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Comparison of early versus delayed strategies for repair of congenital diaphragmatic hernia on extracorporeal membrane oxygenation☆

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ABSTRACT

Purpose: For the last seven years, our institution has repaired infants with CDH that require ECMO early after cannulation. Prior to that, we attempted to decannulate before repair, but repaired on ECMO if we were unable to wean after two weeks. This study compares those strategies.

Methods: From 2002 to 2016, 65 infants with CDH required ECMO. 67.7% were repaired on ECMO, and 27.7% were repaired after decannulation. Data were compared between patients repaired ≤5 days after cannulation ("early protocol", n = 30) and >5 days after cannulation or after de-cannulation ("late protocol", n = 35). We used Cox regression to assess differences in outcomes between groups.

Results: Survival for the early and late protocol groups was 43.3% and 68.8%, respectively (p = 0.0485). For patients that were successfully decannulated before repair, survival was 94.4%. Moreover, the early repair protocol was associated with prolongation of ECMO (16.8 ± 7.4 vs. 12.6 ± 6.8 days, $p = 0.0216$).

After multivariate regression, the early repair protocol was an independent predictor of both mortality (HR = 3.48, 95% CI = 1.28–9.45, $p = 0.015$) and days on ECMO (IRR = 1.39, 95% CI = 1.07–1.79, $p = 0.012$). All bleeding occurred in patients repaired on ECMO (29.5%, 13/44).

Conclusions: Our data suggest that protocolized CDH repair early after ECMO cannulation may be associated with increased mortality and prolongation of ECMO. However, early repair is not necessarily harmful for those patients who would otherwise be unable to wean from ECMO before repair. Further work is needed to better move towards individualized patient care.

Type of study: Treatment Study.

Level of evidence: Level III.

Despite significant advances in treatment strategies, between 20% and 40% of neonates with congenital diaphragmatic hernia (CDH) and persistent pulmonary hypertension will fail medical stabilization and require support with extracorporeal membrane oxygenation (ECMO) [1]. ECMO is often necessary to stabilize the patient prior to correction of the defect. While use of ECMO has been associated with increased survival in a subset of patients with severe disease [2,3], the optimal timing of repair once an infant has been cannulated is controversial.

Repair on ECMO removes the compressive effects of herniated abdominal viscera, in theory allowing postoperative lung recruitment and hopefully reducing pulmonary hypertension, and it provides cardiopulmonary support during the repair and in case of an exacerbation of pulmonary hypertension postoperatively [1,4,5]. For these reasons, proponents of early repair on ECMO suggest that repair may ultimately facilitate weaning from ECMO and that repair will be technically easier prior to development of anasarca and enlargement of the liver and spleen, which often occurs with prolonged ECMO owing to resuscitation and sequestration of blood products [1,6]. On the other hand, repair on ECMO is associated with a significantly increased risk of bleeding [7], and so repair after decannulation may lead to fewer surgical complications.

Our approach to repair of CDH in infants requiring ECMO has evolved. From 1992 to 2009 we favored a delayed repair protocol. Our strategy from the start of the study period in 2002 to 2009 was to attempt to decannulate before repair but to repair on ECMO if we were unable to wean after two weeks. However, for the last seven years,

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our institution has elected to repair the defects in these patients early after initiation of ECMO without first attempting to wean. This study was designed to compare those two strategies.

1. Methods

1.1. Patient population and study design

From March 2002 to May 2016, 165 infants with CDH were treated at the University of Michigan C.S. Mott Children's Hospital. ECMO support was required in 41.8% (69/165). Four of these patients were excluded: two for missing data regarding timing of either ECMO or operative repair and two because they underwent ECMO following repair, meaning their clinical course did not require a decision on whether to repair on ECMO or after decannulation. Only five patients in this study were transferred in after birth from another institution. One transferred on day of life #10 after first being cannulated on VA ECMO at the referring institution, and one transferred on day of life #12 after a successful VA ECMO run and decannulation at another hospital. The remaining three transferred on day of life #3. All of these patients underwent repair at the University of Michigan, and all five patients survived. Three of them were included in the late repair protocol group and two were included in the early repair protocol group.

Of patients requiring ECMO, 67.7% (44/65) underwent CDH repair while on ECMO. Of these, 65.9% (29/44) of infants were repaired ≤5 days after cannulation ("early repair protocol"), and the remaining 34.1% (15/44) were repaired >5 days after cannulation. An additional 27.7% (18/65) of patients were repaired following decannulation. For the purposes of our study, the "late repair protocol" group combined those patients repaired on ECMO >5 days after cannulation with the patients repaired following decannulation. The decision to combine these two groups was made to reflect the clinical realities of our protocol from 2002 to 2009: specifically, attempts to repair after decannulation yielded a percentage of patients that were unable to be decannulated and ended up being repaired "late" on ECMO. For the same reason, patients that died on ECMO before repair were included in the analysis to reflect the potential hazard of missed opportunity for repair with delayed surgery. It is important to note that the "late" repair protocol patients were all operated on between 2002 and 2009 and the "early" repair protocol patients were all operated on between 2009 and 2016. The two groups are reflective of management shifts within our institution, as described below.

A retrospective analysis was performed, and the "early" and "late" protocol groups were compared under institutional IRB approval (HUM00121205). Data were collected from the Vermont Oxford Network (VON) database and supplemented with specific prenatal, operative and pharmacologic data obtained through review of the electronic medical record. Our primary outcome was in-hospital mortality. Secondary outcomes were days on ECMO, bleeding complications, intracranial hemorrhage, hospital length of stay and days on the ventilator.

1.2. ECMO initiation and management

Following delivery, all infants underwent full, goal-directed resuscitation with a gentle ventilation strategy. Acceptable parameters were preductal O_2 saturations >85%, postductal PaO_2 > 30 mmHg, pH > 7.25, $PaCO_2$ = 45–65 mmHg and mean arterial pressure 40–45 mmHg. Acute deterioration with failure to meet these goals with conventional ventilator peak inspiratory pressures (PIP) 26–30 and mean airway pressures (MAP) >12 prompted consideration of high frequency jet ventilation (HFJV) or high frequency oscillatory ventilation (HFOV). PIP > 30 on the conventional ventilator or MAP > 22 on the oscillator with maximal inotropic/pressor support prompted initiation of ECMO. Infants at high-risk for severe pulmonary hypoplasia and pulmonary hypertension were identified prenatally based on liver up and prenatal lung-to-head ratio (LHR) ≤ 1.0, observed to expected (O/E) LHR ≤ 25% and/or MRI derived O/E total lung volume (TLV) ≤ 25%. ECMO circuits were on standby at delivery for these infants. Since ECMO utilization in this population has been near 100% in our experience, we elected to initiate ECMO immediately after the initial resuscitation to avoid barotrauma and provide a smooth early transition to ECMO when the infants were relatively stable after delivery. However, infants on the most severe end of the spectrum underwent our trial of life or Severe Pulmonary Hypoplasia and Evaluation for Resuscitative Efforts (SPHERE) protocol in an effort to identify those that have pulmonary hypoplasia that is incompatible with life and not expected to improve with time on ECMO. If the infant was unable to obtain a pH >7.0, $PaCO_2$ ≤ 100, preductal SaO_2 ≥ 80%, and a PaO_2 ≥ 40 on ventilator support utilizing the maximum settings (described above) with appropriate sedation and optimization of blood pressure over the first 2 h of life, or if the infant was clearly moribund or coding, redirection of goals of care to comfort was strongly considered. If, however, the baby met these criteria at any point during the two hours of observation, ECMO cannulation was performed. A small number of patients were born using an ex-utero intrapartum treatment (EXIT) to ECMO protocol, but despite good outcomes that approach was abandoned owing to unclear benefits and potential maternal risks. For all patients, steroids were utilized to empirically treat adrenal insufficiency, and inhaled nitric oxide (iNO) was utilized sparingly as a bridge to ECMO support. ECMO was not offered to infants with serious coexistent genetic anomalies, uncorrectable cyanotic heart disease, moribund condition, severe intracranial hemorrhage, or weight < 1.5 kg.

From 2002 to 2009, our protocol was to attempt to wean ECMO before repair but to repair CDH on ECMO if the patient was unable to wean after about 2 weeks of support. Two weeks was selected because in our experience patients that have required the circuit for that long have a diminishing likelihood of successfully weaning from ECMO, and the hope was that repair would provide a boost in lung recruitment that was enough to help those patients come off ECMO. If decannulation was successful, repair was further delayed until respiratory insufficiency and hemodynamic status improved and plateaued without expectations for further improvement. In particular, we attempted to stabilize infants on conventional ventilators prior to repair so that we had means for escalation (other than re-cannulation of ECMO) if they became sicker for a period after surgery. Since 2009, the protocol for CDH repair for infants requiring ECMO is to repair them as early as 24–48 h following cannulation.

Patients were maintained on ECMO with ACT goals of 210–230. Six hours prior to surgery, Amicar was bolused at 100 mg/kg, and it was continued as an infusion at 33 mg/kg/h for 24 h. Furthermore, ACT goals were adjusted to 170–190, platelets were maintained >100,000 and hematocrit was kept >40 before repair on ECMO. The lowered ACT goal was continued for the duration of the amicar infusion. Repairs on ECMO were performed through subcostal incisions with meticulous hemostasis, and abdominal wall silos were routinely placed unless the abdominal domain was capacious [8,9]. Of note, head ultrasounds were performed every Monday, Wednesday and Friday to evaluate for intracranial hemorrhage. Echocardiograms were obtained on day 1 to exclude congenital heart disease, at 1 month, and, otherwise, as needed to assess pulmonary hypertension. Diuresis with lasix was typically initiated after 48–72 h. We first assessed for trial off ECMO following optimization of hemodynamics, volume status, and pulmonary mechanics, as appropriate, after approximately one week of support, and there were no differences in attempts to decannulate between protocol groups.

1.3. Statistical analysis

Data are described as mean ± standard deviation or percentage. Patient characteristics were compared by timing of repair. Continuous variables were compared using the Mann–Whitney test, and categorical