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Relative Adrenal Insufficiency (RAI): Unrecognized in Neonates with Cyanotic Congenital Heart Disease

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Keywords
Relative Adrenal Insufficiency, Congenital Heart Disease, Neonates.

Abbreviations
AC: Adrenal Cortex ACTH: Adreno Cortical Trophic Hormone, CCHD: Cyanotic Congenital Heart Disease, CHD: Congenital Heart Disease, CRH: Corticotrophin Releasing Hormone, HPA: Hypothalamic Pituitary Adrenocortical Axis. NICU: Neonatal Intensive Care Unit. RAI: Relative Adrenal Insufficiency.

Introduction
At any age, functional hypothalamic-pituitary-adrenocortical (HPA) axis is essential for the maintenance of homeostasis during physiologic and stressful (illness) states [1-4]. Though the mechanisms of elevated serum cortisol in maintaining body milieu under these conditions remain unclear, even relative cortisol insufficiency leads to hypoglycemia, hypotension, shock and even death [1-8]. Relative adrenal insufficiency (RAI) occurs when serum cortisol concentration does not increase appropriately in response to stress or illness [1-10]. The definition of RAI in ill adults is a random serum cortisol of <15 µg/dl or an increase of less than 9 µg/dl in response to exogenous ACTH stimulation [2-6]. The incidence of RAI varies from 5 to 50% in adults, children and neonates with other critical illnesses [2-8].

Neonates with cyanotic congenital heart disease (CCHD) constitute a large population (~20%) at tertiary neonatal intensive care units (NICU). These infants manifest stress of ongoing hypoxemia, hypotension, congestive heart failure and assisted ventilation including the use of a mechanical ventilator and cardiotonic drugs. However, it is unknown if these infants are able to mount an adequate cortisol response to ongoing illness before and after a cardiac surgery.

Methods
In this retrospective study of infants with congenital heart disease (CHD), the IRB at UCLA approved collection of patient data from the medical records, IRB approval number 13-001484. Clinical database and electronic records were used to identify all infants with the diagnosis of CHD who were admitted in the NICU between October 2009 and June 2013. Exclusion criteria included: fetal hydrops, Trisomy-13 or Trisomy-18, multiple congenital anomalies in addition to CHD, uncomplicated atrial or ventricular septal defect, peripheral pulmonary stenosis, persistence of foramen ovale. very complex CHD leading to death within two days of life and babies with CCHD needing surgery within 12 hours of delivery. In addition to the basic demographics, the diagnosis of specific cardiac anomaly was retrieved from the report of the echocardiogram by the Pediatric Cardiologist. Measurement of serum cortisol concentration was ordered by the attending physician at his discretion between the age of one to thirty days. Serum cortisol (µg/dl) was quantitated by a standard electro-chemiluminesence assay.

Statistical analysis
Infant parameters were summarized using means and standard deviations. Descriptive statistics were computed for all eligible infants. Analysis was performed using SAS v 9.4 (SAS Institute Inc, Cary, NC).

Results

There were 290 babies admitted to the NICU with a diagnosis of CCHD. Table 1 depicts the demography of these infants. Interventions in the delivery room included: Use of supplemental oxygen, endotracheal intubation, cardiopulmonary resuscitation and administration of epinephrine. The major cardiac diagnosis included (Table 1): Tetralogy of Fallot, Transposition of great arteries, Total anomalous pulmonary venous return, Coarctation of aorta, Hypoplastic left heart syndrome, Pulmonary atresia, Arteriovenous canal, Double outlet right ventricle, Truncus arteriosus and Epstein anomaly. Babies were treated with assisted ventilation, inhalational Nitric Oxide and cardiopulmonary bypass as indicated. Out of 290. 156 babies had cardiac surgery prior to discharge. Sixteen babies had a major surgery within 24 hours of age. While 11 babies developed necrotizing enterocolitis, 37 eventually died. Average length of stay was 45 days.

Table 1: Demography of 290 babies with CCHD (1/10/09-6/30/13).

Male / Female	164 (55%) / 130 (45%)
Average B.W. and G.A	2.8 kg and 37 weeks
Intra Uterine Growth Restriction	27 (9 %)
Inborn / Out born	127 (44 %) / 163 (56%)
Vaginal or Caesarian Delivery	148 (51%) / 142 (49%)
Delivery Room Interventions:	
Supplemental Oxygen	145 (50%)
Endo-tracheal Intubation	28 (10%)
CPR	13 (5%)
Epinephrine administration	5 (2 %)
Assisted Ventilation	246 (85%)
Inhalational Nitric Oxide	37 (13%)
Cardiac surgery within 24 hours of age	16
Cardiac surgery before discharge	156 (54 %)
Cardio-pulmonary bypass	21 (7%)
NEC	11 (3.8 %)
Mortality	37 (13%)
Length of stay	45 days
Cardiac Lesions:	
Tetralogy of Fallot	35
Transposition of Great Arteries	34
Total anomalous pulmonary venous return	26
Hypoplastic Left Ventricle	22
Coarctation of Aorta	20
Pulmonary Atresia	22
Arterio-venous canal	19
Double Outlet Right Ventricle	14
Truncus Arteriosus	8
Epstein Anomaly	6

Out of 290, 144 (49.7 %) infants had at least one cortisol level within 30 days of life while 146 (50.3%) did not (Table 2). Total number of cortisol measurements during this period were 243. Seventy babies had only one cortisol level while 64 had > one such measurement. Babies delivered by vaginal delivery had a higher first cortisol level (73 ± 116 µg/dl, n= 67) when compared to those delivered by a caesarian section (43 ± +75, n=67, p <0.02). There was no difference in the cortisol level if the blood was drawn between 4 AM and 12 noon (34 ± 78, n=46) or noon and 4 AM (65 ± 100, n=88).

Out of 134, 57 infants had a serum cortisol level before surgery (Table 2). While 16 babies had a cortisol level of >15 µg/dl before surgery, 41 had a cortisol level <15 µg/dl (i.e. RAI). Out of these 41 babies, 11 and 30 had a cortisol level between 10-15 or <10 µg/dl respectively. Number of babies with cortisol level between 6 -10 or <6 µg/dl before surgery was 15 in each group.

Table 2: Serum Cortisol Measurements (µg/dl).

Babies with at least one serum cortisol	134
Total no. of cortisol measurements	243
Babies with one cortisol	70
Babies with > 1 cortisol	64
Babies with 1 cortisol before surgery	57
Babies with cortisol > 15 µg/dl **(No RAI)**	16 / 57 (28%)
Babies with cortisol < 15 µg/dl **(RAI)**	41 / 57 (72%)
Babies with cortisol between 10-15 µg/dl	11 / 41 (19 %)
Babies with cortisol between 6-10 µg/dl	15 /41 (36 %)
Babies with cortisol < 6 µg/dl	15 / 41 (36 %)

Out of 134, 96 babies had a cortisol level within 24 h after surgery (Table 3). Out of these, 22 babies had a serum cortisol level <15 µg/dl (i.e. RAI). Out of 134, 19 babies had a serum cortisol measurement before and within 24 h after surgery. Of these 19 babies, 7 (37%) did not demonstrate an adequate (> 9 µg/dl) increase in serum cortisol concentration above baseline value (i.e. RAI).

Table 3: Serum cortisol and cardiac surgery.

Cortisol measurement within 24 h after surgery	96
Number of babies with Cortisol > 15 µg/dl (No RAI)	74 (77%)
Number of babies with Cortisol < 15 µg/dl/ (RAI)	22 (23%)
Number of babies with cortisol before and after surgery	19
Number of babies with cortisol >10 µg/dl above basal (no RAI)	12 (73%)
Number of babies with no increase in cortisol by10µg/dl above basal (RAI)	7 (37%)

Discussion

The phenomenon of RAI has been well established in sick premature, late preterm and full-term neonates with respiratory failure due to a variety of disorders [2-17]. These include respiratory distress syndrome due to surfactant deficiency, primary pulmonary hypertension, meconium aspiration syndrome, congenital diaphragmatic hernia, bacterial sepsis and pneumonia [2-17]. For the first time we report that there is high incidence of RAI in neonates with CCHD before and after cardiac surgery.

In a retrospective study [18], serum cortisol was measured in 41 neonates in the immediate postoperative period needing cardiopulmonary bypass. Of whom 15 were treated with steroids because of high concentrations of inotropic support [18]. In this study, the investigators did not quantitate serum cortisol before cardiac surgery [18]. While the mean cortisol concentration was 12 µg/dl, indicative of RAI, babies with a cortisol level of <10 µg/dl did not manifest any clinical variables indicative of increased illness severity [18]. Authors concluded that use of an absolute cortisol threshold to identify RAI and/or guide supplemental steroid therapy is not justified [18]. In another prospective study involving 119 children >3 months old undergoing heart surgery, cortisol was measured before and after 18 hours of surgery [19]. While the incidence of RAI was 78%, there was no difference in

the complex postoperative course in children with or without RAI [19]. In our study of infants <30 days of age, a large number of babies with CCHD had RAI before (72%) and after (37%) cardiac surgery. Because of a small number in each sub-group, we were unable to establish the clinical significance of RAI. It is tempting to speculate supplementation with steroids in babies with RAI before, during and after surgery may improve short or the long-term outcomes. Carefully designed closely monitored controlled trial seems warranted in this vulnerable neonatal population.

The cascade of events that produce changes in cortisol release by the adrenal cortex (AC) begins with release of CRH in the paraventricular nuclei of the hypothalamus [1-4]. CRH in turn stimulates the release of ACTH by the anterior pituitary which then stimulates the secretion of cortisol by the AC [1-4]. The HPA axis is protected by a feedback loop whereby cortisol affects the pituitary and the hypothalamus including the hippocampus and prefrontal cortex [1-6]. The potential mechanism(s) of RAI in these babies are unknown. It may be due to structural or functional aberrations in the HPA axis at the hypothalamic, pituitary or AC including dysfunction of the respective receptors [1-6]. The incidence of congenital heart disease (CHD) varies from 0.5 to 1% of all live births. With an improvement in prenatal care, increasing number of fetuses with CHD are diagnosed prenatally. As a result, increasing number of babies with CHD are delivered at a tertiary NICU centers. Since these babies are at a high risk of developing RAI, future studies should be undertaken to determine the possible mechanisms of this phenomenon.

Limitations of our study include

A single center retrospective study spanning over a period of ~ 45 months. Only about half of the eligible patients had quantitation of at least one cortisol level ordered at the discretion of the attending physician rather than at a predetermined time and age of the patient.

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