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Sex steroids in cardiopulmonary bypass

Andreas Trotter[1], Hans-Jörg Grill[2], Wolfgang Hemmer[3], Andreas Hannekum[3], Dieter Lang[1]

Abstract

Background: Sex steroids have immunomodulatory effects. No data exist on alterations of sex steroids during cardiopulmonary bypass (CPB). Cardiac surgery with CPB releases an immunological response with complement and cytokine activation.

Results: Plasma estradiol and progesterone levels before and immediately after CPB were measured in 11 patients. During CPB, mean estradiol levels decreased from 29 to 15 pg/ml and progesterone levels rose from 0.13 to 0.90 ng/ml. These changes were statistically significant.

Conclusions: These are the first preliminary results evaluating plasma levels of sex steroids during CPB. Whether alterations in estradiol and progesterone levels influence complement and cytokine activation during bypass or vice versa is currently being investigated.

bypass cardiopulmonary, sex steroid

Introduction

Several studies have shown interactions between sex steroids and cytokines. In female mice, estradiol demonstrated a protective effect on interleukin-1-induced cartilage breakdown [1]. High progesterone levels decreased interleukin-6 production in gingival fibroblasts [2]. In a recent randomized, controlled animal study, polymicrobial sepsis was induced using the model of cecal ligation and subsequent puncture. Splenic immune function and survival rates were significantly better in female animals [3]. The immunomodulatory effects of sex steroids have been confirmed by clinical observation of a higher incidence of mortality in boys after thermal burns [4].

We previously studied, in an experimental setting, the ability of 3H-marked estradiol and progesterone, in solution with lipids, to absorb on to synthetic surfaces such as the bypass circuit. Both steroids adsorbed on to the synthetic surface, with a higher adsorption for progesterone than for estradiol (unpublished data). Prior to this study, no data existed on the behavior of sex steroids passing through a bypass circuit during CPB, where a considerable amount of synthetic surface is present.

Patients and methods

We analyzed 11 patients (three female) with a median age of 66.8 years undergoing cardiac surgery with CPB mainly for coronary repair. The non-pulsatile technique was used, with slight hypothermia of 32–34°C depending on the duration of CPB. The median duration of CPB was 85 min (range 40–115 min). No corticoids were given before or during CPB. Patients were heparinized with 300 IU/kg body weight to prevent clotting in the bypass circuit. After disconnection from the circuit, protamine was given to antagonize this heparinization. Two blood samples were taken from an indwelling arterial catheter, the first before connecting the patient to the CPB circuit and after heparin administration, the second after reperfusion and after protamine administration. Estradiol and progesterone concentrations were measured using an enzyme-linked immunoassay (ELISA test kit, Fa Böehringer-Mannheim, Mannheim, Germany). The lowest detection level for the test kit was 10 pg/ml estradiol and 0.1 ng/ml progesterone. Values beneath the detection level were set to 10 pg/ml and 0.1 ng/ml for estradiol and progesterone, respectively.

For statistical analyses, Wilcoxon signed rank test was used.

Results

Estradiol mean levels were 29 *vs* 15 pg/ml before and after CPB, respectively (ranges 12–44 *vs* < 10–29 pg/ml)

[1]Section of Pediatric Cardiology, Children's Hospital, Prittsitzstraße 43, 89075 Ulm, Germany
Full list of author information is available at the end of the article

Table 1 Plasma levels of estradiol and progesterone before and after cardiopulmonary bypass (CPB)

	n	Before CPB	After CPB	*P*
Estradiol (pg/ml)	11	29 (12-44)	15 (< 10-29)	0.005
Progesterone (ng/ml)	11	0.13 (< 0.1-0.18)	0.90 (0.26-3.23)	0.003

Values are shown as mean (range). Statistical analysis by Wilcoxon signed rank test.

and progesterone levels were 0.13 vs 0.90 ng/ml before and after CPB, respectively (ranges < 0.1–0.18 *vs* 0.26–3.23) (Table 1). Thus, while estradiol levels decreased, progesterone levels rose. These differences were statistically significant (P = 0.005 and 0.003 for estradiol and progesterone, repectively). Figures 1 and 2 illustrate the measured estradiol and progesterone levels of each patient before and after CPB. The increase in progesterone level was evident in all patients. Estradiol decreased in all patients except one.

Discussion

To our knowledge, these are the first preliminary results evaluating changes in levels of estradiol and progesterone during CPB. Estradiol decreased during CPB; this may be explained by the adsorption of sex steroids on to the bypass circuit. On the other hand, progesterone levels increased suggesting that the theory of adsorption is questionable. However, if we assume a marked endogenous production of progesterone during CPB, the net result could be a rise in progesterone even though adsorption to the circuit had occurred. Progesterone is a precursor for cortisol production, which has been found to increase during and after CPB in several studies [5]. Progesterone, however, is not the primary precursor for estradiol.

All patients received heparin before CPB. There are limited data on the effect of heparin on the metabolism of sex steroids. In vitro studies on hormone-dependent breast cancer cells showed heparin to have no effect on estrone sulfatase's activity as an estradiol-forming enzyme. However, progesterone did inhibit estrone sulfatase activity [6]. Whether the observed decrease in estradiol levels during CPB is because of a progesterone-mediated inhibition of estrone sulfatase activity is not clear.

As protamine is isolated from fish sperm it is conceivable that the observed alterations in sex steroids are due to protamine administration after reperfusion. We tested protamine as well as heparin for its cross-reactivity, using the ELISA test kit with which estradiol and progesterone levels were determined. These results exclude any measurable effect on the observations made regarding the sex steroid levels before and after CPB.

Estradiol and progesterone may suppress interleukin production. If the observed changes in sex steroids influence CPB-induced interleukin activation then the relationship needs to be researched. The discordant findings of decreasing estradiol and increasing progesterone level may antagonize one another in this setting. the intra-an-postoperative changes in estradiol and

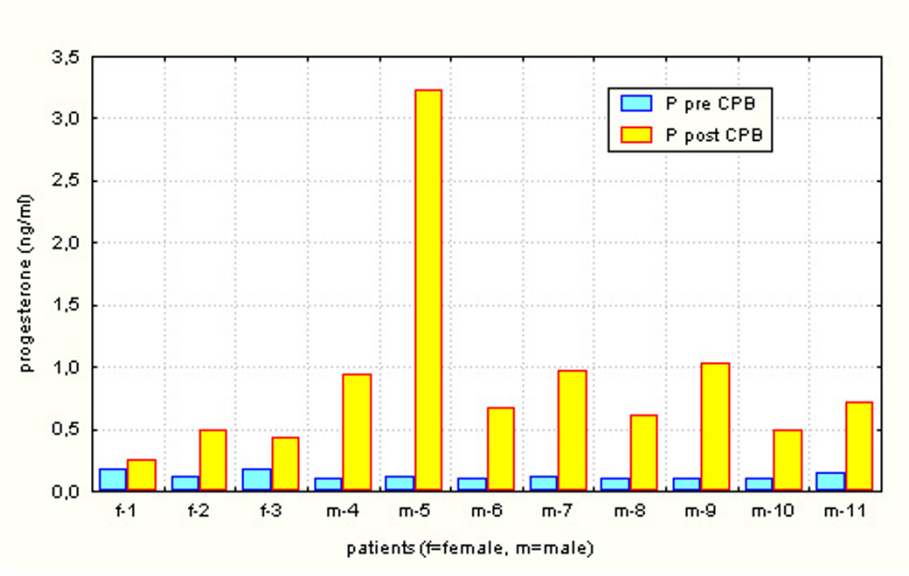

Figure 1 Progesterone levels before and after cardiopulmonary bypass (CPB) in 11 patients.

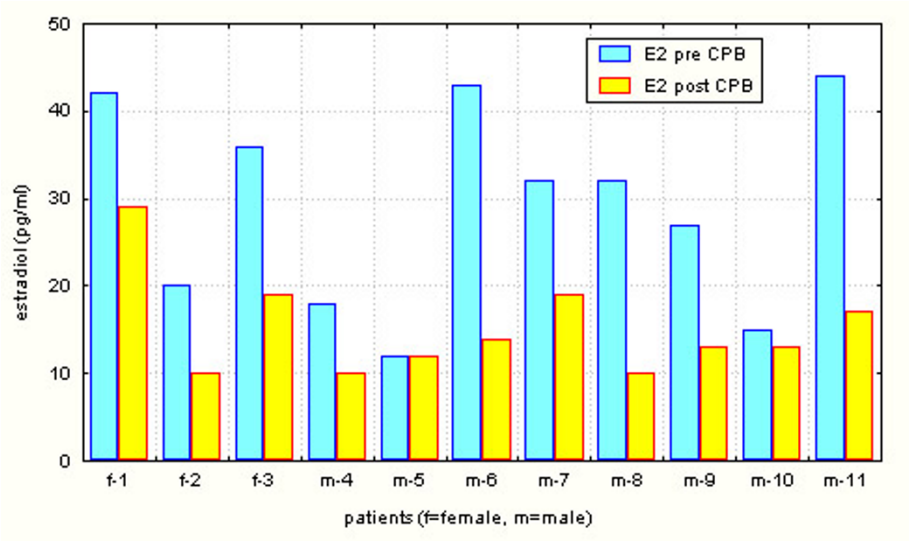

Figure 2 Estradiol levels before and after cardiopulmonary bypass (CPB) in patients.

progesterone level in relation to cytokine activation is the subject of further investigation.

Author details
[1]Section of Pediatric Cardiology, Children's Hospital, Prittsitzstraße 43, 89075 Ulm, Germany. [2]Division of Obstetric Endocrinology, University of Ulm, Frauensteige 14, 89075 Ulm, Germany. [3]Division of Cardiac Surgery, University of Ulm, Steinhövelstrasses 9, 89075 Ulm, Germany.

Received: 3 July 1997 Revised: 17 October 1997
Accepted: 20 October 1997 Published: 26 November 1997

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doi:10.1186/cc109
Cite this article as: Trotter *et al*.: Sex steroids in cardiopulmonary bypass. *Critical Care* 1997 **1**:85.