Follow-up papers - Congenital

Perfusion temperature, thyroid hormones and inflammation during pediatric cardiac surgery

Rune Eggum a, b, *, Thor Ueland c, d, Tom E. Mollnes e, Vibeke Videm f, Arnt E. Fiane e, Pål Aukrust c, g, Harald L. Lindberg a

a Department of Thoracic and Cardiovascular Surgery, Oslo University Hospital, Rikshospitalet, University of Oslo, Oslo, Norway
b Department of Vascular Surgery, Buskerud Hospital, Drammen, Norway
c Research Institute for Internal Medicine, Oslo University Hospital, Rikshospitalet, University of Oslo, Oslo, Norway
d Department of Endocrinology, Oslo University Hospital, Rikshospitalet, University of Oslo, Oslo, Norway
e Institute of Immunology, Oslo University Hospital, Rikshospitalet, University of Oslo, Oslo, Norway
f Institute of Laboratory Medicine, Children’s and Women’s Health, Norwegian University of Science and Technology, and Department of Immunology and Transfusion Medicine, St Olav University Hospital, Trondheim, Norway
g Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital, Rikshospitalet, University of Oslo, Oslo, Norway

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Abstract

Objectives: During cardiopulmonary bypass (CPB) surgery there are several alterations in concentrations of thyroid hormones. Although hypothermia and inflammation have been implicated in the disturbed thyroid axis during CPB, these issues are far from clear. Methods and results: We measured serum/plasma concentrations of thyroid hormones and inflammatory mediators in children with body weight < 10 kg, undergoing open heart surgery, randomized to mild (n = 15, 32 °C) or moderate (n = 15, 25 °C) hypothermia. During CPB there was a marked decrease in triiodothyronine (T3), free thyroxin (FT4) and thyroid-stimulating hormone (TSH), followed by a slight increase after 24 h, but without normalization 48 h after CPB. There was no difference in the thyroid response between the two hypothermia groups. During CPB the maximal changes in plasma levels of interleukin (IL)-6 and the chemokines, regulated on activation normal T cell expressed and secreted (RANTES) and monocyte chemoattractant protein (MCP)-1 were inversely correlated with the maximal changes in serum levels of T3. Conclusion: Our findings in this randomized trial do not support a role for hypothermia as a major cause of altered thyroid responses. Further studies are needed to clarify the role of inflammatory cytokines in SES during CPB.

Keywords: CPB; Thyroid hormones; Pediatric; Congenital heart disease; Hypothermia; Inflammatory mediators

1. Introduction

Several diseases and conditions can cause abnormalities in the concentrations of thyroid hormones in the absence of primary thyroid disease, among others starvation, trauma, sepsis, major surgery, myocardial infarction and cardiopulmonary bypass (CPB) procedures [1]. The alterations involve the entire thyroid axis, and during CPB this Sick Euthyroid Syndrome (SES) is predominantly characterized by low concentrations of triiodothyronine (T3) and thyroid-stimulating hormone (TSH) with variably low or low normal concentrations of free thyroxin (FT4) [2, 3]. In children, the reduction in serum levels of some of these parameters can persist for up to eight days after CPB [4]. These changes related to the thyroid axis should not be regarded as a

strict ‘laboratory phenomenon’ as the degree of SES seems to have a significant influence on patient outcome under various conditions [1, 5]. Whether these changes are adaptive or potentially harmful are not clear. Beneficial effects of T3 supplementation are demonstrated, but studies on peri-operative administration of thyroid hormones in CPB are inconclusive [5–7].

Several not mutually exclusive mechanisms have been linked to the development of SES during CPB, including hemodilution, medication, hypothermia and increased concentrations of inflammatory mediators [2–5, 8–10]. In cardiac surgery CPB is a major cause of inflammatory activation. This activation is enhanced by leukocyte-containing transfusion which adds a second insult to the systemic inflammatory response [11]. Most studies on inflammation and SES during CPB have focused on ‘traditional’ inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF) α, and the role of inflammation in SES during CPB is not fully elucidated. Moreover, although hypothermia may induce alterations related to
the thyroid axis during CPB, very few studies have examined these issues in prospective randomized trials.

The aim of the present prospective study was to compare the degree of SES in children with body weight <10 kg, undergoing open heart surgery, randomized to mild or moderate hypothermia. We also examined the relationships between serum levels of thyroid hormones and several inflammatory parameters.

2. Materials and methods

2.1. Patients

The study population has previously been described [12]. Briefly, 30 consecutive patients with body weight <10 kg were included. At admission, the patients were randomized into two groups (Table 1). In group A, nine girls and six boys underwent cardiac surgery at mild hypothermia (lowest body temperature 32 °C). In group B, eight girls and seven boys underwent cardiac surgery at moderate hypothermia (lowest body temperature 25 °C). Surgery was performed with standard techniques by the same surgeons in both groups. Patients with functionally univentricular congenital heart defects, isolated atrial septal defects, inflammatory or autoimmune disorders, coagulopathies or with an expected CPB time <30 min were excluded from the study. The diagnoses of the patients included are shown in Table 1. Anesthesia was the same in the two groups and has been described in detail elsewhere [12]. Mean Aristotle Basic Complexity score [13] was 7.2 and 7.6 in group A and B, respectively. The study was approved by the regional Ethics Committee. Written consent was obtained from the parents before inclusion of their children in the study.

2.2. CPB

The CPB procedure has been described in detail elsewhere. Briefly, we used a Stöckert roller pump (Sorin group, Mirandola, Italy) with oxygenator and tubing from Dideco (D-901) with Phisio coating (Sorin group) [14]. The priming volume of the heart-lung machine was 350 ml. The composition of the priming solution was of heparin (20 mg/l), mannitol (3 ml/kg), sodium bicarbonate (50 mmol/l) and albumin (200 mg/ml) up to 4% of total volume, as well as erythrocytes (saline, adenine, glucose [SAG]) aiming for a target hematocrit of 25–30% while on CPB. Heparin (3 mg/kg) was given intravenously to the patient after sternotomy, and CPB was started when the activated clotting time passed 480 s. The temperature of the perfusate was set on target before going on CPB to achieve immediate cooling. The pump flow was 2.4 l/m²/min at mild hypothermia and 1.5 l/m²/min during moderate hypothermia, which provided a central venous saturation above 60%. Rewarming was started after removal of the aortic clamp. The hematocrit before weaning from CPB was above 30%, and the rectal temperature 36 °C or more.

2.3. Blood sampling protocol

Blood samples were obtained from the arterial and central venous canula at the following times: preoperatively after the induction of anesthesia (Pre); at the time of skin closure (SC); 2 h postoperatively (2 h PO); 24 h postoperatively (24 h PO) and 48 h postoperatively (48 h PO). The blood samples for the inflammatory markers were drawn into pyrogen-free tubes with ethylenediaminetetraacetic acid as anticoagulant, immediately cooled on melting ice and centrifuged within 20 min (2000 g for 10 min at 4 °C). All samples were stored at −80 °C in multiple aliquots and thawed only once.

2.4. Biochemical analyses

T3, FT4 and TSH were analyzed by radioimmunoassay using Coat-A-Coat kits (Diagnostic Products Corporation,
Los Angeles, CA). Parameters of complement activation product (C3bc and terminal complement complex (TCC)) were analyzed by a double-antibody enzyme immunoassay (EIA) using neoeptope-specific antibodies as coat [15]. Plasma concentrations of IL-6, IL-8, IL-10, monocyte chemotactic protein (MCP)-1, regulated on activation normal T cell expressed and secreted (RANTES) were quantified by EIA obtained from RED System (Minneapolis, MN). Myeloperoxidase (MPO) was quantified by EIA as previously described [16]. Hematocrit, leukocyte and platelet counts were determined by an automated analyzer (CELL-DYN 4000, Abbott Laboratories, Abbott Park, IL). Lactate concentrations and arterial and central venous oxygen saturation were obtained from a blood gas analyzer (Kardiometer, Copenhagen, Denmark).

2.5. Statistical analyses

The groups were compared by the Mann–Whitney rank-sum test for unpaired data. For paired data, multiple analyses of variance (MANOVA) were performed and P-values for the effect of time, group and the interaction between time and group were calculated. Coefficients of correlation were calculated by the Spearman rank test. P-values are two-sided with P<0.05 considered statistically significant. All values were compared statistically with and without correction for hemodilution performed using a hematocrit-based formula [17].

3. Results

As previously reported [12] the median age was six (2–14) months and seven (1–18) months, the median weight was 5950 (4040–9599) g and 6300 (4720–9900) g, the median aortic cross-clamp time was 30 (10–78) min and 23 (14–81) min and the median CPB time was 49 (33–125) min and 56 (40–123) min in group A and B, respectively, with no significant differences between the two treatment groups [12]. Moreover, we did not observe any significant differences in the clinical outcomes (i.e. time on ventilator, urine output, transfusion of SAG, need of inotropic support, length of stay in intensive care unit and operative mortality) between the two groups.

3.1. Serum concentrations of thyroid parameters in relation to the degree of hypothermia

In both treatment groups, there was a gradual decline in serum concentrations of T3, FT4 and TSH from the pre-values, reaching a nadir at 24 h PO. Thereafter, there was an increase in TSH concentrations, accompanied by no or a very modest increase in T3 and FT4. At 48 h PO, all thyroid parameters were still very low compared with the pre-values (Fig. 1). Importantly, the same pattern was seen in both treatment groups, with no significant differences between those with mild and those with moderate hypothermia in any of the parameters (Fig. 1).

3.2. Correlations between serum concentrations of thyroid parameters and the inflammatory response during CPB

We have previously reported plasma/serum concentrations of inflammatory mediators in this study population [12]. When investigating the correlations between the changes in thyroid parameters and the changes in inflammatory markers as assessed by maximal changes, several significant findings were revealed (Table 2). First, in the patient group as a whole, the increase in IL-6, RANTES and MCP-1 was significantly correlated with the decrease in T3 (IL-6 and RANTES) and FT4 (MCP-1). Second, while a similar pattern was seen in those who underwent CPB in moderate hypothermia (group B), no such correlations were seen in the mild hypothermia group (group A). Third, in contrast to these negative correlations, parameters of complement activation were positively correlated with FT4 (TCC, all patients) and TSH (C3bc, all patients and the mild hypothermia group). As for maximal changes in IL-8, IL-10 and MPO, there were no significant correlations with maximal changes in thyroid parameters (data not shown). Finally, lactate concentrations showed a similar pattern as IL-6, RANTES and MCP-1, with an inverse correlation with T3 in
Mild hypothermia to a disturbed thyroid axis postoperatively
CPB with hypothermia during the operation has been linked after 24 h PO, but without normalization 48 h PO after decrease in T3, FT4 and TSH, followed by a slight increase hypothermia groups. In fact, in both groups there was a marked concentrations of thyroid hormones between the two hypothermia groups. In fact, in both groups there was a marked decrease in T3, FT4 and TSH, followed by a slight increase after 24 h PO, but without normalization 48 h PO after CPB. Previously, Ririe et al. reported an enhanced pituitary-thyroid response (i.e. increased TSH concentrations) during CPB in children undergoing surgery in deep hypothermia (18 °C) as compared with those undergoing CPB at moderate hypothermia (25 °C) [8]. However, the study was not randomized, and the two hypothermia groups were not matched. In another study, Taggart et al. showed that randomization to deep (18 °C) as compared to moderate (25 °C) hypothermia during CPB, significantly reduced the plasma adrenaline response to CPB, but not the other components of the endocrine response such as, thyroid hormones and cortisol [18]. However, in contrast to the present study in infants, the study by Taggart et al. was performed in adult patients. In fact, the present study is, to the best of our knowledge, the first randomized trial that examines the influence of hypothermia on the thyroid response during CPB in children. Our findings do not support a major influence of the degree of hypothermia on SES during CPB in this population. However, we did not include any group with deep hypothermia, and we cannot exclude that very low body temperature (i.e. 18 °C) could influence the thyroid parameters during CPB.

Inflammatory cytokines such as IL-1 and IL-6 have been implicated in the pathogenesis of SES. Suggested mechanisms are suppression of an adequate TSH response, inhibition of hepatic conversion of thyroxin to T3, altered binding of thyroxin to serum proteins, and direct binding of cytokines to cytokine receptors that are expressed in thyroid follicles (i.e. the IL-6 receptor-subunit gp130) [19, 20]. We and others have previously reported a correlation between IL-6 and serum concentrations of T3 in children during CPB [21, 22] and in the present study we extend this finding in several ways. We show that in addition to IL-6, also certain chemokines (i.e. RANTES and MCP-1) were inversely correlated with serum concentrations of T3 in children undergoing CPB, and as for MCP-1, a similar correlation was also seen in relation to FT4. Moreover, while the negative correlations between IL-6, RANTES and MCP and T3 were seen in patients undergoing CPB with moderate hypothermia, these correlations were not found in the mild hypothermia group. Thus, although the degree of hypothermia did not influence the thyroid response during CPB, mild as opposed to moderate hypothermia seems to have some attenuating effects on the interaction between inflammation and the thyroid axis. Finally, in contrast to the negative correlations between thyroid hormones and inflammatory cytokines, parameters of complement activation were positively correlated with FT4 (TCC) and TSH (C3bc). Although this finding potentially may reflect leakage of thyroid hormones from the thyroid gland secondary to complement mediated tissue damage, the reason for these data is at present unknown. Nonetheless, our data on the relation between inflammation, temperature and thyroid function during CPB should be interpreted with some caution. Correlations do not necessarily mean any causal relationship, and owing to a large number of comparisons in a relatively small study population, some of our findings may be by chance. Further mechanistic studies are needed to elucidate the role of inflammatory mediators in the thyroid response during CPB in children. Moreover, although several significant correlations were revealed, they where mostly restricted to T3. In fact, it has been suggested that SES is a non-specific response to stress, and CPB procedures should not be considered as the sole trigger of SES in cardiac surgical patients [23]. Moreover, in the present study the priming volume in the CPB system was relatively large (350 ml in patients <10 kg), possibly influencing the inflammatory and thyroid response, independent on the temperature.

Our findings in this randomized trial do not support a role for hypothermia as a cause of altered thyroxin responses in children undergoing CPB. Our finding may suggest that in addition to IL-6, other inflammatory cytokines such as chemokines should be further investigated for their possible influence on the thyroid axis during CPB.

### Table 2
Correlations between thyroid parameters and inflammatory markers during CPB

<table>
<thead>
<tr>
<th>All patients</th>
<th>Mild hypothermia</th>
<th>Moderate hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>-0.54*</td>
<td>-0.31</td>
</tr>
<tr>
<td>TCC</td>
<td>-0.04</td>
<td>0.37*</td>
</tr>
<tr>
<td>C3bc</td>
<td>-0.24</td>
<td>0.10</td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.51*</td>
<td>-0.23</td>
</tr>
<tr>
<td>RANTES</td>
<td>-0.38*</td>
<td>0.01</td>
</tr>
<tr>
<td>MCP-1</td>
<td>-0.31</td>
<td>-0.34</td>
</tr>
</tbody>
</table>

*IP < 0.05 and *IP < 0.01. All parameters are assessed as maximal change. TCC, terminal complement complex; IL, interleukin; RANTES, regulated on activation normal T cell expressed and secreted; MCP, monocyte chemoattractant protein.
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References