

Perioperative Corticosteroid Levels and the Adrenal Response Following Infant CPB

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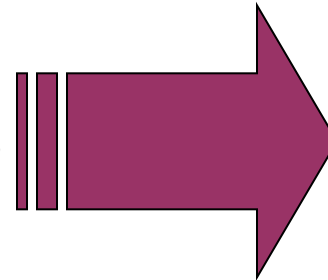


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No disclosures

Cardiopulmonary Bypass (CPB) and Children

- Induces a systemic inflammatory response
 - Complement activation
 - Cytokine release
 - Cortisol levels increase
- Clinical manifestations
 - Low cardiac output
 - Hemodynamic lability
 - Fluid retention
 - Fever



**Multisystem
Organ
Failure**

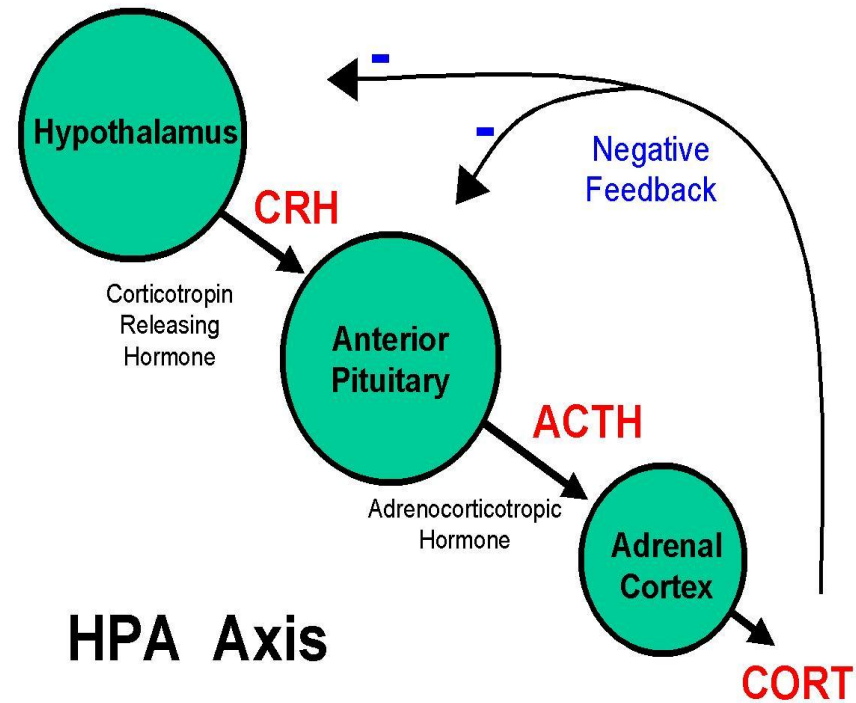
Potential Solution



Glucocorticoids

Consequences of Corticosteroids

- Immunosuppression:
 - Lymphocyte
 - T helper cell
 - Cytotoxic T cell
- Neutrophil induction
- Cortisol suppression
- Glucose induction



Clinical Consequences

- Pediatric Health Information System Database
- 46,730 children (0-18 yrs) undergoing CPB
 - 54% received corticosteroids
- Corticosteroid treated children had increased:
 - Infection rates
 - Insulin requirement
 - ICU and hospital length of stay
- Potential causes:
 - Over suppression of inflammatory/stress response

The “appropriate” infant stress response???

- Unknown
- Wide range of post-op cortisol levels reported
- Variation in results are due to:
 - Study design
 - Corticosteroid dose and timing
 - Diverse patient populations
- **Post-operative corticosteroid drug levels??**

Objective

- To determine whether a standard 1mg/kg intraoperative dose of dexamethasone results in similar drug levels for all patients
- Characterize the relationship between dexamethasone levels and the innate stress response following infant CPB

Hypothesis:

Postoperative dexamethasone levels after standardized intra-operative dosing are highly variable and inversely related to the infant stress response

Eligibility

- Inclusion Criteria
 - Diagnosis of Congenital Heart Disease
 - Age: 0-365 days
 - Planned cardiac surgery utilizing CPB
- Exclusion Criteria
 - Premature Birth: < 36 weeks GA
 - Corticosteroids within 24 hours before surgery
 - Pre-operative mechanical circulatory support

Congenital Heart Patients N=32

Dex mg/kg

Post-Induction

Post-CPB
Pre-MUF

ICU Arrival

4, 8, and 12
hours

24 hours

TIME 1

Cortisol
ACTH
IL 6,8,10

TIME 2

Cortisol
ACTH
IL 6,8,10

TIME 3

Cortisol
ACTH
IL 6,8,10

TIME 4, 5, 6

Cortisol
ACTH
IL 6,8,10

TIME 7

Cortisol
ACTH
IL 6,8,10

*Sta
fent
anes

High Dex
≥ 15 mcg/dL

Low Dex
< 15 mcg/dL

Patient Characteristics

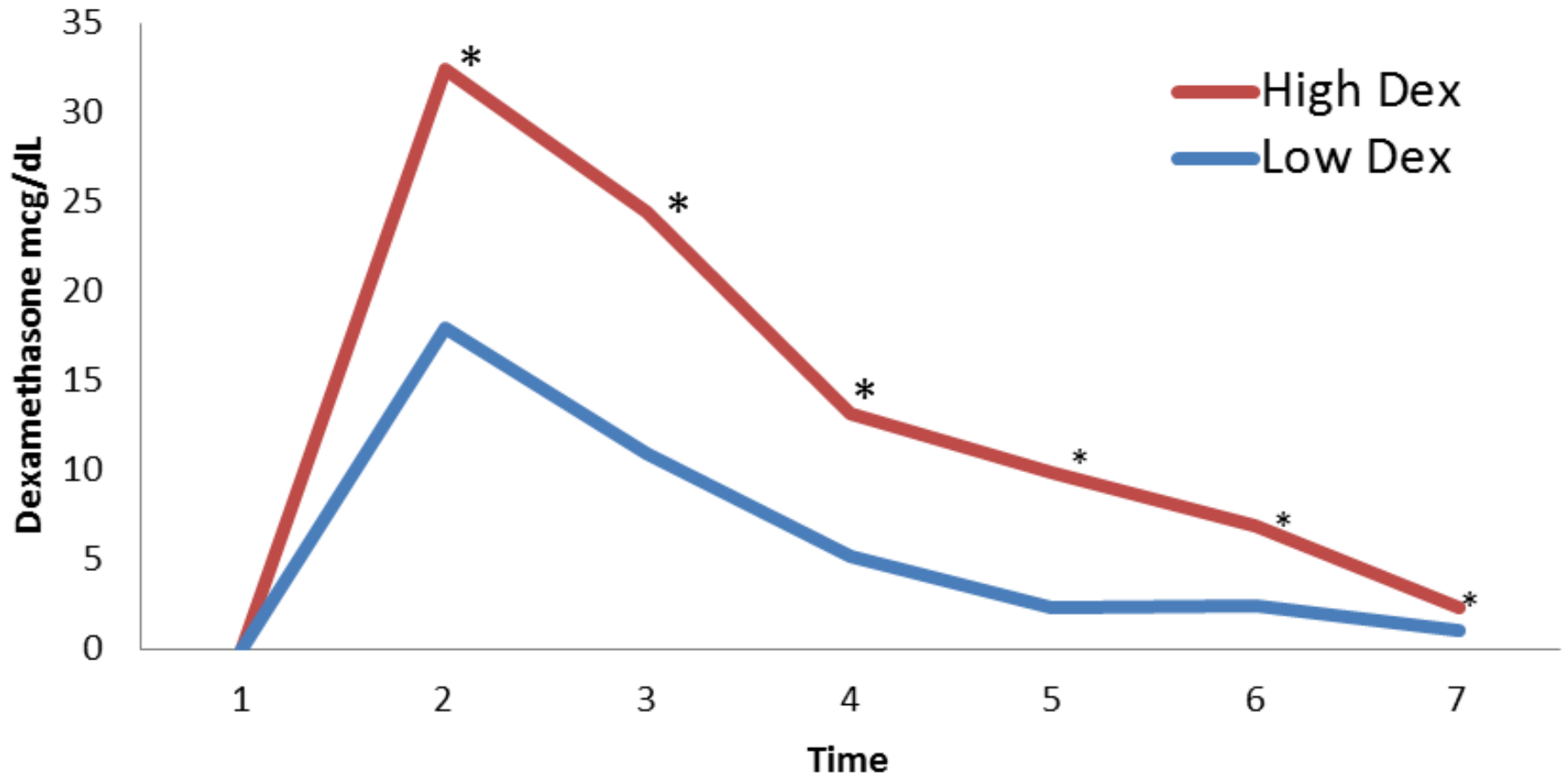
Table 1. Patient Characteristics

	Low Dex n=22	High Dex n=10	<i>P</i> value
Demographic variables			
Age (days)	199 ± 114	225 ± 363	0.827
Male, n (%)	10 (45%)	3 (30%)	
RACHS-1 score			
1-3, n	18	9	
4-6, n	4	1	
CPB time (min)	104 ± 44	90 ± 35	0.35
Cross-clamp time (min)	51 ± 32	45 ± 28	0.63
Modified ultrafiltration (ml)	365 ± 192	293 ± 295	0.49
Mechanical ventilation duration (days)	3.9 ± 8.0	1.6 ± 1.4	1.00
ICU length of stay (days)	12 ± 14	11 ± 11	0.71

RACHS-1 score, risk adjustment for congenital heart surgery. CPB, cardio pulmonary bypass.

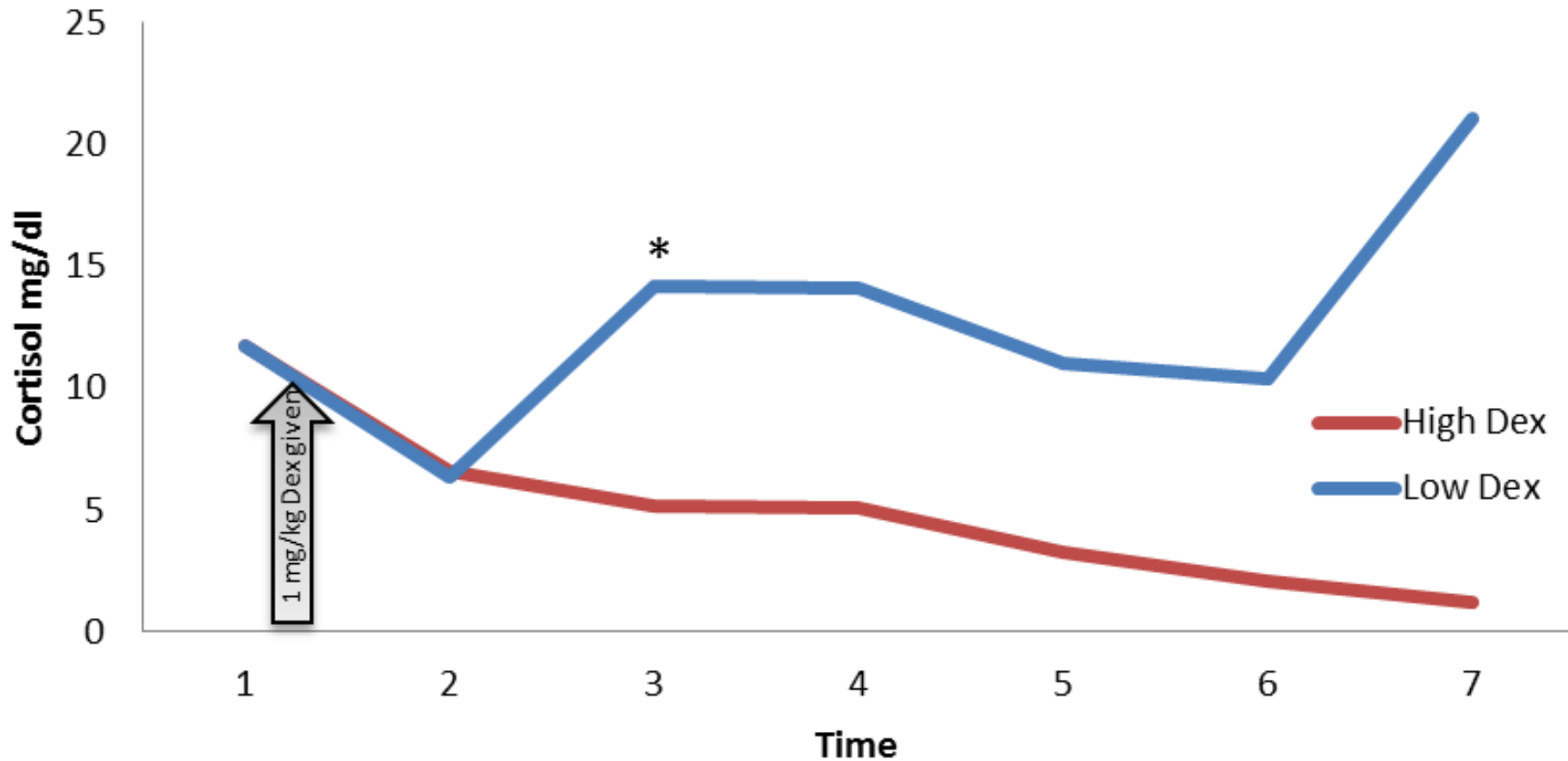
Data reported as mean ± standard deviation

Dexamethasone Levels



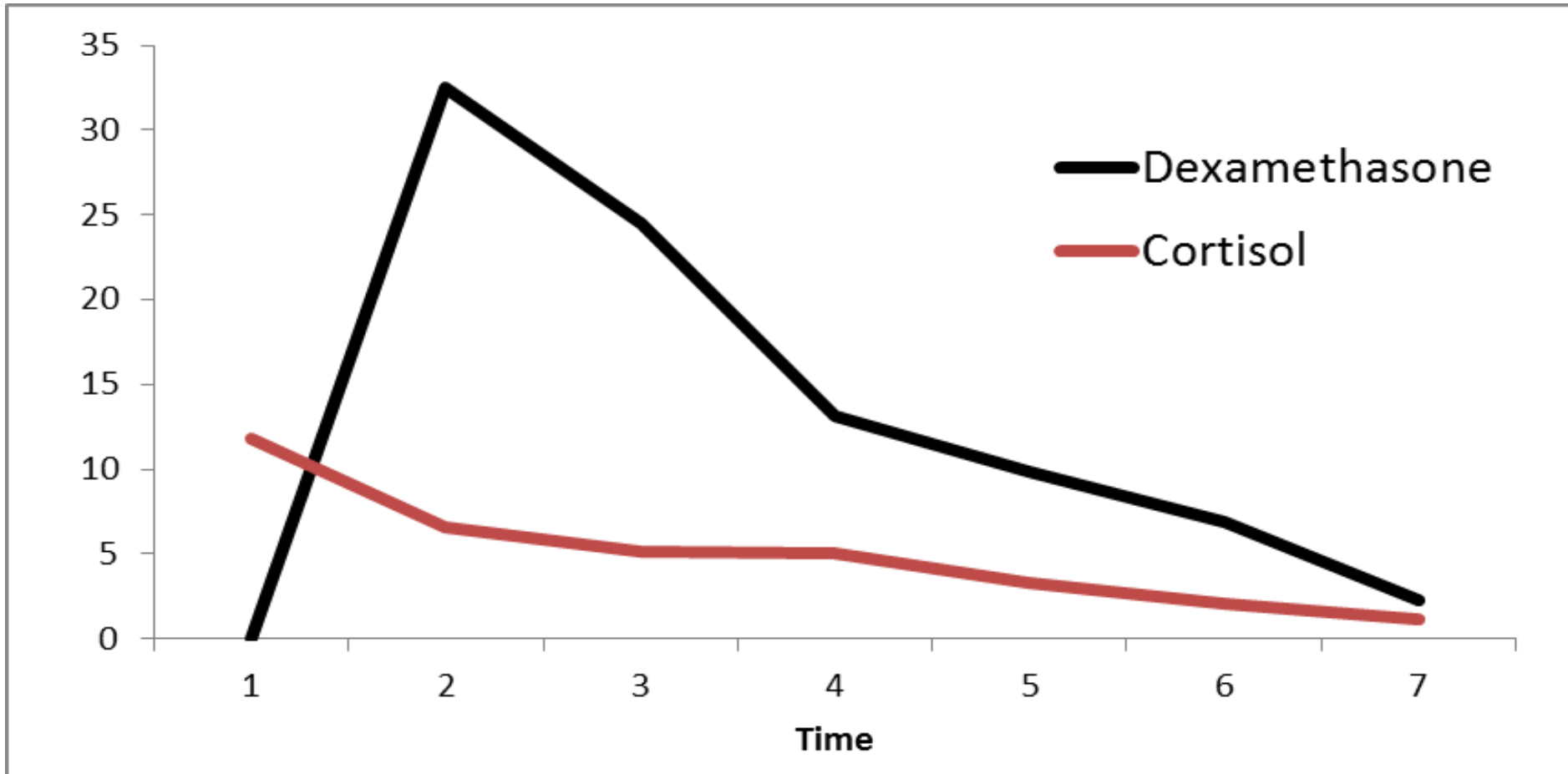
***denotes significant difference between groups**

Cortisol Responses



* Denotes a significant difference between groups, $p=0.016$

High Dex and Cortisol Response



- **Persistent cortisol suppression**

Study Limitations

- Single center investigation
- Small sample size precludes linking cortisol levels with clinical outcomes

Conclusions

- First comparison of post-CPB dexamethasone drug levels and the infant stress response
- Dexamethasone levels vary significantly between patients after a standard pre-CPB 1 mg/kg dose
 - **High and low dex responders**
- Cortisol suppression persists even after dexamethasone levels decline in high dex responders
 - **Iatrogenic adrenal insufficiency??**
- Dexamethasone levels are an important variable to consider in past and future studies seeking to link cortisol response with clinical outcomes

The “Optimal” Corticosteroid Approach

- Avoid overtreatment
 - Infection risk
 - Adrenal suppression- “iatrogenic adrenal insufficiency”
 - Glucose induction
- Avoid under suppression in “at risk” patients
- **Ultimate Goal:** To develop an individualized approach to corticosteroid mediation of the infant CPB inflammatory/stress response

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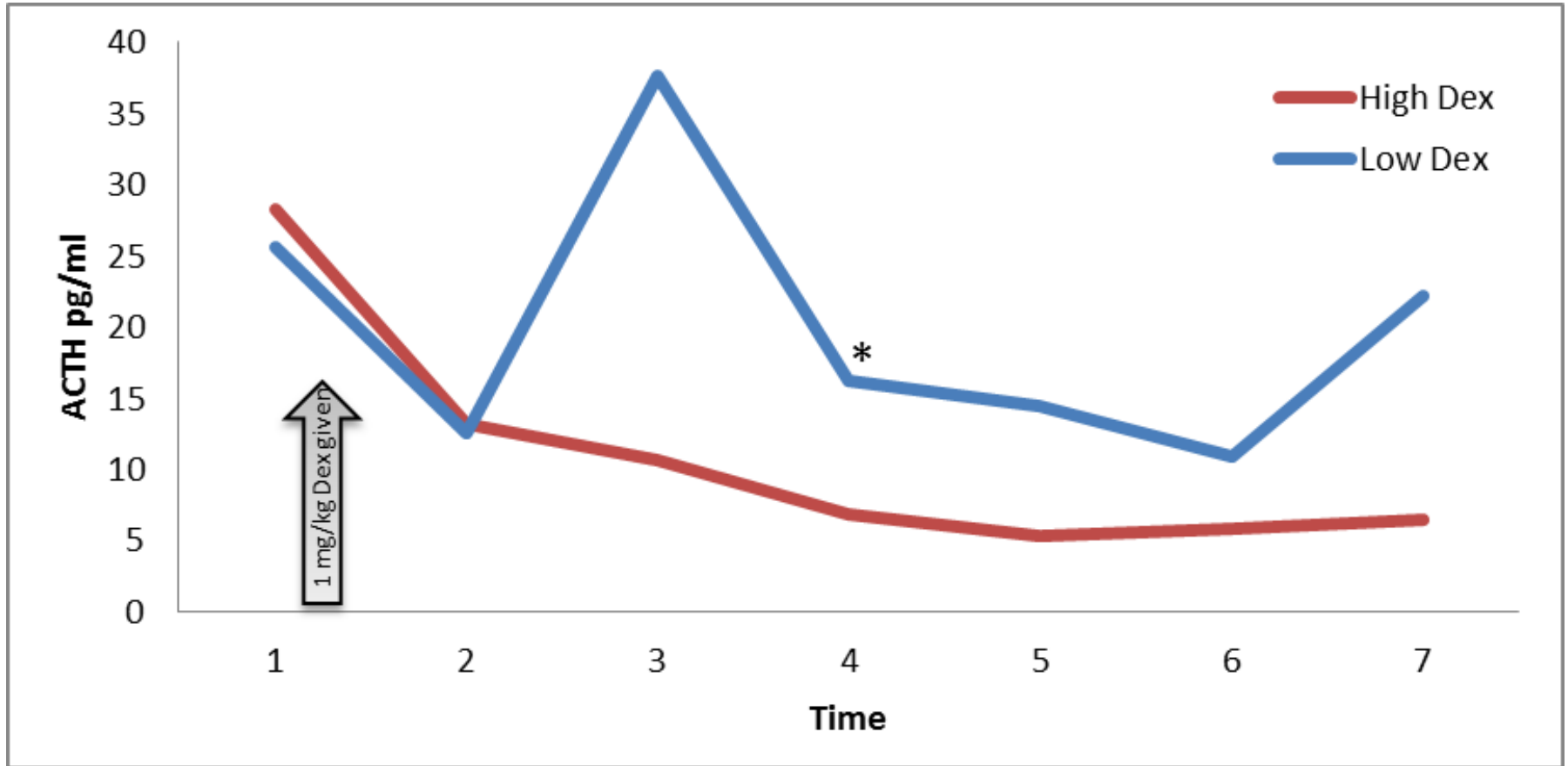
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Questions?

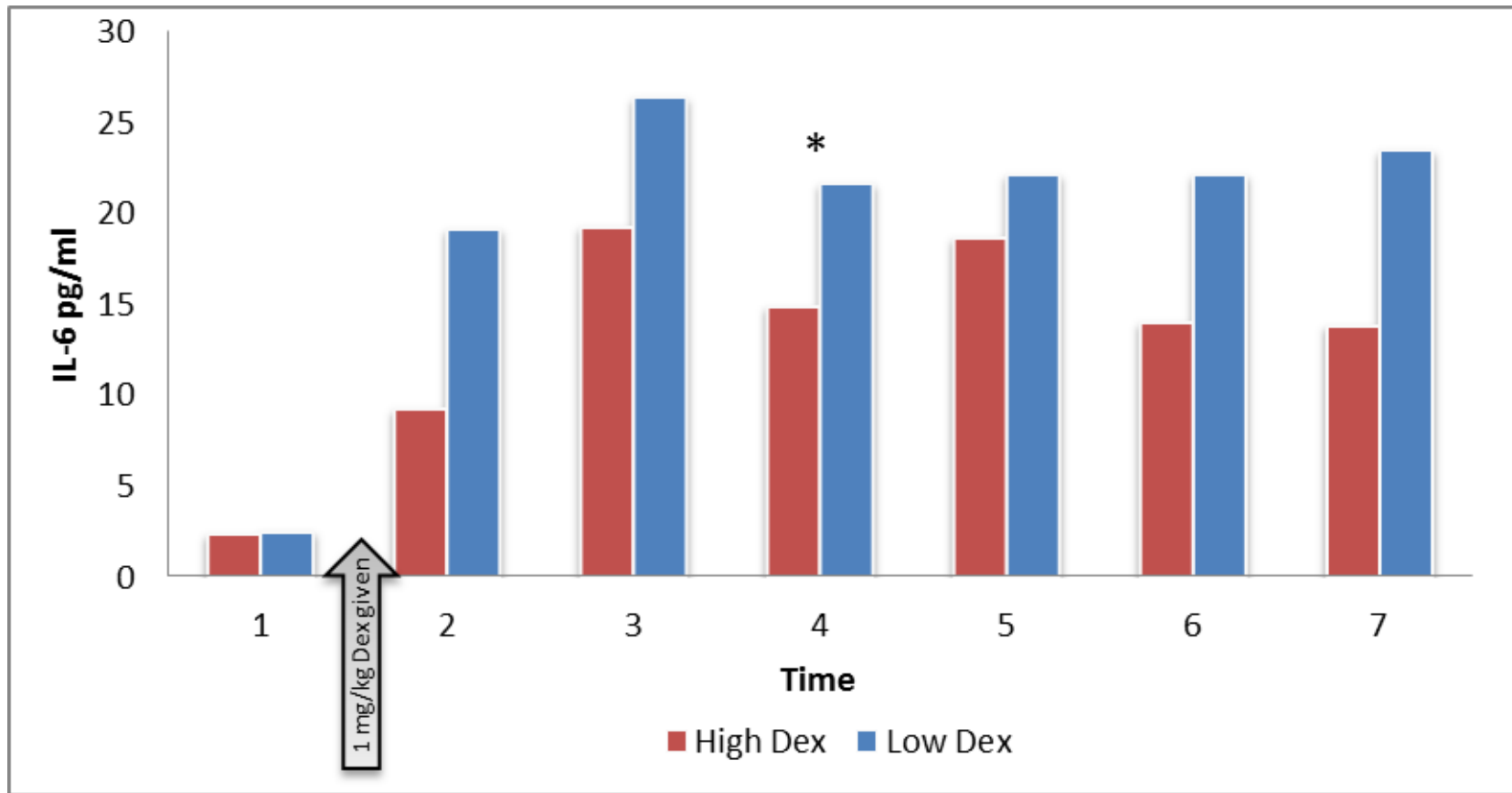


ACTH Responses



* Denotes a significant difference between groups, $p=0.025$

Dexamethasone Level and IL-6



- IL-8 levels were similar between groups
- IL-10 was lower at Time 4 in High Dex group (p=0.015)

IL-8 and IL-10

Table 3. Cytokine responses for times 1 through 7

	n	Low Dex	n	High Dex	P Value
IL-8					
1	15	1.33 ± 1.72	10	1.30 ± 0.62	0.127
2	15	5.40 ± 4.91	10	5.93 ± 6.59	0.890
3	15	7.79 ± 5.11	10	6.74 ± 4.80	0.637
4	15	5.69 ± 4.24	9	5.12 ± 3.10	1.000
5	12	5.43 ± 3.69	8	4.41 ± 2.35	0.758
6	12	5.41 ± 3.70	6	3.23 ± 1.51	0.098
7	9	7.57 ± 7.49	5	2.96 ± 1.05	0.240
IL-10					
1	15	1.58 ± 3.61	10	0.95 ± 0.78	0.518
2	15	54.76 ± 40.46	10	40.11 ± 27.95	0.296
3	15	46.64 ± 27.87	10	44.77 ± 32.13	0.879
4	15	11.96 ± 6.41	9	7.14 ± 10.29	0.015
5	12	7.46 ± 6.23	8	3.77 ± 2.22	0.097
6	12	5.64 ± 5.58	6	2.51 ± 0.67	0.174
7	9	13.87 ± 30.87	5	1.78 ± 1.49	0.518

IL, interleukin.

Post-op
hr #4

Potential Contributors to Drug Level Variability

- Age
- Gender
- Protein binding
- Patient genetics
- CPB related factors

Intra-Operative Steroid Practices

- Survey of Pediatric Cardiac Intensive Care Society
 - 97% report intra-operative steroid use
 - Only 40% use steroids with every case
 - Decision for use based on:
 - Age of patient
 - Anticipated CPB time, DHCA
 - Surgeon preference

Checcia et al Ped Crit Care Med 2005