Title: Cardiopulmonary Bypass Alters Intracellular Glucocorticoid Receptors

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Background: Critical illness-related corticosteroid insufficiency (CIRCI) describes the state of inadequate steroid activity relative to illness severity. CIRCI, which contributes negatively to patient outcomes, is often triggered by systemic inflammatory conditions such as sepsis. Cardiopulmonary bypass (CPB) triggers systemic inflammation, and biochemical evidence of CIRCI has been widely reported in children following CPB, especially when coupled with perioperative steroids administered to attenuate inflammation. Among the various etiologies of CIRCI, alteration in intracellular receptor profiles contributing to cellular steroid resistance has been increasingly described. Specifically, the ratio of two glucocorticoid (GC) receptor isoforms, alpha (GR-α) and beta (GR-β), act to alter downstream gene transcription. Following GC binding, GR-α, a transcription factor, interacts with steroid response elements to alter gene expression, while GR-β is unable to bind cortisol and functions as a dominant negative regulator of GR-α. An increased GR-β:GR-α ratio has been studied as a mechanism of cellular GC resistance in several acute and chronic inflammatory conditions. However, the GR-β:GR-α response has not been described following exposure to CPB and steroids (CPB+S). We hypothesize that exposure to CPB+S will increase the GRβ:GRα ratio as reflected in peripheral blood mononuclear cells (PBMCs).

Methods: A single-center prospective observational study enrolling consecutive patients requiring CPB+S. Patients were excluded if exposed to inhaled or systemic steroids or etomidate three months prior to surgery, or within 24-hours post-operatively. Blood was obtained immediately prior to CPB+S and again 18-28 hours post-operatively. PBMC were purified using Ficoll, RNA isolated, and cDNA used for qPCR to detect GR-α and GR-β transcripts. The Wilcox signed rank test was employed to evaluate differences in pre- and post-CBP+S exposure in the GR-β/GR-α mRNA levels using the ΔCT method.

Results: Fifteen patients (2 days-21 years) were exposed to CPB+S during the study period. Analysis revealed a significant increase (fold increase 1.9 ± 0.5, $p<0.05$) in the GRβ:GRα ratio comparing pre- to post-CPB+S exposure. These data support the hypothesis that exposure to CPB+S increases the GRβ:GRα ratio.

Conclusion: Similar to other acute systemic inflammatory disorders, including sepsis and ARDS, exposure to CPB+S markedly elevated the GRβ:GRα ratio. This novel finding suggests a possible mechanism for CIRCI in this population. Analysis of a larger data set suggests a bimodal response, revealing cohorts with either an increased or decreased GRβ:GRα ratio, suggesting that there may be responders and non-responders to CPB+S induced GC resistance. Ongoing analysis will reveal the expression profile of genes known to be activated/suppressed by GC, which when correlated to the GRβ:GRα ratio should illuminate the functional cellular response.