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Identifying Neonatal and Pediatric Cardiac and Congenital Diaphragmatic Hernia Extracorporeal Membrane Oxygenation Patients at Increased Mortality Risk

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Abstract: A previous review from our institution established clinically measured cut-points that defined the late implementation of extracorporeal membrane oxygenation (ECMO) correlating to increased mortality in neonatal and pediatric respiratory patients. Using the same methods, this review evaluates pediatric and neonatal cardiac and congenital diaphragmatic hernia (CDH) patients to determine if the same cut-points exist in this higher risk patient population. Neonatal and pediatric cardiac and CDH patients placed on ECMO between November 1989 and December 2008 were retrospectively reviewed to determine the first adjusted anion gap (AGc), the first venoarterial carbon dioxide (CO_2) gradient (p[v-a]CO_2), and the first Viability Index (AGc + p[v-a]CO_2 = INDEX) on ECMO. These markers were then analyzed to identify the presence of specific cut-points that marked an increased risk of mortality. The timing of surgery was also reviewed to assess the surgical morbidity on survival. The review of neonatal and pediatric cardiac and CDH patients (n = 205) with an overall survival of 46% showed that all three markers were elevated to varying degrees in the expired patients (n = 110). Histograms identified the following specific cut-points for increased mortality: the AGc ≥ 23 mEq/L, the p[v-a]CO_2 ≥ 16 mmHg, and the INDEX ≥ 28. An elevated AGc and INDEX correlated with a significantly higher risk for mortality ($p < .05$), survival to discharge being 20% or less. Patients under the cut-points had survival rates of 51% or higher. The timing of surgery (before or after ECMO initiation) did not significantly impact survival in the combined cardiac and CDH group. An INDEX ≥ 28 correlates with non-survival. We speculate that the late implementation of ECMO may lead to reperfusion injury, which causes reduced survival, and that ECMO intervention prior to reaching the cut-points may improve survival in neonatal and pediatric cardiac and CDH patients. **Keywords:** cardiac, congenital, diaphragmatic, extracorporeal membrane oxygenation, neonate, pediatric. *JECT. 2010;42:183–190*

Extracorporeal membrane oxygenation (ECMO) patients are classified into two major categories: cardiac and respiratory (1). The determinant for each classification is the primary diagnosis, although some patients with differing diagnoses can have similar conditions. For example, a newborn with a normal heart and pulmonary hypertension is classified as a respiratory ECMO patient while a newborn with congenital heart disease who fails to wean from cardiopulmonary bypass due to pulmonary hypertension is classified as a cardiac ECMO patient. The primary differences are the presence of a congenital defect and the need for surgical repair or palliation.

A recognized set of formalized indicators, in conjunction with the clinician's own experience, are usually used to determine when to implement ECMO (2–5). However, a previous review from our institution suggested that about 10% of neonatal and pediatric patients with respiratory disease who require support are placed on ECMO too late to optimize survival (6). ECMO was deemed "too late" when, at the beginning of ECMO, certain physiologic markers exceeded specific cut-points beyond which the survival rate plummeted to very low levels compared to patients that did not exceed the cut-points. The cut-point

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is defined as a physiologic tipping point at which survival greatly declines beyond the normally expected level. The conclusion of the previous review was that patients placed on ECMO too late are susceptible to the added morbidity of reperfusion injury caused by the sudden reperfusion and reoxygenation of hypoxic/ischemic tissues. The cut-points identified in respiratory ECMO patients were markers for a detrimental physiologic change that was independent of diagnosis. This review is to determine if these same cut-points delineate similar survival declines in neonatal and pediatric cardiac and congenital diaphragmatic hernia (CDH) patients. We hypothesize that the cut-points identified in respiratory ECMO patients will also be identified in the cardiac and CDH ECMO population, which already have an added level of morbidity.

This review analyzes the predictive value of the first Viability Index (INDEX) after the implementation of ECMO in neonatal and pediatric cardiac and CDH patients from November 1989 through December 2008. The majority of cardiac patients reviewed had congenital defects requiring surgical repair or palliation before, during, or after ECMO. Need for surgery, abnormal cardiovascular anatomy, a propensity toward pulmonary hypertension, and other associated complications add a level of morbidity not present in respiratory ECMO patients and contribute to a greatly reduced survival rate. We grouped CDH patients with cardiac patients because CDH infants also have a congenital anomaly requiring surgery and many require ECMO before, during, or after surgery. CDH patients also have abnormal cardiovascular anatomy, including hypoplastic pulmonary vasculature, reduced left ventricular muscle mass, a propensity toward pulmonary hypertension, and other associated complications (7–9). Though CDH patients are in the Extracorporeal Life Support Organization (ELSO; Ann Arbor, MI) respiratory classification, their survival rate is significantly less than other respiratory patients and only marginally better than patients in the cardiac classification. Like cardiac patients, CDH patients have an added level of congenital and surgical morbidity not seen in respiratory patients that contributes to their decreased survival rate.

The adjusted anion gap (AGc) and the venoarterial carbon dioxide (CO_2) gradient ($p[v\text{-}a]CO_2$) are physiologic markers that can quantitatively measure the magnitude of hypoxic ischemia that, beyond a specific cut-point, makes the use of ECMO more hazardous than usual (10). The three previously identified cut-points were an $AGc \geq 23$ mEq/L, a $p[v\text{-}a]CO_2 \geq 16$ mmHg, and an INDEX = $AGc + p[v\text{-}a]CO_2 \geq 28$ (6). Our previous review suggested that patients with elevations of these markers are susceptible to reperfusion injury that is induced by the sudden restoration of capillary perfusion by the ECMO pump. The morbidity of pump induced reperfusion injury combined with the on-going pathology results in reduced survival rates. Consequently, late ECMO intervention and its presumed reperfusion injury may contribute as much to a patient's demise as the underlying pathology. Accordingly, knowing when it is too late for ECMO may make it possible to intervene earlier. If late ECMO implementation is unavoidable, a strategy specifically designed to prevent reperfusion injury could be implemented to improve otherwise dismal outcomes (11).

Similarly to what we have observed in respiratory patients, initiating ECMO in a cardiac or CDH patient after a cut-point is exceeded may further reduce the likelihood of survival in patients who already have a significant mortality. We hypothesize that similar cut-points for poor survival will be identified in cardiac and CDH ECMO patients as were identified in respiratory ECMO patients. We speculate that if the INDEX were monitored prior to ECMO, late ECMO implementation might be avoided.

METHODS

Institutional Review Board Authorization

This review was authorized by Children's Mercy Hospitals and Clinics of Kansas City, MO, Pediatric Institutional Review Board protocol # 03–06–067X entitled "A Descriptive, Retrospective Review of all Patients with Congenital Heart Disease presenting to The Children's Mercy Hospital from 1980 to present." It was approved in June 2003, reviewed and renewed annually and was amended in February 2005 to specifically include "A Descriptive, Retrospective Review of Patients undergoing Extracorporeal Membrane Oxygenation (ECMO) from 1987–present". This amendment is also reviewed and renewed annually. Patient consent was not required by the Institutional Review Board for this retrospective review.

Data Collection

The first measured Viability Index values on 205 cardiac and CDH ECMO patients were retrospectively examined to determine the correlation with survival. Survival was defined as survival to discharge. All patients were ELSO classified as cardiac or CDH ECMO patients.

The first AGc was drawn within a few hours after the initiation of ECMO. Blood was drawn from the venous line of the ECMO pump. Serum electrolytes were used in all calculations. The anion gap was calculated using the following formula:

$$\text{Anion gap} = \text{serum sodium} - (\text{serum chloride} + \text{serum bicarbonate})$$

Albumin and blood urea nitrogen (BUN) measurements were sampled concurrently and used to calculate the AGc using this formula:

$$\text{Adjusted anion gap} = \text{anion gap} + ((4 - \text{albumin}) \times 2.5) - ((\text{BUN} - 15) / 7)$$

The first p[v-a]CO_2 was drawn at the same time as the AGc. The p[v-a]CO_2 was calculated using the post-ductal arterial blood gas ($paCO_2$) and a venous blood gas ($pvCO_2$) from the venous return line to the ECMO pump. In the few patients who were on venovenous ECMO, the $pvCO_2$ was drawn from a cephalic vein drainage cannula to avoid mixing with blood recirculated from the oxygenator. The following formula was used:

$$\text{Venoarterial } CO_2 \text{ gradient} = pvCO_2 - paCO_2$$

The first INDEX was calculated using the following formula:

$$\textit{First INDEX} = \textit{first AGc} + \textit{first } p[v-a]CO_2$$

Data Analysis

All data were recorded in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA) for creation of tables and figures. Data was then transferred for analysis to the GraphPad Instat® statistical package (version 3.01 for Windows 95/NT, GraphPad Software, San Diego, CA).

Continuous variables are expressed as averages and standard deviations. Categorical variables are summarized with frequencies and percentages except the receiver operating characteristic derivatives that are displayed as fractions. The only clinical outcome evaluated is survival to hospital discharge.

RESULTS

Table 1 reviews the population demographics of the two broad categories of cardiac and CDH patients. There were 95 surviving and 110 expired patients for an overall survival of 46%. No statistically significant difference was identified between survivors and expired patients in relation to age, weight, or time on ECMO. Additionally, there is no statistically significant difference between survival as a neonate (<30 days old) and survival in older children.

Table 2 is a review of the timing of surgery to assess the impact of the surgical procedure on ECMO survival. Complications commonly associated with surgery, such as operative stress or bleeding, are not detailed. In the combined population (cardiac plus CDH patients), the timing of surgery in relation to the implementation of ECMO demonstrated no significant survival difference; 100 patients in category B: SURGERY BEFORE ECMO (48% survival) versus 77 patients in categories C: ECMO BEFORE SURGERY and D: SURGERY WHILE ON ECMO (52% survival). Table 2 details the timing of surgery and survival numbers for the cardiac and CDH subgroups separately. Among cardiac patients there was no difference in survival when surgery was performed before ECMO was initiated (B: SURGERY BEFORE ECMO, $n = 80$ with 39% survival) or if ECMO was initiated after surgery or if no surgery was performed (C + D + E, $n = 32$ with 41% survival). Cardiac patients who required ECMO both before and after surgery (D: SURGERY WHILE ON ECMO) did the poorest with only 14% survival. However, this made up only 6% of the cardiac population and was not statistically significant. CDH ECMO patients had a significantly higher survival rate (Fisher's exact test $p = .0023$) when surgery was performed before ECMO was implemented (B: SURGERY BEFORE ECMO, $n = 20$ with 85% survival) compared to patients whose surgery was delayed until after ECMO implementation or who never received surgery (C + D + E, $n = 73$ with 47% survival). Twelve CDH patients whose surgery was delayed died of complications while on ECMO or soon after weaning from ECMO, surgery never having been performed. Fourteen percent of the combined population received ECMO, but did not undergo surgery, (E: ECMO BUT NO SURGERY, $n = 28$ with 25% survival). In this category, 44% (7 of 16) of the cardiac patients survived. None (0/12) of the CDH patients survived. This contributed 16% to the 53% mortality rate of CDH patients whose surgery was delayed until after ECMO was initiated.

Table 1. Cardiac and Congenital Diaphragmatic Hernia ECMO Patients Combined: Averages of Age, Weight, Hours on ECMO and % Survival (Means ± SD)

	All			<30 Days (Neonates)			≥30 Days		
	Survived	Died	*t*-test	Survived	Died	*t*-test	Survived	Died	*t*-test
n	95	110	*p*	69	83	*p*	26	27	*p*
Age (days)	169 ± 68	114 ± 567	.53	4 ± 6	5 ± 6	.45	607 ± 1230	449 ± 1092	.62
Weight (kilograms)	5.1 ± 8.5	4.3 ± 5.1	.40	3.2 ± .5	3.1 ± .5	.07	10.2 ± 15.2	8.2 ± 9.3	.56
ECMO hours	186 ± 114	198 ± 141	.41	204 ± 110	216 ± 138	.58	125 ± 94	141 ± 138	.62
Survival	46%			45%			49%		

There is no statistical difference between survivors and expired patients in relation to age, weight, or time on ECMO. There is no statistical difference between survival as a neonate and survival in older children (Fisher's exact test $p = .75$).

Table 2. Cardiac and Congenital Diaphragmatic Hernia (CDH) ECMO Patients: Age, Weight, ECMO Hours (Ranges), % Survival, and Timing of Surgery

	Cardiac Patients		CDH Patients	
A: ALL	Survived	Died	Survived	Died
n	44	68	51	42
Age (days)	0–4709	0–5739	0–10	0–12
Weight (kilograms)	2.6–72	2.2–53	2.1–4.2	2.1–4.1
ECMO hours	16–384	5–642	82–533	3–662
Survival	39%		55%	
B: SURGERY BEFORE ECMO				
n	31	49	17	3
Age (days)	4–4709	2–5739	0–10	2–12
Weight (kilograms)	2.9–72	2.2–53	2.1–3.7	3.1–3.6
ECMO hours	16–384	5–642	82–292	3–338
Survival	39%		85%	
C: ECMO BEFORE SURGERY				
n	5	4	29	14
Age (days)	1–202	0–15	0–7	0–2
Weight (kilograms)	2.6–4.3	2.2–3.8	2.4–3.1	2.3–3.8
ECMO hours	48–193	123–350	101–430	77–508
Survival	56%		67%	
D: SURGERY WHILE ON ECMO				
n	1	6	5	13
Age (days)	1	1–8	1–7	0–5
Weight (kilograms)	3.5	2.5–4.1	3.1–4.2	2.1–4.1
ECMO hours	112	70–321	363–553	95–662
Survival	14%		28%	
E: ECMO BUT NO SURGERY				
n	7	9	0	12
Age (days)	0–812	0–896	N/A	0–6
Weight (kilograms)	3.2–10.0	2.9–11.7	N/A	2.3–3.3
ECMO hours	28–247	19–222	N/A	4–381
Survival	44%		0%	
C + D + E: LATE OR NO SURGERY				
n	13	19	34	39
Age (days)	0–812	0–896	0–7	0–6
Weight (kilograms)	2.6–10.0	2.2–11.7	2.2–4.2	2.1–4.1
ECMO hours	28–247	19–350	101–533	41–662
Survival	41%		43%	

In the combined population (cardiac plus CDH patients), the timing of surgery in relation to the implementation of ECMO demonstrated no significant survival difference; 100 patients in category B: SURGERY BEFORE ECMO (48% survival) versus 77 patients in categories C: ECMO BEFORE SURGERY and D: SURGERY WHILE ON ECMO (52% survival). There was no significant difference in survival among cardiac patients undergoing surgery before, during, or after ECMO. Cardiac patients requiring ECMO both before and after surgery, D: SURGERY WHILE ON ECMO, did poorly but only made up 6% of the cardiac population. E: ECMO BUT NO SURGERY surviving cardiac patients had improvement in cardiac function without the need for surgery; expired patients were either inoperable or had a lethal non-surgical condition or complication. Four of the E: ECMO BUT NO SURGERY cardiac patients had either cardiomyopathy or myocarditis and no congenital lesion. Two survived and two expired.
CDH patients who underwent surgical repair before ECMO implementation (B: SURGERY BEFORE ECMO) had higher survival than those whose surgery was delayed (C + D + E: LATE OR NO SURGERY) (Fisher's exact test $p = .0023$). E: ECMO BUT NO SURGERY CDH patients died of a complication while on ECMO or soon after being removed from ECMO, never having received surgery.

Table 3 compares the three markers in surviving and expired patients. In the combined population (cardiac plus CDH patients), expired patients overall had significantly higher first AGc values ($p < .05$) and higher first INDEX scores ($p < .05$) than survivors. The p[v-a]CO_2 was higher in expired patients, but was not statistically significant. This held true for the cardiac subgroup but not the CDH subgroup.

The impact of the elevated markers on the expired patients was determined using frequency distribution histograms. Figures 1, 2, and 3 are histograms for the first AGc, the first p[v-a]CO2, and the first INDEX values for the combined cardiac and CDH ECMO patients. These histograms identified the specific cut-points where mortality greatly increased. Patients with a first AGc value ≥ 23 mEq/L, a first p[v-a]CO2 value ≥ 16 mmHg, and a first INDEX ≥ 28 had a higher mortality than patients with lower scores.

Table 4 compares the mortality below and above the identified cut-points in the combined population (cardiac

Table 3. Cardiac and Congenital Diaphragmatic Hernia (CDH) ECMO Patients: Survivors versus Expired by Adjusted Anion Gap, Venoarterial CO_2 Gradient and the Viability Index (Means ± SD)

	Survived	Died	% β Power	*t*-test *p*
All patients (*n* = 205)	95	110		
First adjusted anion gap	14 ± 4	17 ± 6	95%	.0001
First venoarterial CO_2 gradient	8 ± 3	9 ± 5	40%	.1744
First Viability Index	21 ± 5	26 ± 10	99%	.0002
Cardiac patients (*n* = 112)	44	68		
First adjusted anion gap	14 ± 4	18 ± 7	95%	.0002
First venoarterial CO_2 gradient	8 ± 4	9 ± 5	20%	.3475
First Viability Index	22 ± 6	27 ± 9	90%	.0003
CDH patients (*n* = 93)	51	42		
First adjusted anion gap	13 ± 3	14 ± 5	20%	.5491
First venoarterial CO_2 gradient	8 ± 2	8 ± 5	10%	.4758
First Viability Index	21 ± 4	22 ± 10	10%	.3668

The first adjusted anion gap and the first Viability Index are correlated negatively with survival in the combined group and the cardiac subgroup. In the CDH group, none of the markers correlated significantly with survival. Expired patients have higher first venoarterial carbon dioxide gradient values than survivors although this is not statistically significant. β power is the percentage probability that the result is not a Type II error.

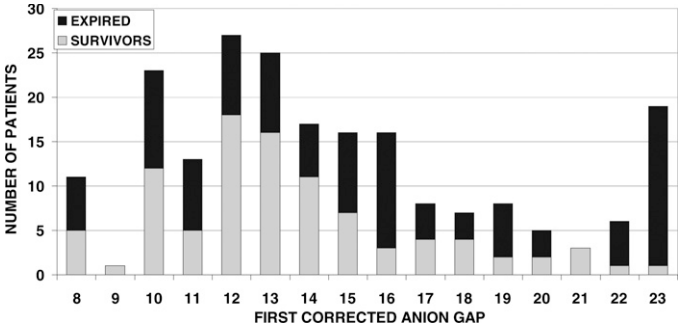

Figure 1. Cardiac and congenital diaphragmatic hernia ECMO patients: first adjusted anion gap frequency histogram, survivors and expired patients. The category of "8" includes all patients with values 8 mEq/L or less, "23" includes all patients with values 23 mEq/L or greater. The cut-point for survival falls between 22 and 23 mEq/L.

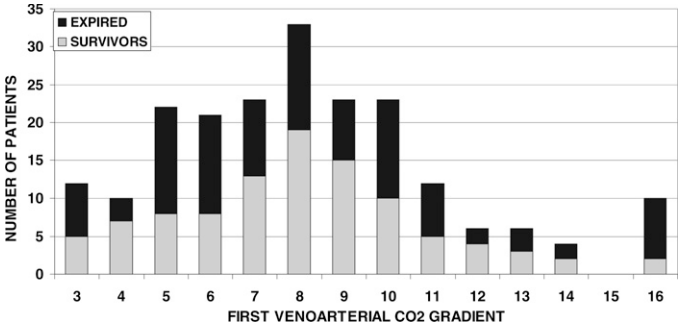

Figure 2. Cardiac and congenital diaphragmatic hernia ECMO patients: first venoarterial carbon dioxide gradient frequency histogram, survivors and expired patients. The category of "3" includes all patients with values 3 mmHg or less, "16" includes all patients with values 16 mmHg or greater. The cut-point for survival falls between 15 and 16 mmHg.

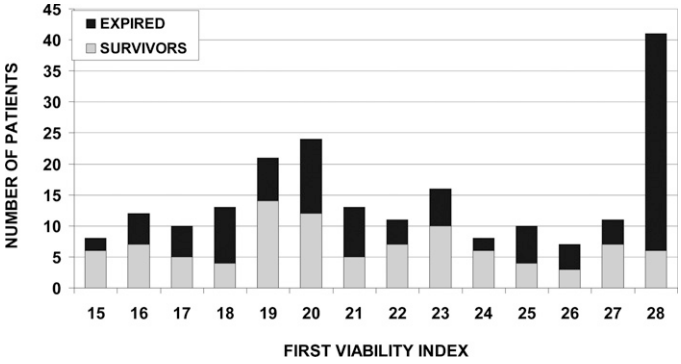

Figure 3. Cardiac and congenital diaphragmatic hernia ECMO patients: first viability index frequency histogram, survivors and expired patients. The category of "15" includes all patients with values 15 or less, "28" includes all patients with values 28 or greater. The cut-point for survival falls between 27 and 28.

Table 4. Cardiac and Congenital Diaphragmatic Hernia ECMO Patients: Survival Below and Above the Cut-Points (Fisher's exact test)

	First Adjusted Anion Gap		
	<23 mEq/L	≥23 mEq/L	Totals
Survived	94 (46%)	1 (0%)	95 (46%)
Expired	92 (45%)	18 (9%)	110 (54%)
Totals	186 (91%)	19 (9%)	205 (100%)
	p = .0001, Odds ratio = 18.391		
	First Venoarterial Carbon Dioxide Gradient		
	<16 mmHg	≥16 mmHg	Totals
Survived	93 (45%)	2 (1%)	95 (46%)
Expired	102 (50%)	8 (4%)	110 (54%)
Totals	195 (95%)	10 (5%)	205 (100%)
	p = .1012, Odds ratio = 3.647		
	First Viability Index		
	<28	≥28	Totals
Survived	89 (43%)	6 (3%)	95 (46%)
Expired	75 (37%)	35 (17%)	110 (54%)
Totals	164 (80%)	41 (20%)	205 (100%)
	p = < .0001, Odds ratio = 6.922		

These contingency tables show a statistically significant difference for survival between patients below and above the first adjusted anion gap and the first Viability Index cut-points. While not statistically significant due to the small number involved (*n* = 10), the ratio of surviving to expired patients is large at one-to-four among the high venoarterial carbon dioxide gradient patients versus about one-to-one among the low gradient patients (*n* = 195). The Viability Index identifies a greater number of patients at risk (20%) than the adjusted anion gap (9%) or the venoarterial carbon dioxide gradient (5%).

plus CDH patients). The first AGc ≥ 23 mEq/L identified 19 (9%) and the first p[v-a]CO_2 ≥ 16 mmHg identified 10 (5%) of the 205 ECMO patients as being high risk. By comparison, the first INDEX ≥ 28 identified 41 (20%) of the 205 ECMO patients as high risk. In the subgroups (not shown in Table 4) the INDEX identified 9% of the CDH patients (8 of 93) as being high risk and is near the 10% figure for other respiratory patients seen in the previous review (6). The INDEX identified 29% of the cardiac patients (33 of 112) as being high risk; three times the rate seen in respiratory patients.

Figure 4 illustrates patient survival below and above the cut-points. Patients with values below the cut-points had a survival of 48–54%, and patients with values above the cut-points had a survival of 5–20%.

Table 5 lists the receiver operating characteristic derivations for patients below and above the cut-points. Due to the increased congenital and surgical morbidity associated with these types of ECMO patients, the ability of an INDEX < 28 to predict survival is only about 54%, roughly equal to the flip of a coin. However, the ability of an INDEX ≥ 28 to predict death is about 85%.

Twenty percent of all the patients placed on ECMO in this review had a first INDEX value ≥ 28, suggesting that these 41 patients were placed on ECMO too late for optimal survival; only six of the 41 survived (survival = 15%). Lower score patients had a survival rate of 55%. The absolute risk increase for high INDEX patients was 40% and the relative risk increase was 266% (Fisher's exact test $p < .0001$). Among all the higher INDEX patients, the number needed to treat (NNT) by earlier intervention to realize improved survival is 2.5 patients; for CDH patients the NNT is 3.1 and for cardiac patients the NNT is 2.6. Theoretically, earlier intervention could improve overall survival from 46–55%. Cardiac patients would benefit most from earlier intervention, potentially increasing survival from 39–51%. Survival for CDH patients would potentially increase from 55–60%.

Conclusions drawn from the data are as follows:

1) The timing of surgery tends not to be a major factor in the overall survival of cardiac and CDH patients (Table 2).
2) Expired patients tend to have higher markers than surviving patients (Table 3).
3) The INDEX value ≥ 28 is the cut-point identifying a greatly decreased expectation of survival in neonatal

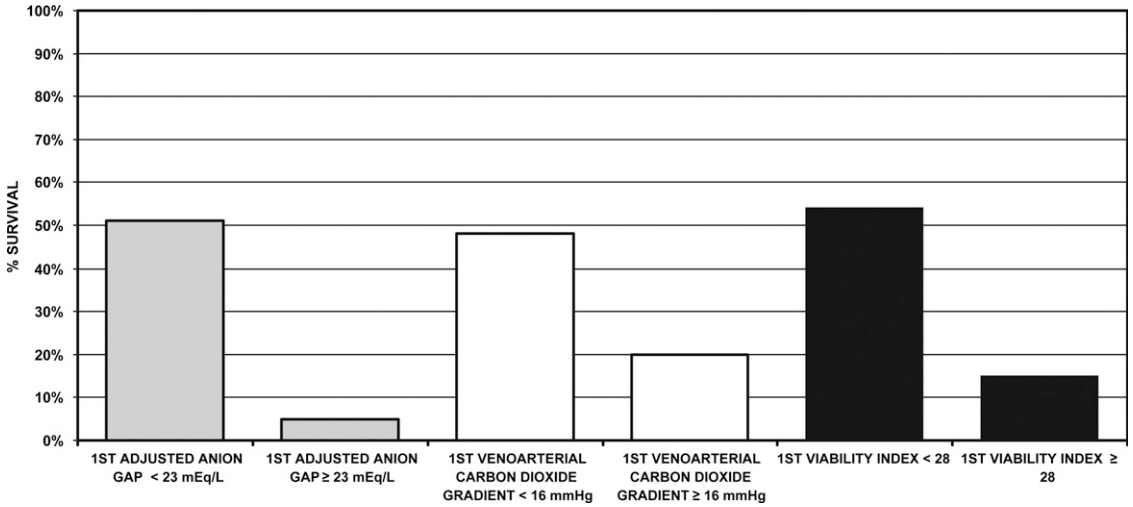

Figure 4. Cardiac and congenital diaphragmatic hernia ECMO patients: survival below and above the three cut-points by percentage.

Table 5. Cardiac and Congenital Diaphragmatic Hernia ECMO Patients: Receiver Operating Characteristic Derivations

	Adjusted Anion Gap		Venoarterial Carbon Dioxide Gradient		Viability Index	
Derivative	<23 mEq/L: Predicting Survival	≥23 mEq/L: Predicting Death	<16 mmHg: Predicting Survival	≥16 mmHg: Predicting Death	<28: Predicting Survival	≥28: Predicting Death
Sensitivity	.51	.95	.48	.80	.54	.85
Specificity	.95	.51	.80	.48	.85	.54
Positive Predictive Power	.99	.16	.98	.07	.94	.32
Negative Predictive Power	.16	.99	.07	.98	.32	.94
Likelihood Ratio	9.6	1.9	2.4	1.5	3.7	1.9
Accuracy	.55		.52		.60	
p	.0001		.1011		<.0001	

This table shows the comparison of predictive power for survival below and death above the three cut-points. Derivations are calculated from values in Table 4. Sensitivity is the true positive rate in predicting the outcome. Specificity is the true negative rate in predicting the outcome. Positive predictive power (precision) = true positive rate/(true positive rate + false positive rate). Negative predictive power = true negative rate/(true negative rate + false negative rate). The likelihood ratio = sensitivity/(1.0-specificity). Accuracy = (true positive prediction + true negative prediction)/total population. The high morbidity of the cardiac and congenital diaphragmatic hernia diagnoses is mostly related to a congenital anomaly and the need for surgery. Because of this, the sensitivity for predicting survival in patients below the cut-points is relatively low (48–54%). However, the sensitivity for predicting mortality in patients above the cut-points is very high (80–95%).

and pediatric cardiac and CDH ECMO patients (Table 4). This is true in neonatal and pediatric respiratory ECMO patients as well (6).

This analysis supports the hypothesis that when the first Viability Index on ECMO is elevated beyond a certain cut-point then the survival of neonatal and pediatric cardiac and CDH ECMO patients will be greatly diminished. Our speculation is that if any patient thought to have a reversible or repairable condition, regardless of diagnosis, is placed on ECMO before the first INDEX value reaches 28, the likelihood of survival will be significantly higher than those patients whose first INDEX value is ≥28. This even includes those populations considered high risk due to the additional congenital and surgical morbidity. The conclusion can be summarized as follows:

1) Timely ECMO implementation, as indicated by markers below the cut-points, correlates with higher survival.
2) Late ECMO implementation, as indicated by markers equal to or above the cut-points, correlates with higher mortality.
3) ECMO intervention before reaching the cut-points may avoid reperfusion injury and an increased mortality rate.
4) If ECMO needs to be initiated "late", strategies to temper reperfusion injury may be prudent (11).

DISCUSSION

The timing of surgery tended not to be a major factor in the overall survival of the combined population (Table 2). However, there are two subsets of the subgroup of CDH patients worthy of note. In the first subset, CDH patients with circumstances allowing for surgical repair prior to needing ECMO demonstrated significantly higher survival (Table 2, category B). This may be a reflection of a congenital anomaly less severe than other CDH patients. In the second subset, some CDH patients requiring ECMO before surgery died either of a complication while on ECMO or soon after weaning from ECMO, never having an opportunity for surgical repair (Table 2, category E). Mortality in this subset was 100% and may be a reflection of a combination of a more severe anomaly and complications of ECMO.

Expired patients tended to have higher markers than surviving patients (Table 3). Expired CDH ECMO patients did not have significantly elevated markers suggesting that overall mortality in these patients may be primarily related to congenital and surgical factors. However, there is a subset of CDH patients (9% of the CDH ECMO population) who are at increased risk due to physiologic derangements as identified by an elevated INDEX. These patients would likely benefit from earlier ECMO intervention. In Table 3, the absence of statistical significance in some categories may be a Type II error due to the low β power.

The INDEX value ≥ 28 is the cut-point identifying a greatly decreased expectation of survival in neonatal and pediatric cardiac and CDH ECMO patients (Table 4). In these types of patients, higher than normal AGc values indicate that the tissues are experiencing some degree of hypoxia and higher than normal $p[v\text{-}a]CO_2$ values indicate that the tissues are experiencing some degree of carbon dioxide retention. Moderately elevated AGc values or moderately elevated $p[v\text{-}a]CO_2$ values by themselves are not necessarily indicative of a lethal state. Vital tissues can tolerate one or the other up to a certain point: <23 mEq/L for the AGc and <16 mmHg for the $p[v\text{-}a]CO_2$ (Figures 1 and 2). However, if both indicators are moderately elevated (even to levels less than their corresponding cut-points), vital tissues seem to be less capable of tolerating the dual effects of hypoxia and carbon dioxide retention simultaneously. Evidently, these effects are cumulative. The INDEX appears to be a better predictor of lethality because it measures the extent of this dual effect that seems to reach its lethal tipping point at 28 (Figure 3). The best window of opportunity to implement ECMO might be missed if only the AGc or only the $p[v\text{-}a]CO_2$ is monitored.

Patients with a first INDEX value ≥28 are likely to have a higher mortality because of the physiologic changes represented by the risk markers used. At the micro-vascular tissue level, the AGc detects tissue anoxia and the $p[v\text{-}a]CO_2$ detects carbon dioxide accumulation, both being caused by poor capillary perfusion (12). Together, these risk markers detect tissues with localized hypoxic ischemia that is caused by various types and degrees of shock. These tissues may tolerate a period of poor perfusion without apparent damage, but are predisposed to reperfusion injury (13). The intracellular acidosis of the hypoxic/ischemic tissues inactivates the protective enzymatic antioxidants (14). Upon the restoration of perfusion, as occurs when a patient is placed on ECMO, the tissues are rapidly re-oxygenated and subsequently damaged by the uncontrolled reactive oxygen species, among other things (15–18). This re-oxygenation may occur more rapidly than antioxidant activity can be restored. The damage from the pump-induced reperfusion injury, combined with the already present congenital anomaly and pathology, may greatly increase the mortality. Intervening with ECMO before the INDEX value exceeds 27 may avoid the added morbidity of reperfusion injury damage and result in a higher survival rate. Otherwise, additional strategies may be considered to blunt the lethal effects of reperfusion injury (11).

Potentially, the clinical utility of this INDEX value lies in the ability to monitor patients prior to ECMO to provide a more timely intervention before the risk of reperfusion injury becomes a compounding factor. Reliance on pulmonary function and hemodynamic assessments to determine

the timing for ECMO intervention fails to take into consideration the physiologic cut-points that determine when ECMO is too late to optimize survival. Tracking the cut-points prior to ECMO may provide the clinician insight into the effectiveness of less invasive treatments and provide a time scale on how long these treatments can be used before ECMO must be initiated. Our data do not support use of this predictor to limit selection of or therapy for an individual patient.

This review is limited by its retrospective design encompassing two decades and changes in management that may have occurred during that time period, making outcome analysis difficult. However, the prospective validation of these risk predictors may lead to additional hypotheses that may identify therapies or treatment strategies useful for reducing mortality or decreasing the effects of reperfusion injury.

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