Review
Extracorporeal membrane oxygenation after cardiac arrest in children: what do we know?
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Summary
The use of extracorporeal membrane oxygenation (ECMO) as a resuscitative measure during or after manual cardiopulmonary resuscitation (CPR) shows sharply contrasting results. To assess the added value of ECMO in this situation and looking for predictors of mortality we performed a meta-analysis of individual patients collected from observational studies. An electronic Pubmed search restricted to English language publications between 1990 and 2007 using a consensus restrictive criterion retrieved 462 titles. Of those, 93 abstracts were considered appropriate for full text evaluation with 37 articles being included in our meta-analysis. In addition, unpublished data on a series of 98 non-duplicated patients from the author of one of the included studies was added. Data on 288 individually identified patients with a median age of 0.50 years and a median weight was 4.5 kg and demonstrated an overall survival to hospital discharge of 39.6% (114/288). Neurological complications were common, affecting 27% of all patients (77/288) and 14% of those discharged alive (16/114). Other common complications were renal failure (25%) and sepsis (17%). Odds ratios for mortality were higher for the presence of: any complication (OR 3.9, 95% CL 2.3–6.4), neurological (OR 3.3, 95% CL 1.7–6.1), renal (OR 5.1, 95% CL 2.5–10.3) and when the implementation of ECMO took >30 min (OR 2.1, 95% CL 1.1–3.8). Neck vessels cannulation had a lower association with mortality (p < .001). Simple rate comparison between manual CPR alone and the use of emergency ECMO shows a difference on survival to discharge of 12–23%. Its effectiveness is higher when implemented in the first 30 min after arrest. Age and weight do not seem to influence mortality. The incidence of complications is high, particularly neurological and renal, having a strong influence on survival. The specific characteristics of the neurological complications and their long-term effects on survivors are poorly reported in the literature.

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1. Introduction
In 1976, Bartlett et al. reported on the first neonate suffering from meconium aspiration syndrome successfully treated with extracorporeal membrane oxygenation (ECMO) [1]. Since then the indications for use of ECMO have expanded considerably, including support for respiratory distress syndrome (RDS), burns [2], myocarditis [3], bridge to transplant [4], cardiac support after cardiac surgery [5] and meningitis [6].

One of those expanded indications is the use of ECMO as a resuscitative measure in the presence of cardiac arrest. The results of this approach are widely variable and based on a number of small case series and case reports. Indications for ECMO under these circumstances are based on personal experiences, subjective considerations and ECMO availability at a particular center rather than evidence based criteria.

The objective of our review and meta-analysis was primarily to find predictors of mortality for this group of patients in extreme conditions. We were also interested in assessing the added value of the use of ECMO in the presence of cardiac arrest of any cause.

2. Methods
2.1. Search strategy
After obtaining an IRB review and exemption, we performed an electronic database search of Pubmed from January 1990 to March 2007 with the following search terms: ECMO, extracorporeal life support (ECLS), heart arrest, resuscitation, cardiopulmonary resuscitation (CPR), and using the limit function for ‘humans’ (Search Terms: Appendix A).

One reviewer (MT) read the 462 abstracts retrieved in the search to identify articles appropriate for full text evaluation. The complete article was reviewed if no abstract was

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available. All selected articles met the pre-established inclusion criteria and individual patients were identifiable throughout the course of therapy and very detailed information (demographic and clinical) was retrieved.

Once a paper was accepted for inclusion in the meta-analysis (MA), individual patients were identified from each publication and a unique identifier was assigned. Data on a number of variables were tracked and recorded (demographic, hospital course and survival to discharge) for each individually identified patient. We also contacted the authors of the included papers when the data available in the study was insufficient.

In addition, unpublished data on a series of patients from the author of one of the included studies was then added [7].

2.2. Inclusion and exclusion criteria

All case reports and observational studies reporting on pediatric patients treated with ECMO after a witnessed cardiac arrest were considered and individually evaluated. All the included patients were children (0—18 years) who underwent treatment with ECMO for cardiac arrest independently of cause. We defined cardiac arrest as chest compressions or defibrillation being administered for a non-perfusing cardiac rhythm.

Publications in languages other than English were excluded. Studies reporting on patients with an out-of-hospital cardiac arrest, uncertain onset time of cardiac arrest or elective treatment with ECMO were also excluded.

To achieve further accuracy in our estimations, individual authors of papers that fell short of our inclusion criteria were contacted to request a full set of data for each patient. If, after contacting the author, the individual patient data were still insufficient to validate our statistical analysis those studies were excluded.

Information on the authors, institution, population and dates were reviewed to identify duplicate publications. When identified, duplicated patients in consecutive reports from the same institution or author were excluded. Patient data not reported in the original article but available in the duplicated article were included without duplicating patients.

In summary, our search yielded 462 titles, in turn leading to 93 abstracts considered appropriate for full text evaluation, of which 37 articles were included in the MA, including 19 clinical series and 18 case reports [2—6,8—39]. The reasons for article exclusion were: failing the predetermined inclusion criteria [40—52], involving adult patient population [53—68] and inability to obtain detailed patient information [69—94]. For a search strategy explanation see Fig. 1.

2.3. Statistical analysis

Unadjusted odds ratios of dying before hospital discharge were calculated using logistic regression with single independent variables. The independent variables crudely associated with dying by discharge were considered when developing multiple logistic regression models (SAS System Software package).

2.4. Rationale for selection and coding of data

Due to the large number of non-standardized diagnoses reported in the included studies we created a classification system that included six groups of patients to facilitate analysis.

Because of the variety and nomenclature issues, all patients included in the MA and diagnosed with congenital heart disease (CHD) were placed under a single group (Group 1). A detailed account of diagnosis and survival for patients within this group is shown in Appendix B.
Groups 2 through 4 included patients with other cardiac/pulmonary diagnoses (i.e. cardiomyopathies, myocarditis, RDS, graft failure after heart transplant, etc.) and Group 5 was used to accommodate miscellaneous patients (burns, drug overdose, meningitis, and others). Diagnostic groups, the number of patients in each and the hospital survival with its percentage are shown in Table 1.

The following data were collected as a dichotomous variable: proximity of ECMO initiation to a perioperative event, CPR during setup, use of rapid deployment ECMO, ECMO mode, complications, and survival to discharge.

The following independent variables were entered as continuous values: age, weight, duration of CPR, ECMO timing, setup time, cannulation technique, cannulation site, initiation setting of ECMO, length on ECMO, and outcome. For a list the all the variables collected and their data format see Table 2.

Technique used for left heart decompression, reason for withdrawal of ECMO support, and cause of death were recorded for each individual, but not used in the MA analysis due to lack of information in a large number of patients.

3. Results

A total of 288 patients were individually identified from the included articles as treated with ECMO as a rescue modality after suffering a witnessed cardiac arrest. The majority of them belonged to Group 1 \((n = 180)\). Median age was 0.50 years (range 0—18.92) and the median weight was 4.50 kg (range 1.40—88.00).

Overall, only 114/288 (39.6%) patients on whom ECMO was used as life support after cardiac arrest survived to hospital discharge.

Extracorporeal membrane oxygenation was initiated concurrently with CPR in 176 (70%) of 251 patients for whom this information was available. Veno-arterial ECMO was used in 283 of the cases (99.6%).

Data on the technique employed for cannulation were available for all 288 patients, with the majority (63%) cannulated through an open chest. The trigger event for initiation of ECMO was a cardiac arrest during the perioperative period in 75% of patients. Extracorporeal membrane oxygenation was initiated in the intensive care unit (ICU) in 166 (70%) of 236 patients for whom this data were accessible.

Duration of ECMO support was available for 270 patients with a median length of 4.3 days (range 0.03—90.00 days). This variable was not significantly associated with survival to discharge.

The overall occurrence of complications was high (59% of all patients). The most commonly occurring complications were neurological (27%), renal (25%) and sepsis (17%). Multisystem organ failure (9%), liver failure (8%) and bleeding (7%) in the included series had a lower incidence than expected.

The outcome of the ECMO course was known for 274 of 288 patients (95.1%). Patients were weaned from ECMO (136/274), died on ECMO (115/274), were successfully bridged to transplant (13/274) or to a ventricular assist device (10/274).
3.1. Univariable analysis

Odds ratio for mortality before discharge were higher for the presence of any complication (OR 3.9, 95% CI 2.3—6.4), neurological complications (OR 3.3, 95% CI 1.7—6.1), renal complications (OR 5.1, 95% CI 2.5—10.3) and when the implementation of ECMO took more than 30 min (OR 2.1, 95% CI 1.1—3.8). Cannulation of the neck vessels had a statistically significant lower association with mortality \( (p < 0.001) \). The use of ECMO after cardiac arrest in surgical patients (OR 1.9, 95% CI 1.6—3.3) and during the post-operative period (OR 2, 95% CI 1.1—3.7) was related to a significantly higher mortality than when used in non-surgical patients.

3.2. Multivariable analysis

A multivariable analysis of the independent variables based on maximum likelihood estimates led to the following conclusions. The absence of a rapid deployment system (ECMO set up under 30 min) and the development of neurological or renal complications were predictors of hospital mortality (Table 3).

Patients with cardiac arrest due to a diagnosis of dilated, restrictive or hypertrophic cardiomyopathy, Chagas disease, endocardial fibroelastosis and myocarditis had a lower mortality than any of the other diagnostic categories (estimate \(-1.3, \text{SE} \pm 0.5\)). Similarly to our univariable findings, cannulation of the neck vessels also had lower hospital mortality (estimate \(-1.7, \text{SE} \pm 0.5\))

4. Discussion

4.1. Limitations of a meta-analysis

When running a meta-analysis like ours, data extracted from the published studies should be homogeneous and representative of the population of patients with similar treatment but not included in the MA. Lack of sample representativeness or ecological bias, may be introduced to a MA by including studies with an incomplete set of data [95] or by the inclusion of publications reporting only positive results, a phenomenon known as publication bias. Patients taken from such studies may not share some of the characteristics of the population subjected to the treatment in question [95].

To assess for these forms of confounding we compared data between included and excluded studies and found a similar survival rate (39%) for the 321 excluded patients for whom outcome was available. We also retrieved data from the extracorporeal life support organization (ELSO) registry
to corroborate our findings. The international summary listed a 38% and 40% survival to discharge or transfer for pediatric patients recorded in the ELSO database as having undergone extracorporeal life support after CPR [96].

In general, when meta-analyses are conducted, the results from the included studies are summarized, combining biases and differences in the designs of those studies [95]. This shortcoming also applies to our review, where most of the included studies had a retrospective design.

A particularly common statistical error in MA, the so-called unit of analysis error, occurs when individual patient data is analyzed as independent observations after extraction from cluster randomized trials. We believe our MA is free from such error since our data was extracted from non-randomized small group series and case reports.

4.2. Clinical discussion

Several recent studies show that pediatric patients who undergo CPR after experiencing a cardiac arrest in a hospital setting have a poor survival rate [97–104]. The survival to hospital discharge after cardiopulmonary resuscitation varies from 16% to 22% on small series using the Utstein Guidelines [97,98,102] and from 22% to 27% in studies reporting on patients from the National Registry of Cardiopulmonary Resuscitation (NRCPR database) [99,104] (Appendix C). Variations on CPR outcomes may be due to a soft definition of cardiac arrest or unclear CPR protocols [100,101,103]. Using a more uniform system like the one used by the American Heart Association (Pediatric Utstein reporting style) [105] on their NRCPR, allows for more relevant comparisons among studies.

Without further statistical manipulation, a simple rate comparison between range of CPR survivorship (16–27%) and the survival rate found in our meta-analysis (39.6%) would indicate that, when faced with cardiac arrest, the use of ECMO may have a rough ‘added value’ of between 12% and 23% on the survival rate over manual CPR alone [97,98,99,102,105].

Since its institution as a rescue modality for cardiac arrest, ECMO has continued to gain followers reporting encouraging results when compared to the use of CPR as therapy [70,100,106]. Despite the growing enthusiasm, to date only small series and case reports [2,4,20,23] on the use of ECMO after CPR, have been published. To our knowledge, no large series or meta-analysis on ECMO as a rescue modality after witnessed cardiac arrest in pediatric patients has been done.

The literature on cardiac arrest unresponsive to CPR treated with ECMO as a resuscitative measure of last resort shows sharply contrasting results. Very small series (4–5 patients) showing survivals as low as 0% [27] or as high as 100% [17] are unlikely representatives of the general experience. Larger series (12–19 patients) show equally dispersed results with survivals between 6% and 79% [8,11,18].

More representative survival rates (between 25% and 42%) have been reported in studies from institutions using ECMO and/or ventricular assist devices after CPR in their pediatric patients [70,100], but the populations included in these studies show wide diagnostic diversity, some controversial indications for the use of ECMO and inconsistencies in outcome measures.

When confronted with such a wide spectrum of results the need for a review and meta-analysis seems not only justified but also essential. It is only when solid data becomes available that evidence based medicine can be practiced, truly informed consent can be given and health officials can plan cost-effective strategies.

A recurring point in the cardiopulmonary resuscitation literature is the relationship between duration of CPR, return of the systemic circulation (ROSC) and outcome.

Our review shows that patients placed on ECMO to restore systemic circulation had a longer duration of CPR than those children with spontaneous ROSC (55 min vs 34 min), although this difference did not have a statistically significant impact on survival to discharge.

Accordingly, de Mos et al. found that the median resuscitation period was shorter in children with ROSC than those without it (4 min vs 23 min, p = 0.009), yet the length of the resuscitation period had no influence on ICU stay (4 min vs 10 min, p = 0.40) or hospital discharge (4 min vs 10 min, p = 0.31) [70].

A number of authors have speculated that expeditious establishment of ECMO shortens the duration of CPR therefore positively influencing the outcome, yet none of these studies found a significant difference in CPR duration between survivors and non-survivors [8,11,13,20,85]. A study by Aharon et al. found that CPR time beyond 45 min in patients treated with ECMO tended to have poor survival, however the sample size was small (n = 10) and no statistical value is mentioned [69]. Several other studies did not find a statistically significant relationship between the duration of CPR and hospital survival [8,11,13,20,85].

On his seminal paper on rapid ECMO deployment as a means of shortening CPR time, Duncan et al. showed that the resuscitation period was over 30 min shorter when compared to historical patients, although this was not statistically significant (p = 0.085) [13]. In concordance with our findings, survival in his paper was better for the rapid deployment group (7/11 survivors, 64%) compared to the historical controls (2/7 survivors, 29%), however, these results did not reach statistical significance probably due to the low number of patients (p = 0.15) [13].

We could speculate that a rapid deployment ECMO setup can be readied in a shorter amount of time, theoretically shortening the duration of CPR and limiting the chances of neurological injury and end-organ damage [8,13]. Consequently, some of the above mentioned authors concluded that a rapid deployment ECMO circuit should be on stand-by at their own institutions [18,22].

Overall, the development of any type of complications among patients included in the MA was high (59%) with neurological complications being the most commonly reported (27%). After survival, a neurological complication would have the biggest impact on the quality of life for the patients discharged alive with it. Unfortunately, the assertion of impaired neurological outcome in ECMO survivors is often poorly defined as they are reported as secondary outcomes in the included studies [4,12,13,17,22]. The literature on ECMO and neurological
complications reflects the results on mixed populations, with small subgroups of patients undergoing CPR before ECMO initiation. No study that we know of specifically addresses neurological outcomes after CPR followed by ECMO support.

Studies reporting on neurological outcome after ECMO support show a wide spectrum of results and major limitations due to differences in assessment of neuro-developmental outcome, small survivor numbers or weak study design [4,8,17,18,74,81,85]. Consequently, the rates of neurological complications in our review are at best an underestimation.

The relationship between neck vessels cannulation and survival to discharge is an open question. One may assume that patients cannulated through the chest had, in the majority undergone open-heart surgery and since surgical patients did fare worse than medical ones the results are obvious. We may also speculate that neck vessel cannulation is an indirect marker of the calmness of the situation, meaning that ROSC has occurred and CPR was interrupted, allowing for a relatively less dramatic form of cannulation. Regardless of the reason, further visitation on this matter is probably needed.

Age and weight disparity among patients in this cohort makes analysis of this variable as a predictor of mortality unreliable. Nevertheless, when patients were separated in two groups, neonates (age <30 days) and everyone else, age and weight continued to have no statistical effect on mortality. Bleeding was reported as a complication in only 7% of patients included in the MA. Such a low rate for an otherwise expected complication in patients undergoing mechanical circulatory support is likely due to under-reporting in the original studies.

Finally, technological and critical care management changes over the last 18 years have greatly transformed the way ECMO is carried out. Data on the majority of patients included in the MA (232/288) came from studies published after the year 2000. Even though our meta-analysis was not designed to specifically address the evolution of ECMO, we speculate that these results closely reflect currently used techniques and protocols.

5. Conclusions

When faced with witnessed cardiopulmonary arrest in children, the use of extracorporeal membrane oxygenation is more effective than CPR alone, but still carries a very high mortality and morbidity.

The incidence of complications, particularly neurological and renal is high, having the strongest influence on hospital survival. A non-surgical admitting diagnosis, the availability of a rapid deployment ECMO system and cannulation of the neck vessels seem to have a beneficial effect on outcome. With neurological complications being so frequent and their reporting so unspecific, a standardization of neurological outcomes should be instituted for patients on ECMO in order to improve long-term quality of life comparisons. This work could serve as the foundation for a cost-benefit analysis of the emergency use of ECMO during cardiac arrest in hospitalized children.

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Our gratitude to the contacted authors, who generously responded our multiple inquiries.

We would also like to thank Dr Kamala Littleton for her effort in reviewing and editing this paper.

References

[7] Huang S-C, Wu E-T, Chen Y-S, Chang C-I, Chiou I-S, Wang S-S, Lin F-Y, Ko W-J. Data on 98 patients provided to the authors by Dr. Wen-Je Ko, SICU director, Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan.


Appendix A. Text of the query as entered on PubMed.


Appendix B. Detailed account of diagnosis and survival for patients for Group 1

Subcategories under congenital heart disease patient group according to the anatomical classificatory categories of the Society of Thoracic Surgeons database for CHD

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>#Cases</th>
<th>Survival to hospital discharge</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Septal defects, ASD, VSD, CAVC, AP window, truncus, hemitruncus</td>
<td>29</td>
<td>10</td>
<td>35.5</td>
</tr>
<tr>
<td>8. Pulmonary vein anomalies, TAPVR, PAPVR, core tri-atriatum, pulmonary vein stenosis or obstruction, pulmonary atresia or stenosis</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9. Right heart lesions, TOF, pulmonary atresia, pulmonary stenosis, tricuspid atresia or stenosis, ebstein</td>
<td>33</td>
<td>14</td>
<td>42.4</td>
</tr>
<tr>
<td>10. Left heart lesions, aortic stenosis, aortic atresia, mitral stenosis, mitral atresia, HLHS</td>
<td>32</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>11. Single ventricle, heterotaxy</td>
<td>28</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>12. Transposition of the great arteries and DORV</td>
<td>28</td>
<td>15</td>
<td>62.5</td>
</tr>
<tr>
<td>13. Aortic malformations, CoA, ALCAPA, vascular ring, IAA</td>
<td>3</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>14. Congenital heart disease, not further defined</td>
<td>22</td>
<td>1</td>
<td>4.5</td>
</tr>
</tbody>
</table>

ASD, atrial septum defect; VSD, ventricular septum defect; CAVC, complete atroventricular canal; AP, aortopulmonary; TAPVR, total anomalous pulmonary venous return; PAPVR, partial anomalous pulmonary venous return; TOF, tetrology of Fallot; HLHS, hypoplastic left heart syndrome; DORV, double outlet right ventricle; CoA, coarctation of aorta; ALCAPA, anomalous origin of the left coronary artery from the pulmonary artery; IAA, interrupted aortic arch.

Appendix C. CPR outcomes

CPR outcomes on papers reporting according to the Utstein Guidelines [106]

<table>
<thead>
<tr>
<th>Author</th>
<th>Reporting method</th>
<th>Design</th>
<th>n</th>
<th>24 h survival</th>
<th>Hospital discharge</th>
<th>1 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reis(^a)</td>
<td>Utstein</td>
<td>Prospective</td>
<td>129</td>
<td>43 (33%)</td>
<td>21 (16%)</td>
<td>19 (15%)</td>
</tr>
<tr>
<td>Suominen</td>
<td>Utstein</td>
<td>Retrospective</td>
<td>118</td>
<td>44 (37%)</td>
<td>23 (19%)</td>
<td>21 (18%)</td>
</tr>
<tr>
<td>Lopez(^b)</td>
<td>Utstein</td>
<td>Prospective</td>
<td>213</td>
<td>67 (36%)</td>
<td>47 (22%)</td>
<td>45 (21%)</td>
</tr>
<tr>
<td>Meaney</td>
<td>NRCPR</td>
<td>Retrospective</td>
<td>464</td>
<td>174 (37%)</td>
<td>105 (22%)</td>
<td>—</td>
</tr>
<tr>
<td>Nadkarni</td>
<td>NRCPR</td>
<td>Prospective</td>
<td>880(^c)</td>
<td>—</td>
<td>236(^c) (27%)</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\) No cardiac surgery and no inborn neonatal care.
\(^b\) Does not differentiate between in- and out-of-hospital arrest.
\(^c\) Based on pediatric patients reported in the study.