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Major cardiac surgery induces an increase in sex steroids in prepubertal children ☆

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ABSTRACT

While the neuroprotective benefits of estrogen and progesterone in critical illness are well established, the data regarding the effects of androgens are conflicting. Surgical repair of congenital heart disease is associated with significant morbidity and mortality, but there are scant data regarding the postoperative metabolism of sex steroids in this setting. The objective of this prospective observational study was to compare the postoperative sex steroid patterns in pediatric patients undergoing major cardiac surgery (MCS) versus those undergoing less intensive non-cardiac surgery. Urinary excretion rates of estrogen, progesterone, and androgen metabolites (μg/mmol creatinine/m^2 body surface area) were determined in 24-h urine samples before and after surgery using gas chromatography–mass spectrometry in 29 children undergoing scheduled MCS and in 17 control children undergoing conventional non-cardiac surgery. Eight of the MCS patients had Down's syndrome. There were no significant differences in age, weight, or sex between the groups. Seven patients from the MCS group showed multi-organ dysfunction after surgery. Before surgery, the median concentrations of 17β-estradiol, pregnanediol, 5α-dihydrotestosterone (DHT), and dehydroepiandrosterone (DHEA) were (control/MCS) 0.1/0.1 (NS), 12.4/11.3 (NS), 4.7/4.4 (NS), and 2.9/1.1 ($p = 0.02$). Postoperatively, the median delta 17β-estradiol, delta pregnanediol, delta DHT, and delta DHEA were (control/MCS) 0.2/6.4 ($p = 0.0002$), −3.2/23.4 ($p = 0.013$), −0.6/3.7 ($p = 0.0004$), and 0.5/4.2 ($p = 0.004$). Postoperative changes did not differ according to sex. We conclude that MCS, but not less intensive non-cardiac surgery, induced a distinct postoperative increase in sex steroid levels. These findings suggest that sex steroids have a role in postoperative metabolism following MCS in prepubertal children.

1. Introduction

Pediatric cardiac surgery sometimes induces a systemic inflammatory response syndrome that leads to multiple organ dysfunction [1]. Not only the myocardium, but other organ systems such as the brain, can be affected. Although advances in congenital heart surgery have increased the survival of infants born with complex congenital heart disease, this group has higher rates of neurodevelopmental problems, especially when extracorporal life support is required [2,3]. Furthermore, congenital heart disease is among the most important risk factors for pediatric arterial ischemic stroke [4]. However, a recent review identified the avoidance of extreme hemodilution during cardiopulmonary bypass (CPB) as the only condition that provided neuroprotection in pediatric cardiac surgery [5]. Data from experimental models and clinical studies indicate that gonadal steroids have neuroprotective properties and may be candidates for therapeutic use during cardiac surgery.

Abbreviations: AoX, aortic cross-clamping; ASD, atrial septal defect; AVSD, atrioventricular defect; BSA, body surface area; CPB, cardiopulmonary bypass; DHEA, dehydroepiandrosterone; DHT, 5α-dihydrotestosterone; E2, 17β-estradiol; GC–MS, gas chromatography–mass spectrometry; MCS, major cardiac surgery; MOD, multiple organ dysfunction; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

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Several observational studies have demonstrated the importance of endogenous sex hormones on survival rates and recovery from critical illness. Specifically, higher estrogen concentrations are associated with better outcomes in traumatic and atraumatic cardiac arrest, major head trauma, ischemic stroke, severe burn injuries, sepsis, and pediatric trauma patients [6–8]. Furthermore, the positive effects of estrogen and progesterone treatment have been described in animal models of critical illness. Estrogen inhibits apoptosis and inflammation via mitochondrial receptors, inhibits oxidative stress, and stabilizes membrane potentials [9]. Similar effects are attributed to progesterone, including less brain edema after head trauma [10]. With respect to cardiac disease, estrogen causes vasodilation in the pulmonary vasculature and attenuates the vasoconstrictor response to various stimuli, including hypoxia [11]. Some authors propose preclinical estrogen treatment of all critically ill adults [12].

In contrast, as shown in animal models, testosterone and dihydrotestosterone (DHT) exacerbate ischemic damage [13,14]. However, the role of androgens in myocardial and endothelial function may be different from their effects on the brain. It was shown recently that testosterone protects against global myocardial ischemia [15]. Furthermore, dehydroepiandrosterone (DHEA) inhibits accelerated coronary atherosclerosis in a rabbit model of cardiac transplantation [16].

There are scant data regarding the postoperative metabolism of sex steroids after MCS. A decrease in the plasma concentrations of estradiol and an increase of progesterone was found after CPB in adults [17]. Others found increases in 17β-estradiol (E2) and DHEA and sex-dependent changes in testosterone after CPB [18]. After CPB in pediatric patients, only progesterone was investigated; it showed an increase [19].

Here we used gas chromatography–mass spectrometry (GC–MS), which is a highly specific and nonselective analytical technique, to profile urinary sex steroid metabolites. This method allows noninvasive evaluation of hormonal production rates from 24-h urinary specimens as an integral measure of steroid production before and after surgery [20]. There is no evidence of clinically significant deterioration of renal function in children undergoing repair of cardiac lesions with CPB [21]. Thus, assessing steroid metabolism in urine is a reasonable approach in this setting.

In this prospective study, the urinary excretion rates of steroid metabolites were determined before and immediately after surgical repair of congenital heart defects. Children undergoing conventional non-cardiac surgery served as controls. Only patients with scheduled surgery and selected diagnoses were included to reduce the effects that emergency situations, preoperative heart failure, or complex surgery can have on the endocrine stress response. The aim of this study was to compare the postoperative pattern of endogenous sex steroid metabolism between major cardiac surgery (MCS) and less invasive non-cardiac surgery in prepubertal children.

We found that only MCS induced a distinct postoperative increase in sex steroids. These findings suggest an important role for sex steroids in postoperative metabolism following MCS in prepubertal children.

2. Experimental

The Ethics Committee at the Justus Liebig University of Giessen approved this study, and written informed parental consent was obtained for all patients.

2.1. Patients

Children were prospectively enrolled at the Pediatric Intensive Care Unit of the University Children's Hospital in Giessen, Germany. To generate a nearly homogeneous MCS group, children with congenital heart disease were selected if they suffered from atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular septal defect (AVSD), or Tetralogy of Fallot (TOF) and underwent scheduled cardiovascular surgery ($n = 29$). Children in the control group underwent scheduled conventional non-cardiac surgery ($n = 17$). The first urine sample was collected at home before hospital admission in order to obtain a sample in an almost stress-free environment. Thus, children undergoing emergency surgery were not included.

2.2. 24 h urine collection

In the 24 h before surgery, urine was collected at home using urine bottles or disposable diapers as appropriate. We used two sizes of disposable diapers (Pampers®, Procter & Gamble, Schwalbach, Germany). The small size was from a serial production and was used for children weighing <2.3 kg (Pampers P). For children weighing 2.3–6 kg, medium-sized diapers composed of pure cellulose were manufactured exclusively for use at our clinic. Using diapers for urine collection allowed us to accurately determine glucocorticoid metabolite urinary concentrations as the recovery of steroids after hydraulic extraction is approximately 100% [22]. The postoperative urine was collected by bladder catheter in the MCS group and was collected using urine bottles, cellulose diapers, or bladder catheter in the control group.

2.3. Anesthesia and CPB operation

Anesthetic management substantially attenuates intra- and postoperative stress responses [23]. Children were pre-medicated with oral midazolam (0.5 mg/kg) 20–40 min before transfer to the operation room.

Control group: All surgeries in the control group were performed under general anesthesia. Patient monitoring was based on the requirements of the planned operation (e.g. three-lead electrocardiogram, pulse oximetry, capnography, and invasive or non-invasive arterial blood pressure measurements). For induction of anesthesia, 5–10 mg/kg of thiopental, 2–5 μg/kg fentanyl, and 0.1 mg/kg vecuronium were administered. The trachea was intubated, and balanced anesthesia was maintained with isoflurane (1.0–1.5 vol%), fentanyl (5 μg/kg every 30–45 min), and vecuronium (0.05 mg/kg every 30–45 min). Additional regional anesthesia techniques were not used during the study period.

MCS group: In patients undergoing surgical heart repair, general anesthesia was induced by midazolam (0.05–0.1 mg/kg) and fentanyl (10 μg/kg). Isoflurane (0.4–1.0 vol%), midazolam (0.05–0.1 mg/kg every 60 min), and fentanyl (5–10 μg/kg every 30 min) were administered for anesthesia maintenance. Complete muscle relaxation was provided by pancuronium (0.05–0.1 mg/kg every 60–90 min) throughout the procedure. Following anesthesia induction, the trachea was intubated and the invasive procedures were performed (e.g. central venous, arterial, and urinary catheters). After surgery, patients were transferred anesthetized to the PICU and extubated when appropriate.

Routine surgical techniques and cardioprotective strategies were employed according to the surgeon's preference. CPB was performed using standardized procedures. Mild hypothermia (32–34 °C rectal temperature) was employed during bypass. Blood glucose levels were kept within the range of 4.5–8.0 mmol/l by intravenous glucose infusion. Glucocorticoids were not administered before or during CPB. Conventional hemofiltration was used in CPB for equilibration of electrolytes and water balance. Modified ultrafiltration was not used during CPB. None of the patients received hemofiltration postoperatively.