly the application of HFOV, surfactant therapy, and iNO, demands that the definition of "high likelihood of mortality" be constantly reevaluated. The safety and potential treatment-related morbidity associated with ECMO use must be assessed. Because of evidence indicating that delay in the initiation of ECMO may contribute to the development of CLD,[11] intensivists need reliable criteria so that ECMO can be confidently initiated. Based on our retrospective 6-year clinical experience, we suggest a cut-off OI value of 33.2 for ECMO initiation. Overall survival for our ECMO patients was 87.7%, similar to that in previous reports.[12]

An OI ≥ 40 has previously been reported to be associated with a 21%–90% mortality rate.[9,13] Our data show a mortality rate of 11.5% for patients with OI ≥ 33.2. This data supports the previous reports that OI predicts mortality.[13] We have demonstrated that a one unit elevation in OI increases the probability of ECMO use by 11% and the risk of mortality by 1%. The rising probability of ECMO use and risk of mortality on OI elevation are demonstrated in Fig. 2 and Fig. 3, respectively.

The incidence of CLD in these ECMO-treated newborns was similar to the previously reported data that one-half to one-third of neonatal ECMO survivors were re-hospitalized or received outpatient treatments for recurrent respiratory illnesses.[13,15] Some of the previous studies demonstrated that the outcome in patients treated with ECMO is no worse than it is in neonates with comparable illnesses treated with conventional therapy, whereas other investigators believe the relative risk of abnormal pulmonary outcome following ECMO is even less than that following conventional treatments.[8,15,16] Our data suggest that ECMO-treated patients carry a higher risk of CLD (40.8% vs 11.4%) compared with newborns treated without ECMO. The worst OI scores were associated with outcome. The probability of CLD development increased on OI elevation (Fig. 4). The CLD incidence seems to be much more strongly related with high OI levels than with the use of ECMO itself (Fig. 5). As is seen in Fig. 5, the probability of CLD is constant for ECMO-treated patients, but it shows a direct relationship with OI values for other patients. For OI > 49, the CLD risk for the non-ECMO group exceeds the CLD risk for the ECMO group (Fig. 5). We can thus suggest that the CLD risk is lower in patients with OI > 49 who receive ECMO than in those treated conventionally. The graph of probability is very similar to the one developed particularly for the MAS group. The high risk point for OI is about 44 for MAS patients, and those with OI < 44 have better pulmonary outcomes without ECMO administration (Fig. 6).

As many others have shown, poorer pulmonary outcomes are associated with the presence of diaphragmatic hernia.[8] We found a 40% mortality rate and a 100% CLD risk for CDH patients who received ECMO with an OI ≥ 33.2.

Conclusion

In conclusion, OI is a predictive criterion for the need for ECMO administration. Our 6-year ECMO experience demonstrates that OI = 33.2 is the cutoff value for ECMO initiation. OI is a good predictor for CLD development. The critical OI value for increasing CLD risk if ECMO is not used is approximately 40. In particular, for CDH patients with OI > 33.2, the risk of CLD is 100% with 40% mortality even with ECMO. These analyses support the trend to favor new interventions over ECMO, especially for OI < 33.2. For patients with OI > 49, the CLD risk is less in those undergoing ECMO than in those treated conventionally. In other words, only when the probability of ventilator-associated lung injury becomes significant is it better to consider ECMO over conventional modalities.

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