THYROID HORMONE STATUS AFTER CARDIAC SURGERY IN INFANTS WITH DELAYED STERNAL CLOSURE AND CONTINUED USE OF CUTANEOUS POVIDONE-IODINE

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Objective. The aim of this prospective study was to examine whether povidone-iodine used for sternal wound protection in infants with delayed sternal closure (DSC) influences the thyroid function.

Patients and methods. Thyroid hormones (see bellow) and thyroxine binding globulin (TBG) were estimated by radioimmunoassay and ioduria by mass spectrometry in 20 infants in whom cutaneous povidone-iodine was continuously applied on the skin for 1-7 days before DSC after open heart surgery.

Results. In the early postoperative period the median levels of total triiodothyronine (TT3), total thyroxine (TT4) and thyroxine-binding globulin (TBG) were below the lower limit of normal, while these of reverse triiodothyronine (rT3) were above normal. The median levels of free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) were normal. Two weeks after the sternal closure, the levels of TT3, TT4 and TBG increased significantly ($P<0.001$), while these of rT3 decreased, but not significantly. The levels of TSH increased ($P<0.001$), being above normal in 7 patients. Four weeks after the sternal closure, TSH levels remained markedly increased in 4 infants. These patients were considered to be hypothyroid and were started on thyroxine replacement therapy. Such replacement treatment was withdrawn at a median age of 6.5 months (range 5-8 months). Urinary iodine concentration on the last day of povidone-iodine exposure was several times higher ($P< 0.001$) than that in the control group of healthy infants.

Conclusions. Transient hypothyroidism was found in four of 20 infants with DSC who were exposed to povidone-iodine. It is suggested to monitor TSH level in these patients, optimally at 4 weeks after closure of the sternum, when findings may show true hypothyroidism.

Keywords: Thyroid hormones – Cardiac surgery – Infants – Delayed sternal closure – Povidone-iodine

Alterations in the metabolism of thyroid hormones occur in children undergoing open heart surgery. They are due in part to hemodilution, hypothermia, and nonpulsatile flow during cardiopulmonary bypass and, in part, to "Euthyroid Sick syndrome". These changes have been shown to last typically from the onset of cardiopulmonary bypass until 5-7 days after surgery (Mitchell et al. 1992; Murzi et al. 1995; Bettendorf et al. 2002). Children with DSC with continuous use of povidone-iodine are exposed to an additional risk of thyroid hormone disturbances, since significant quantities of exogenous iodine are absorbed from topical antiseptics used for sternal wound protection which results in a decrease of thyroid function by interfering with the iodine organification and coupling step – the Wolff-Chaikoff effect.

Since the infants may not override this supression of thyroid hormone synthesis, exogenous iodine may produce hypothyroidism (Mace 1977).

There are several studies evaluating the effects of preoperative disinfection of skin with povidone-iodine on thyroid function of infants requiring cardiac surgery (Mitchell et al. 1991; Bettendorf et al. 1997; Brogan et al. 1997). These studies suggest that cardiopulmonary bypass shows a more profound effect on the hypothalamic-pituitary axis than does the povidone-iodine. However, none of these studies followed-up the levels of thyroid hormone beyond the second postoperative week. Furthermore, those studies did not include data on thyroid metabolism of infants with DSC in whom cutaneous povidone-iodine was used repeatedly and in large quantities.

The aim of this study was to evaluate prospectively the effect of perioperative topical use of povidone-iodine on postoperative thyroid depression in infants with DSC after open heart procedures. Thyroid hormone levels were monitored from the immediate postoperative period until 4 weeks after sternal closure. Urinary iodine concentration was evaluated on the last day of povidone-iodine exposure.

Patients and Methods

Patients. Between January 1996 and February 1997, 76 infants (less than 1 year of age) underwent cardiac surgical procedures through median sternotomy. In 30 (39.4 %) of them the chest was left open after the operation. The most common cardiac diagnoses were transposition of great arteries (12 patients), double outlet right ventricle (4 patients), total anomalous pulmonary venous drainage (3 patients) and hypoplastic left heart syndrome (3 patients). Ten (33.3 %) patients died of low cardiac output and multiorgan failure. In 20 patients sternal closure was carried out at a median of 2 days (1-7 days) postoperatively. No patient developed sternal wound infection.

Blood samples for thyroid hormone evaluation were taken in all infants in whom the sternum was left open after cardiopulmonary bypass. Data on patients who died were excluded from further analysis. Thyroid hormone status was continuously evaluated in 20 patients. Fifteen patients (75 %) were newborns with a median body weight of 3.5 kg (range: 2.8-4.2 kg) and five (25 %) patients were infants with a median body weight of 4.0 kg (range: 2.5-5.3 kg). Patients were exposed to topical povidone-iodine for a median of 2 days (range: 1-7 days).

Preoperative disinfection of skin was routinely done with 10 % aqueous povidone-iodine (Betadine, Egis Pharmaceuticals Ltd., Budapest, Hungary). During the surgical procedure, the exposed skin around the wound was covered with an iodophor adhesive drape (Ioban 2, 3M Health Care, St. Paul, MN, USA). After the decision was made to leave the sternum open a sheet of Silastic (Dow Corning Corp., Midland, MI, USA) was tailored to the shape of the median sternotomy incision and attached to the skin edges with continuous monofilament sutures. The circumference of sternal wound was covered with 10 % povidone-iodine ointment (Egis Pharmaceuticals Ltd., Budapest, Hungary). The wound was covered with dressing soaked with 10 % povidone-iodine. The wound dressing was changed twice daily until the sternal closure. The procedure of sternal closure was performed in the Intensive Care Unit. First, the skin was prepared with 10 % povidone-iodine solution, silastic sheet removed, debridement of fibrin peel and tissue debris performed, and the pericardial cavity was irrigated with warm 0.5 % povidone-iodine solution. Then the sternum, subcutaneous tissue, and skin were closed.

Serum samples for thyroid hormone evaluation in the patients with DSC were obtained four times in the postoperative period via indwelling venous catheters: (1) immediately after surgery, at the time of admission to Intensive Care Unit; (2) immediately after sternal closure; (3) 2 weeks after sternal closure; and (4) 4 weeks after sternal closure. Serum was separated and frozen. The aliquots were then analyzed for TT3, TT4, FT3, FT4, TSH, rT3, and TBG. Serum concentrations of TT4, TT3 (Immunotech, Czech Republic), FT3, FT4 (Brahms Diagnostica GMBH, Germany), and rT3 and TBG (Biocode, Belgium) were measured by radioimmunoassay methods. TSH (Immunotech, Czech republic) was measured by immunoradiometric assay. Normal ranges in our laboratory were 1.23-3.0 nmol/l for TT3, 116-203 nmol/l for TT4 in newborns more than 4 days of age, and 57-154 nmol/l for TT4 in infants. Normal values for FT3 ranged from 3 to 9 pmol/l in newborns and from 3.5 to 6.5 pmol/l in infants. Nor-

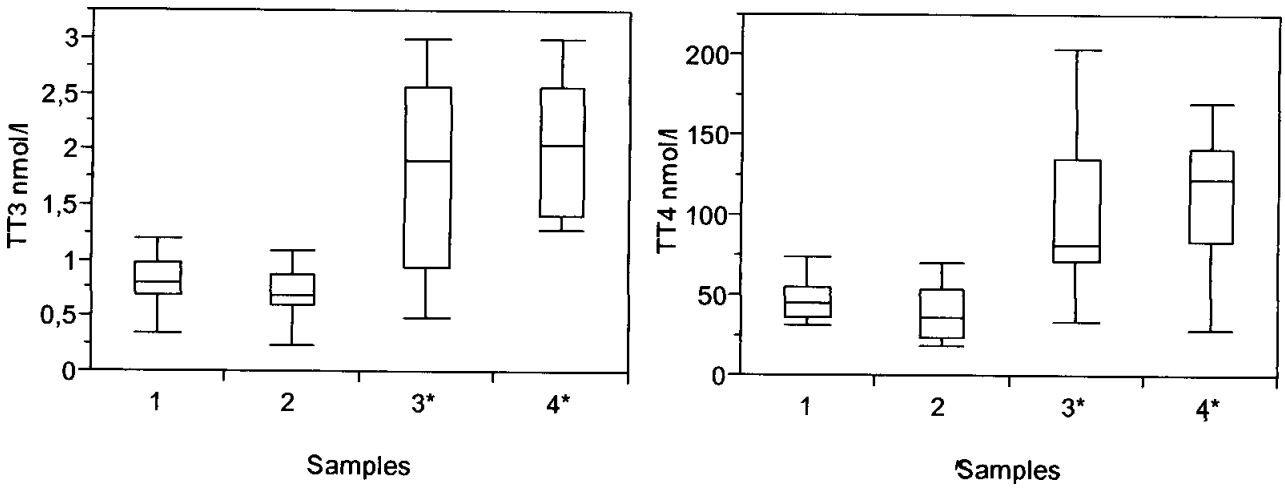

Fig 1 Values of TT3 and TT4. Box plots represent 10th, 25th, 50th, 75th, and 90th percentiles. Sample 1 – immediately after surgery; sample 2 – the day of delayed sternal closure (DSC); sample 3 – two weeks after DSC; sample 4 – four weeks after DSC. * significance: p<0.001 compared to values immediately after surgery. The reference ranges for TT3 1.23-3 nmol/l; TT4 newborns 116-203, infants 57-154 nmol/l. TT3 – total triiodothyronine, TT4 – total thyroxine.

mal ranges for FT4 were 14-28 pmol/l in newborns and 9-20 pmol/l in infants. The normal range for TSH was 0.32-4.5 mIU/l, for rT3 15-35 ng/dl, and for TBG 12-26 μg/ml. Intra-assay variation for TT3 was 2,9 % at concentration 1,12 nmol/l, for TT4 5,1 % at 105 nmol/l, for FT3 5,3 % at 6,79 pmol/l, for FT4 3,4 % at 20,6 pmol/l, for TSH 2,5 % at 1,48 mU/l, for RT3 4,2 % at 56 ng/dl and for TBG 3,7 % at 18 μg/ml. Inter-assay variation for TT3 was 8,3 % at concentration 3,59 nmol/l, for TT4 5,6 % at 206 nmol/l, for FT3 9,5 % at 9,56 pmol/l, for FT4 5,1 % at 17,6 pmol/l, for TSH 4,1 % at 1,46 mU/l, for RT3 5,4 % at 56 ng/dl and for TBG 5,1 % at 18 μg/ml.

Preoperative thyroid hormone levels were not evaluated as it was not possible to predict in which patient the technique of delayed sternal closure would be used. Because TSH neonatal heel prick screening tests were done in all newborns and were within the normal range we assumed initial euthyroid status in all our patients.

A sample of urine for measurement of iodine concentration was obtained on the day of delayed sternal closure (the last day of povidone-iodine exposure). Samples were frozen and analyzed later. Ioduria was examined by mass spectrometry (the measurement of ion mass to charge ratios m/z by direct amplification of ion signals) ICP-MS (Analytica, Czech Republic). The levels were compared to ioduria in control group of 53 healthy infants.

Statistical evaluation. Data are expressed as the median (range) in text and 10th, 25th,50th,75th, and 90th percentiles in figures. Kruskal/Wallis and Wilcoxon tests were used to test the difference between the hormone levels immediately after surgery and at each time point throughout the study. Fisher´s exact test and logistic regression were used to test ioduria as a risk factor for hypothyreosis. The level of significance was set at $P<0.05$. Statistical evaluation was undertaken with JMP software (version: 4.0.2).

Results

Thyroid hormone levels in the patients with DSC. The median serum concentrations of TT3 and TT4 (Fig.1) were below normal at the time of admission to Intensive Care Unit and at the time of sternal closure. Over the next 2 weeks TT3 and TT4 concentrations increased ($P<0.001$). Two and four weeks after DSC, median TT3 and TT4 levels were again within the normal range.

The median FT3 levels (Fig. 2) were within the normal range at the time of admission, 2 and 4 weeks after DSC. However, FT3 concentrations 2 and 4 weeks after sternal closure were higher ($P<0.001$) compared to immediate postoperative concentrations. The median serum FT4 concentrations (Fig. 2) were within the normal range during the postoperative

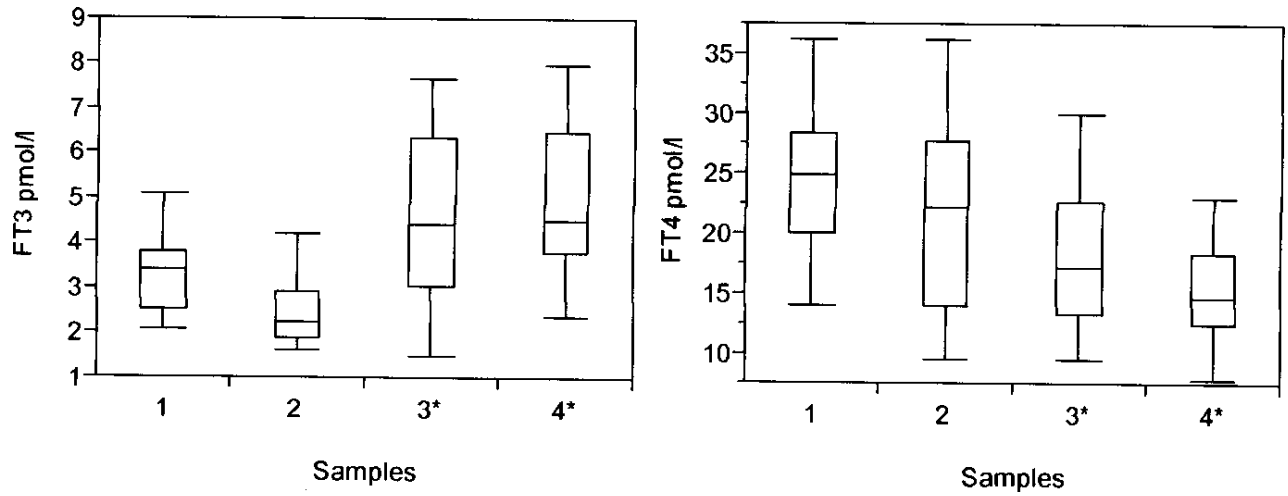

Fig 2 Values of FT3 and FT4. Box plots represent 10th, 25th, 50th, 75th, and 90th percentiles. Sample 1 – immediately after surgery; sample 2 – the day of delayed sternal closure (DSC); sample 3 – two weeks after DSC; sample 4 – four weeks after DSC. * significance: P<0.001 compared to values immediately after surgery. The reference ranges for FT3 newborns 3-9, infants 3.5-6.5 pmol/l; FT4 newborns 15-28, infants 9-20 pmol/l. Sample 1 – immediately after surgery; sample 2 – the day of delayed sternal closure (DSC); sample 3 – two weeks after DSC; sample 4 – four weeks after DSC. FT3 – free triiodothyronine, FT4 – free thyroxine.

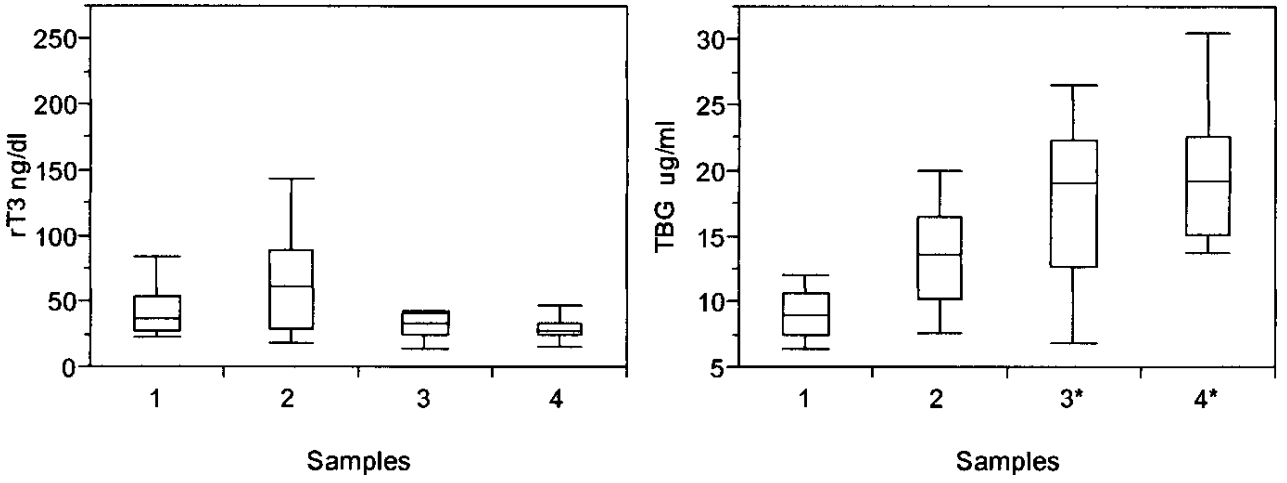

Fig 3 Values of rT3 and TBG. Box plots represent 10th, 25th, 50th, 75th, and 90th percentiles. Sample 1 – immediately after surgery; sample 2 – the day of delayed sternal closure (DSC); sample 3 – two weeks after DSC; sample 4 – four weeks after DSC. * significance: P<0.001 compared to values immediately after surgery. The reference ranges for TBG 12-26 µg/ml, rT3 15-35 ng/dl. rT3 – reverse triiodothyronine, TBG – thyroxine-binding globulin.

Table 1
The demographic data and laboratory characteristics of infants who were started on thyroxine therapy.

Patient No	Age at surgery	P-I exposure	TSH[1]	FT4[1]	Ioduria[2]	Thyroxine th
	days	days	MIU/l	pmol/l	mcg/l	months
1	4	7	31.35	7.97	38,513	7
2	4	3	28.27	8.26	14,814	6
3	17	3	17.97	16.57	11,462	5
4	23	5	10.81	14.85	12,132	8

P-I, povidone-iodine; [1] four weeks after sternal closure, [2] on the day of sternal closure

period, though the concentrations 2 and 4 weeks after sternal closure were lower (P<0.001) than concentrations immediately after surgery.

The median rT3 levels (Fig. 3) were above normal immediately after surgery and at the time of sternal closure. Throughout the observation period, rT3 levels did not change significantly, though the median levels of rT3, at 2 and 4 weeks after sternal closure reached normal values. The median TBG level (Fig. 3) was below normal at the time of admission to the Intensive Care Unit. During the observation period, TBG levels increased, and were higher (P<0.001) at 2 and 4 weeks after sternal closure than the levels in the immediate postoperative period.

The median TSH levels (Fig. 4) were normal at the time of admission and DSC. An increase in TSH levels (P<0.001) was observed 2 weeks after sternal closure. High TSH levels were found in 7 patients two weeks after DSC and in 4 patients four weeks after DSC. The patients with persisting high TSH concentrations were started on thyroxine replacement therapy. The demographic data and laboratory characteristics of these patients are shown in Table 1.

Ioduria. Urinary iodine concentration in patients with DSC was significantly higher (13500 μg/l, range: 3051 to 35064) than in the group of healthy infants (200 μg/l, range: 20-780 μg/l, P<0.001). There was no significant association between the urinary iodine level and the development of hypothyroidism.

Long-term follow-up. After discharge home, patients on thyroxine replacement therapy were followed for 5 years. All infants showed signs of normal growth and neurological development. Replacement therapy was effective and was terminated at a median age of 6.5 months (range: 5 – 8 months).

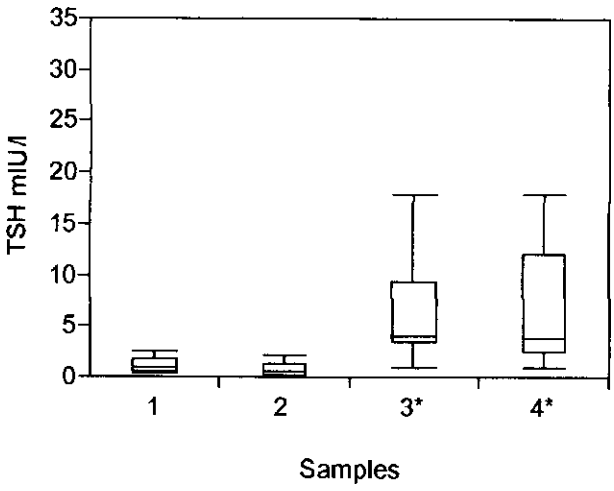

Fig 4 Values of TSH (thyroid stimulating hormone). Box plots represent 10th, 25th, 50th, 75th, and 90th percentiles. Sample 1 – immediately after surgery; sample 2 – the day of delayed sternal closure (DSC); sample 3 – two weeks after DSC; sample 4 – four weeks after DSC. * significance: P<0.001 compared to values immediately after surgery. The reference ranges for TSH 0.32-4.5 mIU/l.

Discussion

The technique of delayed sternal closure is used in pediatric cardiosurgical patients who are difficult to wean from cardiopulmonary bypass. This technique is also used for the control of excessive postoperative bleeding and for the need of extracorporeal circulation (Furnary et al. 1992; Hakimi et al. 1994). Since the mediastinitis may be a life-threatening complication after DSC, effective antiseptic technique is needed for sternal wound protection. Different methods have been described for isolation of the open sternal wound and mediastinal content from the surrounding environment (Odim et al. 1989; Mestres et al. 1991). Most of these methods involve the use of topical povidone-iodine, which is an extremely effective antiseptic agent.

Thyroid hormone changes taking place after open heart surgery in children are well documented. However, clinical impact of these changes for metabolic status and the role of triiodothyronine replacement therapy in the early postoperative period remain unclear (Mitchell et al. 1992; Gotzsche et Weeke 1992; Mainwaring et al. 1994; Bettendorf et al. 2002). Cardiac surgery requiring cardiopulmonary bypass decreases TT3, TT4, FT3, and TBG concentrations. TSH levels may decrease or remain normal. The thyroid hormone changes have been shown to last from the onset of cardiopulmonary bypass until 5-7 days after surgery. The exact mechanism responsible for causing these changes is not thouroughly understood, but it appears to be due in part to hemodilution, hypothermia, and nonpulsatile flow during cardiopulmonary bypass and, in part, to "Euthyroid Sick Syndrome"(Gotzsche et al. 1992; Brogan et al. 1997;

Ross et Petros 2001). Euthyroid Sick Syndrome or low T3 syndrome occurs in patients with severe illnesses, malnutrition and after surgery. The most commonly observed constellation is low TT3, high RT3 and normal to decreased TT4 concentrations. These changes are considered to be an adaptive response to stress, which reduces basal metabolic rate and oxygen consumption.

Children with delayed sternal closure are exposed to an additional risk of thyroid hormone disturbances because they may absorb significant quantities of iodine from topical antiseptics. Excess iodine affects the thyroid function by interfering with synthesis and release of thyroid hormones – the Wolff-Chaikoff effect. Usually the effect is transient, with escape occuring within 48 hours. However, in some patients, prolonged hypothyroidism may occur as a result of inability to counteract the Wolff-Chaikoff effect (Mace 1977; Chabrolle et al. 1978; Fisher 1992; Barakat et al. 1994).

Transcutaneous iodine absorption has been well established in children undergoing cardiac surgery. Large increases in serum and urinary iodine concentrations have been demonstrated in infants receiving only one application of topical iodinated antiseptics for repair of congenital heart defects (Mitchell et al. 1991; Bettendorf et al. 1997; Brogan et al. 1997). In our study thyroid hormone status and ioduria were evaluated in infants in whom the chest was left open after cardiopulmonary bypass. These patients were exposed to a higher amount of povidone-iodine in the perioperative period than infants in whom the chest was closed primarily in operating room.

In the early postoperative period, infants with DSC showed thyroid hormone changes similar to those previously reported in children after cardiopulmonary bypass (Mainwaring et al. 1994; Murzi et al. 1995; Bettendorf et al. 1997). In most of our patients low TT3, TT4 and TBG concentrations, high rT3, and normal FT3, FT4, and TSH concentrations were recorded. Two weeks after sternal closure TT3, TT4, and TBG levels increased significantly and rT3 levels decreased slightly. TSH levels were normal immediately after surgery in all patients. However, 2 weeks after the sternal closure, TSH levels increased, rising above normal in 7 patients. Four weeks after DSC, TSH concentrations returned to normal in 3 patients and remained abnormally high in 4 patients.

The transient increase of TSH levels occurs in children after cardiac surgery at the time of TT3 and TT4 recovery, reflecting recovery of the hypothalamic-pituitary-thyroid axis in convalescence (Mitchell et al. 1992; Mainwaring et al. 1994; Bettendorf et al. 1997). Transient hyperthyrotropinemia may be also a result of exposure to iodine antiseptics (Lin et al. 1994; Brogan et al. 1997; Linder et al. 1997; Kovacikova et al. 2002). However, persisting high TSH levels are a sign of true hypothyroidism that, in the infants, may threaten future development of central nervous system. In our study the patients with high TSH levels in the late postoperative period (4 weeks after sternal closure) were deemed hypothyroid and were started on thyroxine replacement therapy**.** It was observed, however, that such hypothyroidism was transient and thyroxine replacement was withdrawn in all patients after 5-8 months.

Although the alterations in thyroid hormone metabolism in critically ill infants are difficult to interpret, we are of the opinion that hypothyroidism in the late postoperative period was caused by exposure to iodine. As shown by high urinary iodine concentration, patients with DSC had excessive iodine absorption from povidone-iodine antiseptics.

All infants who developed hypothyroidism were less than 28 days of age at the time of exposure to iodine. This finding is in accord with general knowledge that deficient thyroid autoregulation occurs, especially in the neonatal period. Individual differences in response to iodine overload may be explained by constitutional predisposition, related to the HLA histocompatibility system (Konishi et al. 1976).

In conclusion, this study has shown that transient hypothyroidism can occur in infants with delayed sternal closure who are exposed to a high amount of povidone-iodine. Because hypothyroidism induced in the first weeks of life may endanger the development of the central nervous system, we feel it is appropriate to check TSH levels in this group of cardiosurgical patients, optimally at 4 weeks after successful closure of the sternum, when laboratory findings show true hypothyroidism. Whether the risk of hypothyroidism can be reduced by the use of iodophor adhesive drapes instead of povidone-iodine soaked dressings remains to be elucidated.

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