Cardiopulmonary Bypass Temperature Does Not Affect Postoperative Euthyroid Sick Syndrome?*

David N. Thrush, MD; David Austin, MD; and Nick Burdash, PhD

Study objective: To determine if temperature during cardiopulmonary bypass (CPB) has an effect on perioperative and postoperative thyroid function.

Design: Prospective study comparing thyroid function during and after hypothermic and normothermic CPB.

Setting: Cardiac surgical unit at a university-affiliated hospital.

Patients: Twelve patients scheduled to undergo cardiac operations with normothermic (n=6) or hypothermic (n=6) CPB.

Interventions: Blood was analyzed for serum concentration of total thyroxine (TT₄), total triiodothyronine (TT₃), free T₃ (fT₃), reverse T₃ (rT₃), and thyroid stimulating hormone (TSH) preoperatively, 60 min after CPB was initiated, 30 min after discontinuing CPB, and on postoperative days (POD) 1, 3, and 5.

Measurements and results: Patients who underwent either cold (26°±5°C) or warm (35°±1°C) CPB were comparable with regard to age, body weight, duration of CPB, cross-clamp time, use of inotropes, total heparin dose, and length of hospital stay. Incidence of postoperative myocardial infarction, congestive heart failure, and death were similar. In both groups, TT₄ and TT₃ were reduced below baseline values beginning with CPB and persisting for up to 5 days after CPB (p<0.05), free T₃ was reduced for up to 3 days after CPB (p<0.05), mean serum rT₃ was elevated on POD 1 and POD 3 (p<0.05), and TSH remained unchanged. Conclusion: The results of this study suggest that normothermic CPB does not prevent the development of the “euthyroid sick syndrome” during and after CPB. Despite these changes in thyroid function, most patients in both groups had a normal postoperative recovery.

(CHEST 1995; 108:1541-45)

Cardiopulmonary bypass (CPB) has been associated with alterations in thyroid hormone levels that resemble the “euthyroid sick syndrome.” This syndrome is characterized by depression of total triiodothyronine (TT₃) and free T₃ (fT₃) concentrations, a concomitant increase in reverse T₃ (rT₃) levels, and normal concentrations of thyroid stimulating hormone (TSH), total thyroxine (TT₄), and free T₄ (fT₄).¹⁻⁶

The mechanism by which thyroid hormone concentrations change during CPB remains uncertain. Alterations in plasma volume, protein binding, central regulation, and metabolism have been implicated.¹⁻¹⁰ Although marked alterations in thyroid hormone levels have been reported during hypothermic and normothermic CPB, the effect of the temperature maintained during CPB on thyroid function has not been fully investigated.¹⁻⁶ In this study, we wished to determine if maintaining normothermic temperatures during CPB would prevent the euthyroid sick syndrome.

Methods

After obtaining Institutional Review Board approval and informed consent, 13 consecutive patients were scheduled for open heart operations with hypothermic (group 1) or normothermic (group 2) CPB. The use of hypothermic or normothermic CPB was based on the preference of the surgeon.

Patients included in the study were undergoing first-time coronary artery bypass and/or valve replacement operations. Patients with respiratory failure, ejection fraction less than 40%, and those requiring emergency surgery were excluded. Patients were also excluded if they were not euthyroid as determined by history and physical examination and confirmed by thyroid function tests. All patients with a history of endocrine disorders, head and neck irradiation, anemia, liver dysfunction or renal disease, and those requiring transfusion of blood products before or during the data collection period were excluded from the study.

Treatment with all cardiac medication was continued up to the morning of surgery. The patients were premedicated with morphine, 0.1 mg/kg, and scopolamine, 0.05 mg/kg. Radial and

*From the Department of Anesthesiology, University of South Florida, College of Medicine, Tampa.

Supported in part by a grant from Smith, Klein and Beecham.

Manuscript received February 23, 1995; revision accepted May 12.

Reprint requests: Dr. Thrush, Department of Anesthesiology, University of South Florida College of Medicine, PO Box 1289, Tampa, FL 33601.
pulmonary artery catheters were inserted prior to induction of general anesthesia with the following: fentanyl, 30 to 50 μg/kg; midazolam, up to 0.07 mg/kg, and vecuronium, 0.2 mg/kg. Maintenance of anesthesia consisted of increments of fentanyl up to 100 μg/kg, midazolam up to 0.2 mg/kg, and vecuronium as needed. The CPB circuit was primed with 1,500 to 1,800 mL of crystalloid solution. Heparin, 300 U/kg, was administered before CPB, and 10,000 U was added to the pump prime. Further heparin was given as necessary to obtain and maintain an activated clotting time greater than 400 s. After CPB was initiated, the patient was either cooled to an esophageal temperature of 26 to 28°C (group 1) or maintained normothermic (group 2). Mean BP was maintained between 50 and 80 mm Hg with nitroglycerin or sodium nitroprusside. Oxygenated blood cardioplegia was initially administered antegrade via the aortic root to arrest the heart, and subsequently given retrograde via the coronary sinus in a continuous fashion. Patients in the hypothermic group were rewarmed to a temperature of 38°C esophageal and 35°C rectal. During weaning from CPB, inotropes (epinephrine, dobutamine, and amrinone) were used to maintain cardiac index above 1.8 L/min and mean BP greater than 50 mm Hg.

Blood samples were obtained from the radial artery prior to induction of anesthesia on the morning of surgery (pre-CPB), 60 min after CPB was initiated (CPB), 30 min after discontinuing CPB (post-CPB), and on the morning of postoperative days 1 (POD 1), 3 (POD 3), and 5 (POD 5). Body temperature was measured immediately before drawing the blood samples. Serum was stored at −20°C until assayed. Blood samples from each patient were analyzed for serum concentrations of TSH, TT₄, TT₃, and rT₃. Total T₄, T₃, and rT₃ were assayed (Coat-A-Count RIA Kits; Diagnostic Products Corp; Los Angeles) according to manufacturer's instructions. All three procedures used the competitive binding technique. For the rT₃ radioimmunoassay, a kit (Serono Reverse T₃ PEG Method Kit; Serono Diagnostics; Allentown, Pa) was used according to manufacturer's instructions. This procedure also uses competitive binding and polyethylene glycol to separate antibody-bound rT₃ from free rT₃. TSH was assayed, according to manufacturer's instruction, using a kit (TSH Radioisotopic Assay Kit; Nichols Institute Diagnostics; San Juan Capistrano, Calif.). The kit used a sandwich technique that employs biotin-avidin to bind the sandwich complex to a solid phase bead.

Statistical analyses of data between groups were performed using Student's t test or the Mann-Whitney U test when indicated. To identify significant changes in thyroid hormone levels between groups and over time, a two-way analysis of variance for repeated measures was performed, followed by Dunnett's T test for post hoc analysis.

RESULTS

Thirteen patients were studied. Preoperative thyroid levels were within the normal range in all 13 patients. Data from one patient were excluded from analysis because he received a blood transfusion during the data collection period. The other 12 patients who underwent either hypothermic (n=6) or normothermic (n=6) CPB for coronary artery bypass grafting (CABG) were comparable with regard to age, body weight, length of hospital stay, duration of CPB, aortic cross-clamp time, CPB priming volume, total heparin dose, and postoperative complications (Table 1). Medications received prior to surgery were similar in both groups and included isosorbide dinitrate, enalaprilat, atenolol, insulin, nifedipine, diltiazem, furosemide (Lasix), and digoxin (Lanoxin). None of the patients were receiving amiodarone therapy. Eleven patients had CABG procedures and 1 patient in the hypothermic group had a combined CABG and mitral valve replacement. Mean temperatures of the two groups were significantly different during CPB (Table 1).

Inotropic requirement between the two groups was not significantly different. In the normothermic group, three of the six patients received epinephrine (0.05 to 0.15 μg/kg/min) during the initial 30 min after CPB, but none required any subsequently. One patient in the normothermic group had a perioperative myocardial infarction (creatine kinase MB fractions >3%) but recovered uneventfully, as did the other patients in this group.

In the hypothermic group, four of the six patients

| Table 1—Demographic, CPB, and Postoperative Complication Data for Patients Undergoing Normothermic and Hypothermic CPB Surgery* |
|-----------------------------------------------|------------------|
| Demographics                                |                  |
| No. of patients                             | 6                |
| Age, yr                                      | 60±13            |
| Weight, kg                                   | 89±9             |
| Length of stay, d                            | 10±1             |
| CPB prime solution, mL                       | 1,590±120        |
| Total heparin, U/kg                          | 485±67           |
| Duration, min                               | 91±14            |
| Cross-clamp time, min                        | 64±14            |
| Temperature, °C                              | 35±1             |
| Inotrope required after CPB                  | 3                |
| Postoperative complications                  |                  |
| Myocardial infarction                        | 1                |
| Congestive heart failure                     | 0                |
| Death                                        | 0                |

*Data are shown as mean±SD.

1p<0.05.
required inotropic support after CPB. Two of these patients received epinephrine (0.05 to 0.20 μg/kg/min) and were subsequently weaned from this agent by POD 1. One patient required epinephrine (0.50 to 0.30 μg/kg/min), amrinone (10 to 20 μg/kg/min), and an intra-aortic balloon pump for left ventricular failure and died 3 days after surgery. Small distal coronaries with poor runoff were noted by the surgeon intraoperatively. The other patient underwent CABG and mitral valve replacement for ischemic papillary muscle dysfunction, required epinephrine (0.05 to 0.15 μg/kg/ min) and dobutamine (5 to 10 μg/kg/min) for more than 5 days, developed renal insufficiency, and was discharged from the hospital 34 days after admission (Table 1). These latter two patients had creatinine kinase MB fractions greater than 3%, indicating a perioperative myocardial infarction. They also had TT4 and FT3 levels in the low normal range prior to CPB and had the lowest levels of TT4 and FT3 and highest TSH levels after CPB compared with all other patients.

Although significant changes in hormone levels occurred during CPB, body temperature had no significant effect on thyroid hormone concentrations at any given measurement interval (Table 2). TT4 and FT3 levels decreased 38% and 67%, respectively, below normal physiologic range during CPB (p<0.05), and remained below pre-CPB levels for the remainder of the study (p<0.05). FT3 levels followed a similar 53% decline (p<0.05) except that the levels returned to pre-CPB levels by POD 5. TSH concentrations were 100% (p<0.05), 111% (p<0.05), and 70% above baseline values on POD 1, POD 3, and POD 5, respectively. TSH levels were stable for the entire study period.

**Discussion**

We report an extensive evaluation of thyroid function comparing two groups of patients, one receiving hypothermic and the other normothermic CPB. Our results suggest that the postoperative euthyroid sick syndrome develops regardless of the temperature maintained during CPB. Despite significantly depressed thyroid hormone levels for up to 5 days postoperatively, most patients in both groups had a relatively normal recovery.

The mechanism by which CPB affects thyroid hormone levels remains unclear. Hemodilution, altered concentration of thyroid binding globulin (TBG), displacement of hormones by drugs, hypothalamic-pituitary-thyroid axis dysfunction, changes in metabolism, and hypothermia have all been proposed as possible explanations.1-10

Some investigators recommend correcting thyroid hormone levels measured during CPB by a factor based on the dilution of albumin or globulin concentrations by the CPB prime. Despite these corrections, a euthyroid sick syndrome has been reported after CPB, suggesting that hemodilution is not the sole factor affecting thyroid hormone levels.1,4 Others believe that correction for hemodilution is unnecessary because albumin concentrations return to normal by 2 h.
after CPB, while abnormalities in thyroid hormone concentrations similar to the euthyroid sick syndrome continue for several days. For these reasons, and because corrected values have little clinical relevance for the patient, we did not correct for hemodilution.

Additionally, since thyroid hormones (TT4, TT3, fT3, rT3) are structurally similar, they should be equally affected by hemodilution. We found just the opposite; thyroid hormones of similar molecular weight were affected differently during CPB. For instance, while TT4, TT3, and fT3 decreased, rT3 increased and TSH remained stable, suggesting that hemodilution is not solely responsible for the changes in thyroid hormone levels.

Although uptake of thyroid hormone or TBG by the extracorporeal circuit has been cited as a potential cause for the decrease in hormone levels, Bremner et al. observed no significant differences in TBG, TT4, TT3, and TSH between samples drawn from the venous and arterial lines of the CPB machine. They concluded that the changes in hormone levels were most likely secondary to changes in thyroid hormone metabolism and not to uptake by the extracorporeal circuit. Unless temperature had a significant effect on uptake of thyroid hormone or TBG, this factor seems an unlikely cause for the changes in thyroid hormone concentrations in this study.

Heparin administration prior to CPB leads to a sharp increase in fT4 and fT3 levels by displacement of hormones from binding proteins and sequestration of fT4 stored in the liver. Bremner et al. reported a sevenfold rise in the fT4 level 15 min after heparinization for CPB. Although fT4 levels remained elevated above baseline values, TT3 and fT3 levels dropped precipitously once CPB was initiated. Since there were no differences in heparin doses and thyroid hormone levels between groups in this study, it appears that temperature does not modify the effect of heparin on thyroid hormone concentrations.

Other drugs besides heparin can alter binding of thyroid hormones to proteins or the amounts of these proteins. For instance, estrogens can increase TBG and decrease the amount of free thyroid hormone while increasing the total hormone levels. Although the patients in this study received multiple cardiac medications prior to surgery that may have had an effect on thyroid levels, medications were similar between groups and all patients were euthyroid at the beginning of the study. Also, none of the patients were taking amiodarone, which has been reported to cause either hypothyroidism or hyperthyroidism. Postoperatively, the use of inotropes was similar in both groups and the inotropes used have not been shown to affect thyroid function. Although none of the patients received dopamine, it has been shown to decrease TSH secretion.

The secretion of thyroid hormones is controlled by the hypothalamo-pituitary-thyroid axis. Normally, low thyroid hormone levels stimulate the release of thyrotropin releasing hormone (TRH) from the hypothalamus, TSH from the anterior pituitary, and thyroid hormone from the thyroid gland. It has been shown that the TSH response to TRH is blunted or absent during hypothermic CPB. Bremner et al. suggested that the elevation in fT4 secondary to heparin displacement may be sufficient to shut off the pituitary response to lowered fT3 levels. Robuschi et al. believe that hypothermia per se may be responsible for the blunted pituitary response. In the current study, dysfunction of this axis is suggested by the observation that TSH remains stable despite significant decreases in TT4, TT3, and fT3. However, if abnormalities of this axis are the mechanism for the changes in thyroid function observed during CPB, this study suggests that some aspect of CPB other than temperature is responsible for triggering the changes.

Altered metabolism of thyroid hormones, beginning with CPB, is the most likely reason for the observed changes in hormone levels. Although the thyroid gland secretes four times as much T4 as T3, T4 is mostly inactive and undergoes peripheral conversion to the active form, T3, by deiodination. Deiodination of T4 can be accomplished by one of two enzymes; 5'-deiodinase, which converts T4 to T3 and rT3 to 3,3',5'-T2, or 5-deiodinase, which converts T4 to rT3 and T3 to 3,3',5'-T2. Normally, the 5'-deiodinase enzyme is more active. In the euthyroid sick syndrome, a decrease in activity of the 5' enzyme leads to an increased conversion of T4 to rT3 and decreased production of TT3. In this study, rT3 increased and TT3 decreased equally in both groups, suggesting that the change in metabolism occurred independently of temperature.

Results of this study are in agreement with those of Lehot et al. In a comparison of 20 patients undergoing either hypothermic or normothermic nonpulsatile CPB, they reported that TT4 decreased during and up to 3 h after CPB, with no difference between groups and suggested that hemodilution and hypoproteinemia were responsible. Although fewer patients were enrolled in the present study, a more thorough assessment of thyroid function was performed. Bremner et al. reported similar alterations in thyroid hormone levels in ten patients with normothermic CPB, except that TT4 remained unchanged while TT3 and fT3 decreased markedly. Although thyroid function testing was extensive in the study of Bremner et al., the follow-up was limited to the first 15 min after CPB. The present study demonstrated significant thyroid hormone abnormalities for up to 5 days after operation. Results of these studies indicate that the factors responsible for thyroid dysfunction during and after CPB are not dependent on temperature, and that
maintaining normal body temperature during CPB has no beneficial effect as it relates to thyroid function.

Since thyroid hormones alter cardiac contractility, left ventricular work, stroke volume, heart rate, BP, systemic vascular resistance and blood volume, the low cardiac output syndrome seen frequently after CPB may be secondary to depressed levels of active thyroid hormone. Exogenous T₃ has been reported to alleviate left ventricular dysfunction secondary to ischemia in humans and animals. Previous studies indicate that changes in thyroid hormone levels begin with CPB and may not return to normal physiologic range for up to 6 days. In our study, fT₃ returned to normal by the fifth POD while TT₄ and TT₃ remained depressed throughout the study. Therefore, if therapy is administered in the form of exogenous T₃, it seems that the appropriate period is between CPB and, at least, through POD 5.

Because the coefficient of variation for many of the thyroid function levels was large, a larger number of patients would have been necessary to distinguish small differences between groups with greater certainty. However, the consistency of our results suggests that temperature had no effect on change in thyroid hormone levels during CPB.

This prior studies have established the presence of euthyroid sick syndrome during and after open heart operations requiring CPB, regardless of intraoperative body temperature. It is noteworthy that despite active thyroid hormone levels being depressed up to 67% of normal, most patients in this study recovered uneventfully.

REFERENCES
9 Hershman JM, Jones CM, Bailey AL. Reciprocal changes in serum thyrotrophin and free thyroxine produced by heparin. J Clin Endocrinol Metab 1972; 34:774-79

CHEST / 108 / 6 / DECEMBER, 1995

1545