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Critically Low Hormone and Catecholamine Concentrations in the Primed Extracorporeal Life Support Circuit

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Abstract

The first hours of extracorporeal life support (ECLS) are commonly marked by new hemodynamic instability without a known etiology. We measured hormone and catecholamine concentrations in six ECLS primed circuits immediately before joining the patient's circulation to assess a potential role of these agents in this condition. The following hormones were significantly below the lower end of the normal range for the first week of life (data are presented as mean $\pm$ SEM): cortisol 1.95 ± 0.15 μ g/dl ($p < 0.001$), aldosterone 3.73 ± 0.74 ng/dl ($p < 0.05$), free thyroxine 1.2 ± 0.1 ng/dl ($p < 0.05$), free triiodothyronine 0.53 ± 0.03 pg/ml ($p < 0.001$), thyroid stimulating hormone 0.31 ± 0.05 μ U/ml ($p < 0.001$), growth hormone (GH) 0.09 ± 0.01 ng/ml ($p < 0.001$), estradiol 38.3 ± 3.72 pg/ml ($p < 0.001$), IGF-BP1 0.95 ± 0.1 ng/ml ($p < 0.001$), glucagon 26 ± 1.2 pg/ml ($p < 0.001$), epinephrine 17.3 ± 3.7 pg/ml ($p < 0.001$), and norepinephrine 127 ± 27 pg/ml ($p < 0.05$). No dopamine was detected. Normal hormone concentrations included IGF-I, IGF-BP3, insulin, parathyroid hormone, leptin, and testosterone. Critically low concentrations of cortisol, thyroid hormones, GH, IGF-BP1, glucagon and catecholamines were measured in the ECLS circuit even though it was primed with fresh frozen plasma. These concentrations may cause significant and precipitous dilutional reductions in the patient's circulating levels immediately after connection to the ECLS circuit and hence contribute to hemodynamic instability.

Extracorporeal life support (ECLS), also known as extracorporeal membrane oxygenation (ECMO), provides extended cardiopulmonary bypass at the bedside to support critically ill patients, most commonly neonates, who have severe but potentially reversible respiratory or cardiac failure.¹

During the period immediately after initiation of ECLS, patients commonly experience a period of significant hemodynamic instability.² Hypotension around the time of initiation of ECLS is associated with poor neurologic outcome.³

We hypothesized that one component of this instability was dilution of the neonate's stress hormone and catecholamine concentrations by a circuit with potentially low concentrations of these factors. To begin to test this hypothesis, we designed a prospective study to measure concentrations of a broad range of hormones in the primed ECLS circuit before its connection to the patient.

Materials and Methods

This study was approved by the Institutional Review Board of Children's Hospital, Boston (CHB).

Priming of the Extracorporeal Life Support Circuit

The ECLS circuit is primed at CHB with 500 ml packed red blood cells (less than 7 days old, leukopoor *via* filtration, stored in citrate-phosphate-dextrose-adenine [CPDA1] preservative with an average hematocrit of 65–80%), 200 ml fresh frozen plasma (FFP), 2 units cryoprecipitate, 2 units platelets, 50 ml 5% human albumin, 500 units heparin, 50 ml tromethamine, 20 mEq sodium bicarbonate, and 1,500 mg calcium gluconate. It is then treated with additional calcium gluconate as needed to normalize the ionized calcium and with normal saline as needed to reduce the potassium concentration to below 7 mmol/L.

Sample Collection

Blood was prospectively collected from ECLS circuits after all manipulations by the perfusionist were complete but before connection to the patient. Samples were chilled at the bedside to 0°C and delivered to the clinical laboratory. There they were immediately spun and either refrigerated at 4°C for local analysis or chilled to –80°C for analysis in a commercial laboratory.

Measurements

Cortisol, thyroid stimulating hormone (TSH), total triiodothyronine (TT3), thyroid binding globulin index (TBGI), and estradiol were measured by competitive magnetic separation immunoassay. Total thyroxine (TT4) was measured by latex agglutination. Free thyroxine (FT4) was measured by direct dialysis method. Free triiodothyronine (FT3), aldosterone, insulin like growth factor binding protein 3 (IGF-BP3), glucagon, and leptin were measured by radioimmunoassay. Growth hormone (GH), insulin like growth factor I (IGF-I), insulin like growth factor binding protein 1 (IGF-BP1), and parathyroid hormone (PTH) were measured by immune chemiluminescent metric assay. Insulin and testosterone were measured by high pressure liquid chromatography. Epinephrine, norepinephrine, and dopamine were measured by radioenzymatic assay.

Statistical Analysis

Each mean of the measured circuit concentrations of hormones and catecholamines, if lower than normal, was compared with the lower limit of the normal range for a neonate using the one sample, one tailed, Student's t-test. Normal ranges were identified by the age based range published by the clinical laboratory performing the assay when available, as well as by previously published reports.^{4–6} If higher than normal, the mean was compared with the upper limit of the normal range. If a concentration was reported as below the limit of detection of the assay, it was assigned a value equal to that lower limit. Differences were considered to be statistically significant if $p < 0.05$. Data are presented as mean $\pm$ SEM.

Results

Samples were collected from six primed ECLS circuits before connection to the infant. The hormone and catecholamine concentrations are summarized in Tables 1 and 2, respectively.

Concentrations of hormones and catecholamines were significantly below the lower end of the normal range in the case of cortisol, aldosterone, TT3, FT3, TT4, FT4, TSH, GH, IGF-BP1, glucagon, dopamine, epinephrine, and norepinephrine.

Discussion

The hormonal and catecholamine concentrations in primed ECLS circuits have not been reported to date, and the concentrations in the neonates who are about to be cannulated onto ECLS have only recently begun to receive attention.⁷ Based upon previous published data in critically ill infants, however, it is likely that concentrations in “preECLS” infants of cortisol, aldosterone, GH, glucagon, dopamine, epinephrine, and norepinephrine are well above their “normal” ranges.^{4–6} This makes the low concentrations measured here even more significant.

A typical neonatal ECLS circuit at CHB is primed with 580 ml of a standardized mixture of components. An ECLS neonate’s blood volume is approximately 160–320 ml (in a 2–4 kg infant). Upon connection of the neonate to the primed circuit, therefore, one would expect a dilution to as low as 22% ($160/160 + 580$) of a given hormone’s starting concentration, depending upon the size of the infant and the concentration of that hormone in the prime. These events may have serious clinical consequences.

The most clinically significant of these changes are likely to involve the hormones and catecholamines that regulate hemodynamics in a critically ill infant. Cortisol, epinephrine, norepinephrine, and dopamine are the leading candidates. Although a normal baby would be expected to have robust stores of these factors, those who are critically ill have likely expended their stores, and when the serum concentrations are acutely dropped, they may not have the residual production capacity to reconstitute themselves in the typical short timeframe.

CHB uses FFP in its ECLS prime, which is not standard practice in most ECLS centers.⁸ One would expect, therefore, that the concentrations of hormones and catecholamines in ECLS primes would be even lower in institutions that do not use FFP.

Further investigations are underway to determine the actual concentrations of these factors in the preECLS infant and to measure the dilution as well as the rate and extent of reconstitution by the infant after cannulation onto ECLS.

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Table 1**Hormone Concentrations in Primed ECLS Circuits**

Hormone	Normal Range in Neonates	Mean $\pm$ SEM	p Value
Adrenal axis			
Cortisol	5–25 μ g/dl	1.95 $\pm$ 0.15	<0.0001
Aldosterone	7–184 ng/dl	3.73 $\pm$ 0.74	<0.05
Thyroid axis			
Thyroid stimulating hormone	0.7–26 μ U/ml	0.31 $\pm$ 0.05	<0.001
Total thyroxine	9.1–15.3 μ g/dl	2.17 $\pm$ 0.19	<0.0001
Free thyroxine	2.0–4.9 ng/dl	1.2 $\pm$ 0.1	<0.01
Total triiodothyronine	86–170 ng/dl	36.8 $\pm$ 2.0	<0.0001
Free triiodothyronine	2.0–4.0 pg/ml	0.53 $\pm$ 0.03	<0.001
Thyroid binding globulin index	0.88–1.08	1.64 $\pm$ 0.05	<0.0001
Growth hormone axis			
Growth hormone	5–27 ng/ml	0.09 $\pm$ 0.01	<0.0001
Insulin-like growth factor I	15–109 ng/ml	32.9 $\pm$ 12.0	NS
Insulin-like growth factor binding protein 3	0.4–1.7 mg/l	0.9 $\pm$ 0.2	NS
Gonadal axis			
Estradiol	0.5–5.0 pg/ml	38.3 $\pm$ 3.72	<0.001
Testosterone	16–72 ng/dl	13.3 $\pm$ 3.3	NS
Pancreatic hormones			
Insulin	Fasting 3–12 μ U/ml	10.3 $\pm$ 2.3	NS
Insulin-like growth factor binding protein 1	10–500 ng/ml	0.95 $\pm$ 0.1	<0.0001
Glucagon	50–150 ng/l	26.2 $\pm$ 1.2	<0.0001
Other			
Leptin	0.1–0.7 ng/ml	5.1 $\pm$ 2.5	NS
Parathyroid hormone	10.0–65.0 pg/ml	11.2 $\pm$ 3.0	NS

NS, not significant; ECLS, extracorporeal life support.

Table 2

Catecholamine Concentrations in Primed ECLS Circuits

Catecholamine	Normal Range in Stressed Neonates	Mean $\pm$ SEM	<i>p</i> Value
Dopamine	50–500 pg/ml	None detected	<0.0001
Epinephrine	100–1,000 pg/ml	17.3 $\pm$ 3.7	<0.001
Norepinephrine	500–5,000 pg/ml	127 $\pm$ 27	<0.01

ECLS, extracorporeal life support.