Is the low tri-iodothyronine state a crucial factor in determining the outcome of coronary artery bypass patients? Evidence from a clinical pilot study

L Sabatino, A G Cerillo¹, A Ripoli, A Pilo, M Glauber¹ and G Iervasi

Institute of Clinical Physiology, National Council of Research (CNR), Via Moruzzi 1, San Cataldo, 56124 Pisa, Italy
¹Unit of Cardio-Surgery, ‘G. Pasquinucci’ Hospital, IFC-CNR-CREAS, Massa, Italy

Requests for offprints should be addressed to L Sabatino; Email: lauretta@ifc.cnr.it

Abstract

The cardiovascular system is an important target for thyroid hormones. The present study evaluates the changes affecting thyroid hormone metabolism during and 6 days after coronary artery bypass and their relationship with the post-operative outcome of the patients. Thirty-three patients were enrolled in the study; their thyroid hormone profiles were determined at 13 sampling points during surgery and for 6 days afterwards. Serum total tri-iodothyronine (T3) and free T3 (FT3) concentrations decreased significantly after surgery (P<0·001) and they remained significantly low until the end of the study. Free thyroxine (FT4) and T4 declined significantly immediately after surgery (P<0·05 for FT4, P<0·001 for T4) but they returned to baseline values (24 h and 96 h post-surgery respectively). Serum reverse T3 increased remarkably 36 h after surgery (P<0·001) and remained significantly higher than the baseline value throughout the study. A relevant finding was that the days of post-operative hospitalization (10±3 days, means±s.d.) was inversely correlated with the slope of the recovery of T3 concentration (P<0·001) or with the area under the plasma curves of T3 (P=0·024, time range 72–144 h) and the FT3/FT4 ratio (P=0·037, time range 72–144 h) during the post-operative period. Our data suggest a prolonged reduction of T4 to T3 conversion in patients undergoing cardiac surgery and indicate that the recovery period is the most critical in the evaluation of a possibly successful approach for T3 substitutive therapy.

Journal of Endocrinology (2002) 175, 577–586

Introduction

In recent years, the effects of surgical stress on thyroid hormone metabolism has been largely investigated in patients undergoing open-heart operations (Mainwaring et al. 1994, John et al. 1995). Although most of the data reported in the literature on this topic are quite discordant, the rapid and significant decrease in tri-iodothyronine (T3) levels is a confirmed finding (Teiger et al. 1993, Klemperer et al. 1995, Murzi et al. 1995, Novitzky et al. 1996). Investigators have defined this condition as ‘low T3 syndrome’ (Broderick & Wechsler 1997) and have described it as a direct consequence of impairment in the enzymatic mechanism converting thyroxine (T4) to T3 (Holland et al. 1991). For many years, this phenomenon has been described as a temporary adaptive process aimed at restoring correct cardiac function but recently the idea that this is an induced hypothryoid-like state is becoming more common (Bettendorf et al. 2000). Thyroid hormones exert profound effects on the cardiovascular system (Klein & Ojamaa 2000). Consequently, the decrease in T3 levels may be associated with a more compromised cardiac function and an aggravation of many pre-existing conditions. On the basis of these evaluations, in the last decade more and more investigators have been considering the possible benefits of using T3 during surgery and in the first few hours after surgery as a therapeutic agent to improve impaired hemodynamics and changes in thyroid hormone metabolism in patients undergoing open-heart surgical procedures (Mullis-Jansson et al. 1999, Bettendorf et al. 2000). However, the presumed efficacy of T3 replacement therapy remains controversial, mainly because of the lack of a standardized procedure of thyroid hormone administration during and after cardiac surgery and because of the limited period of observation (Mullis-Jansson et al. 1999). The present study was performed to evaluate possible changes affecting thyroid hormone metabolism during cardiac surgery and for a few days afterwards, to investigate the existence of a possible correlation with various outcome parameters and to evaluate the nature and duration of the phenomenon. This study was performed either on patients undergoing cardiopulmonary bypass...
Two groups of patients (group I and group II) were involved in the study. A first group (group I) of 23 patients (age: 66 ± 10 years, means ± s.d., range: 47–79 years) undergoing various open-heart procedures was enrolled. A second group (group II) of an additional ten patients (age: 67 ± 9 years, means ± s.d., range: 56–79 years) was successively enrolled in the study with a shortened sampling schedule (see below) to evaluate the effects of anesthesia on thyroid function profile. Fourteen patients (nine in group I and five in group II) underwent surgery using extra-corporeal circulation while nineteen patients (fourteen in group I and five in group II) underwent surgery using OPCAB. All patients were euthyroid on the basis of clinical and laboratory findings and no drugs known to interfere with thyroid hormone metabolism were given before surgery. Patients with a history of endocrine disorders were excluded from the protocol. In the present study, we define as ‘recovery period’ the time after which thyroid-stimulating hormone (TSH) began to normalize, when free T3 (FT3) gradually returned to normal values and when the overall clinical condition of the patients was more stable than it was after their first day out of the intensive care unit (ICU).

**Sampling criteria**

In group I, hematological thyroid profile and total protein levels were determined the day before surgery, on the morning of surgery, immediately after sternotomy, at the end of surgery, and at 2, 6, 12, 24, 36, 48, 72, 96, 120 and 144 h after the end of the operation. Moreover, in group II, sampling was interrupted at 2 h after surgery. In group I, a new study point was introduced corresponding to the moment immediately before the patients were anesthetized to evaluate whether the hormonal increase observed in group I patients after sternotomy could have been caused by the anesthetic. Since, in both groups, all the measurements in the first two samples were almost superimposable, we chose the second one as the baseline value.

**Assay methods**

Serum T4, T3, free T4 (FT4), FT3 and TSH concentrations were measured by the fully automated AIA 1200 System analyzer (TOSOH Corporation, Tokyo, Japan). To minimize assay errors, all serum samples from the same patient were assayed in the same experiment. The sensitivity of these methods has been previously reported (Iervasi et al. 1996). Serum total protein concentration was measured by the fully automated capillary electrophoresis Paragon CZE 2000 analyzer (Beckman Coulter, Inc., Fullerton, CA, USA). Serum reverse T3 (rT3) concentrations were determined using a commercial radioimmunoassay kit supplied by BioChem Immunosystems (Bologna, Italy). In our laboratory, mean intra-assay coefficient of variation is 3–4% for total T4, total T3, FT4, FT3 and 6–8% for rT3. The mean interassay coefficient of variation is 6–7% for total T4, total T3, FT4, FT3 and 10–11% for rT3.

**Dilution test**

To evaluate if hemodilution interferes with hormonal levels, in the same assay we analyzed thyroid hormone, TSH and total protein levels of 11 baseline blood samples obtained from group I patients, and their 1:2 dilution (in physiological solution, NaCl 0-9%).

**Quantitative analysis of thyroid hormone profile after surgery**

The area under the T3 and FT3/FT4 curves in the 12–144, 24–144, 48–144 and 72–144 h ranges was used as a quantitative integrated measurement of T3 recovery and as an estimate of T4 to T3 conversion recovery (Fig. 1). The slopes of T3 from 12 h, 24 h and 48 h after surgery and 144 h were used to estimate the recovery rate of T3.

**Statistical analyses**

Data are expressed as means ± s.d. Changes of parameters from baseline to subsequent measurements were evaluated by a paired t-test. Differences between two groups were analyzed by an unpaired Student’s t-test or a Fisher’s exact test when appropriate. One-way ANOVA with Bonferroni correction was applied for multiple comparisons. Repeated-measures ANOVA was used to compare changes of parameters between groups with and without extra-corporeal circulation. Pearson correlation coefficient was used to test the association of continuous clinical and hormonal variables with the days of post-operative hospitalization. Univariate linear regression was used to quantify the slope of the association between the days of post-operative hospitalization and the continuous clinical and hormonal variables. Multivariate stepwise linear regression was performed to single out the independent significant covariates among the ones that appeared at univariate analysis. All calculations were performed with SPSS for Windows (Version 10.05, SPSS Inc.). A value of $P<0.05$ was considered significant.
Results

Clinical characteristics of patients

The main clinical data for group I patients are reported in Table 1. There were no hospital deaths. Only one patient from the OPCAB subgroup suffered mild pulmonary complications and needed a longer ICU stay (94 h instead of 21 h on average). In all patients studied, the prolonged post-operative stay reported in our study is inclusive of the cardiac rehabilitation time and the patients were considered discharged only when they went home.

Table 1 Patient baseline and main post-operative parameters. Values are means ± S.D.

<table>
<thead>
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<th></th>
<th>OPCAB (n=14)</th>
<th>CPB (n=9)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>67 ± 11</td>
<td>65 ± 10</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>100 ± 11</td>
<td>94 ± 12</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>52 ± 8</td>
<td>53 ± 6</td>
</tr>
<tr>
<td>Surgery (h)</td>
<td>3·2 ± 1</td>
<td>3·5 ± 1</td>
</tr>
<tr>
<td>ICU (h)</td>
<td>22 ± 5</td>
<td>29 ± 25*</td>
</tr>
<tr>
<td>OTI (h)</td>
<td>10 ± 6</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>Postoperative stay (days)</td>
<td>10 ± 3</td>
<td>11 ± 3</td>
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<tr>
<td>Inotropic drugs (%)</td>
<td>7</td>
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</tbody>
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SBP, systemic mean arterial blood pressure; LVEF, left ventricular ejection fraction; OTI, oro-tracheal intubation.

No significant difference was found between the two subgroups.

*High S.D. is due to only one patient with an exceptional ICU stay of 94 h (see text for details).

In vitro dilution test for thyroid hormone, TSH and total protein serum concentrations

Paired t-test between data obtained on 11 baseline samples from group I and data obtained from successive 1:2 dilutions showed a statistically significant difference both for total protein (6·89 ± 0·48 vs 3·40 ± 0·29 g/dl, P<0·001) and for thyroid hormones (T3=1·6 ± 0·04 vs 0·9 ± 0·04 nmol/l, P<0·001; T4=110·63 ± 23·23 vs 61·28 ± 14·56 µmol/l, P<0·001; FT4=14·48 ± 1·97 vs 11·49 ± 1·23 pmol/l, P<0·001; TSH=1·91 ± 0·61 vs 1·04 ± 0·36 µIU/l, P<0·001) with the only exception being FT3 (3·62 ± 0·52 vs 3·20 ± 0·49 pmol/l, P=0·07, not significant).

Thyroid hormones, TSH and total serum proteins

Thyroid hormone and total protein levels measured during the study are shown in Figs 2 and 3. The baseline levels were in the normal range and, throughout the whole study and for each sampling point, no significant difference was found when comparing thyroid hormone, TSH and total protein levels of the patients undergoing the extra-corporeal circulation and the OPCAB approach. No statistical difference was found between the two subgroups when we analyzed clinical parameters such as age, left ventricular ejection fraction (LVEF), systemic mean arterial blood pressure (SBP), stay in the ICU and use of inotropic drugs. For this reason, data will be discussed without any distinction between the two subgroups.
Figure 2 Time-course of (A) FT3, (B) FT4, (C) total protein (TP) and (D) rT3 in group I patients undergoing extra-corporeal circulation (solid lines) and OPCAB approaches (dashed lines). Error bars are shown on each time point. The normal range is shown by the horizontal lines.
**FT4 and FT3 levels**

Serum FT4 levels significantly increased during sternotomy ($P=0.027$, 125% vs baseline value) to return to baseline levels 24 h after surgery (Fig. 2B). The serum FT3 concentration significantly decreased after surgery when compared with the preoperative levels, reaching the nadir 12 h after surgery ($P<0.001$, 61% vs baseline value) and remaining very low until 72 h after surgery. During the recovery period, from 72 h after surgery to the end of the study, the FT3 levels increased without returning to the baseline values by the end of the study ($P=0.025$, 85% vs baseline value) (Fig. 2A).

**Total protein levels**

Serum total protein levels considerably and significantly dropped after sternotomy, reaching the nadir at the end of surgery ($P<0.001$, 61% vs baseline value). Even though total protein levels remained significantly low throughout the whole study, they increased slightly during the recovery period and they were still 83% of the baseline value ($P<0.001$) at the end of the study (Fig. 2C).

**rT3**

Serum rT3 levels were in the normal range in basal conditions. During the study, rT3 at first showed a significant drop immediately at the end of surgery ($P=0.008$, 86% vs baseline value) but they increased remarkably 12 h after the end of surgery ($P<0.05$, 161% vs baseline value). rT3 levels were significantly higher when compared with the baseline values throughout the whole study, they reached the maximum level 120 h after the end of surgery ($P<0.001$, 240% vs baseline value) and remained significantly high until the end of the study ($P=0.003$, 172% vs baseline values) (Fig. 2D).

**T4 and T3 levels**

The serum T4 concentration curve showed at first a modest increase at the sternotomy stage and, immediately after the peak, a statistically significant drop to the nadir at 12 h after the end of surgery ($P<0.001$, 71% vs baseline value). In the recovery period, the T4 levels increased and 96 h after surgery they returned to the baseline value (Fig. 3A). Serum T3 values significantly and dramatically dropped at the end of surgery reaching the nadir 12 h after surgery ($P<0.001$, 54% vs baseline value). In the recovery period, the T3 levels remained significantly low but they returned to the baseline values at the end of the study, 144 h after surgery ($P<0.05$, 83% vs baseline value) (Fig. 3B).

**Correction of T4 and T3 by total proteins**

Single values of T4 and T3 were further analyzed and corrected for corresponding total protein levels according to the following formula: hormone concentration/ (total protein concentration/baseline total protein concentration). Both corrected T4 and T3 increased during surgery, reaching the maximum value immediately after sternotomy (T4: $P<0.001$, 153% and T3: $P=0.003$, 132% more than baseline values). Corrected T4 values returned to baseline values 24 h after the end of surgery and corrected T3 values 6 h after the end of surgery (Fig. 3C and D respectively).

**TSH levels**

Serum TSH levels (baseline concentration $=1.83 \pm 0.90 \mu IU/l$) tended to increase during the induction of anesthesia ($TSH=2.19 \pm 1.11 \mu IU/l$) without reaching statistical significance and dropped after the end of surgery reaching the nadir 12 h after surgery ($TSH=0.83 \pm 0.54 \mu IU/l$, $P<0.001$, 45% vs baseline value). In the recovery period, 72 h after surgery, the TSH levels returned to basal values ($TSH=1.66 \pm 1.12 \mu IU/l$) (data not shown).

**Analysis of thyroid hormones, TSH and total protein in group II patients**

In group II patients, where a new sampling point was introduced immediately before the anesthesia, no difference was found when comparing the thyroid hormone, TSH and total protein concentrations between the pre-anesthesia sampling point and the baseline value (Table 2).

**FT3/FT4 ratio**

The FT3/FT4 ratio significantly decreased, reaching the nadir point 12 h after the end of surgery ($P<0.001$, 68% vs baseline value). During the recovery period (range 72–144 h) the FT3/FT4 ratio slightly increased, reaching 82% of the baseline value at the end of the study ($P=0.007$) (Fig. 4).

**T3/T4 ratio**

The uncorrected T3/T4 ratio significantly decreased, reaching the nadir point 12 h after the end of surgery ($P<0.001$, 75% decrement vs baseline value) and remained significantly low until the end of the study ($P=0.005$, 82% vs baseline value).

**T3/rT3 ratio**

The T3/rT3 ratio significantly dropped starting from the end of surgery, reaching the minimum concentration 12 h
Figure 3 Time-course of (A) T4, (B) T3, (C) T4 corrected by total protein (TP) and (D) T3 corrected by TP in group I patients undergoing extra-corporeal circulation (solid lines) and OPCAB approaches (dashed lines). Error bars are shown on each time point. The normal range is shown by the horizontal lines.
from the end of surgery ($P < 0.001$, 32% vs baseline value) and remaining very low until the end of surgery ($P < 0.001$, 49% vs baseline value) (Fig. 4).

**Time-course of thyroid hormone recovery and clinical outcome**

In the statistical analysis, the mean value of T3 (MV-T3) concentrations and FT3/FT4 ratio (MV-FT3/FT4) in the recovery period (72–144 h time range) were expressed as percent of the basal value and were considered as an index of T4 to T3 peripheral conversion. The slopes in the T3 curve from 12 h ($s_{12–144}$), 24 h ($s_{24–144}$), 48 h ($s_{48–144}$) and 72 h ($s_{72–144}$) after surgery and 144 h were used to estimate the T3 recovery rate. On bivariate analysis, the days of post-operative hospitalization were significantly associated with MV-T3 ($R = 0.468; P = 0.024$), MV-FT3/FT4 ($R = 0.436; P = 0.037$), $s_{12–144}$ h ($R = 0.651; P = 0.001$), $s_{24–144}$ h ($R = 0.718; P = 0.001$), $s_{48–144}$ h ($R = 0.664; P = 0.001$) and $s_{72–144}$ h ($R = 0.448; P = 0.032$). Other hormonal (i.e. baseline T4, FT4, TSH and rT3) and clinical variables, such as age, baseline (preoperative) LVEF and SBP, stay in the ICU, heart rate and post-operative use of inotropic drugs showed no significant association with the T3 recovery. The slopes of the significant associations were assessed by linear regression analysis. For each covariate, the regression coefficient (B), its significance ($P$), its 95% confidence interval (CI), together with the R value, are reported in Table 3. The strongest linear association was found for $s_{24–144}$ h ($R = 0.718$) (Fig. 5), followed by $s_{12–144}$ h ($R = 0.651$), $s_{48–144}$ h ($R = 0.664$) and $s_{72–144}$ h ($R = 0.448$). Each covariate showed the same kind of interaction with the time of hospitalization, with an all-negative 95% CI for every regression coefficient. When all the slopes found to be statistically significant at the univariate linear regression were considered together in a multivariate linear model, $s_{24–144}$ h was the best independent significant predictor for the time of post-operative hospitalization ($B = -535.429, R = 0.718, P < 0.001$, 95% CI for $B = -770.897$ to $-299.961$) while among the areas under the total or partial (measured in the time range 12–144 h, 24–144 h, 48–144 h, 72–144 h) concentration curves of T3 and FT3/FT4, MV-T3 ($72–144$ h) appeared as the only independent significant predictor for the time of post-operative hospitalization ($B = -6.264, R = 0.436, P = 0.037, 95% CI for B = -12.127 to -0.401$).

**Discussion**

Recent studies suggest that adult patients undergoing CPB and surgical stress may experience a rapid and significant reduction in the levels of circulating thyroid hormones; in particular, decreased concentrations of T3 and FT3 are typically observed (Bacci et al. 1982, Broderick & Wechsler 1997). This condition of transitory hypothyroidism is referred to as the ‘low T3 syndrome’. However, while primary hypothyroidism is a pathological condition of the thyroid gland, the low T3 syndrome is usually observed as an extra-thyroidal manifestation responding to a severe homeostatic alteration (Wartofsky & Burman 1982, Robuschi et al. 1986). The mechanism hypothesized to explain the low T3 state involves the regulation of specific 5’-monodeiodinases converting T4 to T3 which is considered to be the thyroid hormone in the biologically active form (Salter et al. 1992). Data from the literature on thyroid hormone metabolism during and after cardiac surgery are mainly derived from studies based on patients undergoing coronary artery bypass during operations carried out with the extra-corpooreal circulation procedure (Klemperer et al. 1995, Novitzky et al. 1996). The original approach introduced in the present study consisted of the evaluation either of patients undergoing cardiac surgery carried out using extra-corpooreal circulation or patients

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**Table 2** Thyroid hormone, TSH and total protein (TP) in group II patients. Values are expressed as means ± S.E.M.; n = number of patients

<table>
<thead>
<tr>
<th></th>
<th>T3 (nmol/l)</th>
<th>T4 (μmol/dl)</th>
<th>FT3 (pmol/l)</th>
<th>FT4 (pmol/l)</th>
<th>TSH (mIU/l)</th>
<th>TP (g/dl)</th>
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<td><strong>CPB (n=5)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>1.33 ± 0.09</td>
<td>104.4 ± 1.9</td>
<td>3.98 ± 0.21</td>
<td>20.9 ± 2.3</td>
<td>2.21 ± 1.0</td>
<td>6.34 ± 0.3</td>
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<tr>
<td>Pre-anesthesia</td>
<td>1.27 ± 0.09</td>
<td>104.7 ± 0.3</td>
<td>3.59 ± 0.14</td>
<td>17.5 ± 0.7</td>
<td>2.02 ± 0.8</td>
<td>5.96 ± 0.2</td>
</tr>
<tr>
<td>Post-surgery</td>
<td>0.95 ± 0.04</td>
<td>91.7 ± 0.49</td>
<td>3.48 ± 0.22</td>
<td>20.7 ± 1.9</td>
<td>1.85 ± 0.9</td>
<td>4.27 ± 0.3</td>
</tr>
<tr>
<td>2 h</td>
<td>0.96 ± 0.10</td>
<td>92.5 ± 6.0</td>
<td>3.31 ± 0.11</td>
<td>19.5 ± 1.4</td>
<td>1.30 ± 0.6</td>
<td>4.58 ± 0.3</td>
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<td><strong>OPCAB (n=5)</strong></td>
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<tr>
<td>Baseline</td>
<td>1.60 ± 0.07</td>
<td>98.4 ± 2.5</td>
<td>3.46 ± 0.14</td>
<td>15.3 ± 0.5</td>
<td>1.49 ± 0.2</td>
<td>6.22 ± 0.2</td>
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<tr>
<td>Pre-anesthesia</td>
<td>1.40 ± 0.12</td>
<td>93.5 ± 2.3</td>
<td>3.44 ± 0.20</td>
<td>16.0 ± 0.7</td>
<td>1.52 ± 0.1</td>
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<tr>
<td>Post-surgery</td>
<td>1.38 ± 0.05</td>
<td>99.0 ± 3.0</td>
<td>4.13 ± 0.54</td>
<td>19.9 ± 2.7</td>
<td>1.71 ± 0.1</td>
<td>5.59 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>1.14 ± 0.07</td>
<td>89.6 ± 4.3</td>
<td>3.26 ± 0.19</td>
<td>18.2 ± 0.9</td>
<td>1.09 ± 0.2</td>
<td>4.49 ± 0.2</td>
</tr>
</tbody>
</table>

**Note:** The slopes in the T3 curve from 12 h ($s_{12–144}$), 24 h ($s_{24–144}$), 48 h ($s_{48–144}$) and 72 h ($s_{72–144}$) after surgery and 144 h were used to estimate the T3 recovery rate. On bivariate analysis, the days of post-operative hospitalization were significantly associated with MV-T3 ($R = 0.468; P = 0.024$), MV-FT3/FT4 ($R = 0.436; P = 0.037$), $s_{12–144}$ h ($R = 0.651; P = 0.001$), $s_{24–144}$ h ($R = 0.718; P = 0.001$), $s_{48–144}$ h ($R = 0.664; P = 0.001$) and $s_{72–144}$ h ($R = 0.448; P = 0.032$). Other hormonal (i.e. baseline T4, FT4, TSH and rT3) and clinical variables, such as age, baseline (preoperative) LVEF and SBP, stay in the ICU, heart rate and post-operative use of inotropic drugs showed no significant association with the T3 recovery. The slopes of the significant associations were assessed by linear regression analysis. For each covariate, the regression coefficient (B), its significance ($P$), its 95% confidence interval (CI), together with the R value, are reported in Table 3. The strongest linear association was found for $s_{24–144}$ h ($R = 0.718$) (Fig. 5), followed by $s_{12–144}$ h ($R = 0.651$), $s_{48–144}$ h ($R = 0.664$) and $s_{72–144}$ h ($R = 0.448$). Each covariate showed the same kind of interaction with the time of hospitalization, with an all-negative 95% CI for every regression coefficient. When all the slopes found to be statistically significant at the univariate linear regression were considered together in a multivariate linear model, $s_{24–144}$ h was the best independent significant predictor for the time of post-operative hospitalization ($B = -535.429, R = 0.718, P < 0.001$, 95% CI for $B = -770.897$ to $-299.961$) while among the areas under the total or partial (measured in the time range 12–144 h, 24–144 h, 48–144 h, 72–144 h) concentration curves of T3 and FT3/FT4, MV-T3 ($72–144$ h) appeared as the only independent significant predictor for the time of post-operative hospitalization ($B = -6.264, R = 0.436, P = 0.037, 95% CI for B = -12.127 to -0.401$).
undergoing revascularization without CPB. Interestingly, we did not find any significant difference in the thyroid hormone, TSH and total protein curves in the two groups. However, a tendency for a slower recovery may be deduced from the hormonal trend of patients undergoing extra-corporeal circulation when compared with patients undergoing OPCAB (T3=66% of baseline values at 144 h vs 93% respectively). We therefore agree with the idea that the unphysiologic conditions, the relatively short period of time, the low perfusion pressure and the non-pulsatile perfusion are not the factors responsible for the thyroid hormone changes occurring during surgery, as was suggested previously (Baum et al. 1968, Dunn et al. 1974, Pappas et al. 1975, Gøtzsche & Weeke 1991). Moreover, the present analysis was carried out throughout the cardiac operation and the next 144 h. In most studies described in the literature, the analysis was carried out for no more than a few hours after surgery and completely ignore the dynamics of thyroid hormone metabolism in the recovery period. Thus, the common T3 supplementation procedure includes peri-operative T3 administration either by bolus or by short infusion (Mullis-Jansson et al. 1999, Bettendorf et al. 2000). In the first set of data collected in our study, the remarkable decrease in FT3 concentrations and the absence of a reduction in FT4 levels may be explained by a massive reduction in the peripheral conversion of T4 to T3. Furthermore, this idea is also supported by the dramatic drop of the FT3/FT4 ratio after the end of surgery. The unexpected positive peak in the FT4 curve at sternotomy is probably induced by the treatment with various anesthetics interfering with thyroid hormone metabolism (Borner et al. 1995). The fact that TSH and FT3 also tend to increase after the induction of anesthesia (even though not to significant levels) confirms the important role that surgical stress has on hormonal levels. The second part of the study, involving group II patients, was carried out with the specific aim of understanding if anesthesia might contribute to the significant increase in thyroid hormone levels. The fact that, in the analysis on group II, we did not find any relevant difference from the baseline values of thyroid hormone concentrations measured immediately before the induction of anesthesia, supports our hypothesis that the administration of anesthetic can explain the hormonal peak we described after sternotomy. Moreover, these findings showed that the choice of an opportune baseline value is a crucial step and must be done before any of the events involved in the study takes place.

Table 3 Linear regression analysis in the time-range 12–144 h after surgery

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<th>B</th>
<th>R</th>
<th>P</th>
<th>95% CI for B</th>
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<td>MV-FT3/FT4</td>
<td>-6·26</td>
<td>0·436</td>
<td>0·037</td>
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<td>MV-T3</td>
<td>-5·93</td>
<td>0·468</td>
<td>0·024</td>
<td>-11·01 to -0·85</td>
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<td>s12–144 h</td>
<td>-515·89</td>
<td>0·651</td>
<td>0·001</td>
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<td>s24–144 h</td>
<td>-535·43</td>
<td>0·718</td>
<td>&lt;0·001</td>
<td>-770·90 to -299·96</td>
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<tr>
<td>s48–144 h</td>
<td>-571·16</td>
<td>0·664</td>
<td>0·001</td>
<td>-863·26 to -279·05</td>
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<tr>
<td>s72–144 h</td>
<td>-287·80</td>
<td>0·448</td>
<td>0·032</td>
<td>-548·37 to -27·22</td>
</tr>
</tbody>
</table>

Figure 4 Time-course of serum T3/rT3 ratio (▲) and FT3/FT4 ratio (●). Values are expressed as means ± S.E.M. *P<0·05, **P<0·01, ***P<0·001.
significantly low levels maintained throughout the whole study confirmed the authenticity of the reduction in T3 and the long duration of the phenomenon. Since T3/T3 and FT3/FT4 ratios are typically considered to be important indexes of T4 to T3 peripheral conversion, we conclude that the trend of these two curves is strictly correlated to an impairment of the converting enzyme, 5'-monodeiodinase.

Interesting findings were obtained analyzing the relationships between the quantitative measurements of FT3/FT4 and T3 in the post-operative period, their recovery rate and the clinical outcome. In our analysis, analogous to other studies described in the literature (Barriuso Vargas et al. 1999, Contini et al. 1999, Welsby et al. 2002), the days of hospitalization appeared to be the most likely, among all the other possible parameters of clinical outcome, that could be correlated with the thyroid hormone levels.

The strong inverse correlation we found between the days of post-operative hospitalization and the area under the curves of both T3 and FT3/FT4 ratio during post-surgical recovery suggests that a better prognosis is associated with a more efficient thyroidal function and, more specifically, with an amelioration of the peripheral conversion of T4 to T3. Thus, our data indicate T3, FT3 values and FT3/FT4 ratio as reliable and practicable parameters in the evaluation of the efficiency of the recovery of cardio-surgical patients. This result is strongly supported by our other finding that the days of post-surgery hospitalization inversely correlate with the rapidity of the recovery in the T3 levels in the time range 12–144 h. These findings suggest the possibility that the restoration of thyroid hormone metabolism could be a crucial step for an efficient cardio-circulatory function during the recovery period and encourage further studies in this direction. On the other hand, we believe that our findings do not exclude the reverse circumstances: in fact, the severity of the cardiac (and systemic) injury by itself may strongly determine the T3 level. In any case, due to the positive actions of T3 on the cardiovascular system (Hamilton et al. 1998), our data, taken as a whole, encourage T3 replacement therapy in patients undergoing cardiac operation with a persisting low T3 state. However, we believe that this therapeutic approach must be addressed very carefully. Initial data in animal models have suggested that the administration of physiologic doses of T3 produce a significant improvement in myocardial performances (Gay et al. 1987, 1988, Novitzky et al. 1988, Dyke et al. 1991). Recent studies in humans have described the administration of T3 during or immediately after surgery, in order to improve hemodynamics in adults undergoing coronary artery bypass by reversing the low T3 state and ameliorating the performance of the myocardium (Mullis-Jansson et al. 1999). However, we believe that the drastic decrease in thyroid hormone that takes place during surgery is, at least partially, induced and sustained by a noteworthy hemodilution and/or by a more rapid clearance of the hormone that could become important limiting factors in the T3 short-term replacement approach (Klemperer et al. 1995). Moreover, our finding of a prolonged impairment of T4 to T3 conversion after surgery points at that period as the most critical for a successful T3 substitutive therapy.

This result may also help to explain why data reported in the literature on T3 administration by bolus or short infusion during surgery are very controversial (Klemperer et al. 1995, Bettendorf et al. 2000). Taken together, our clinical data are suggestive of a possible new way to treat or prevent low cardiac output and other unbalancing hemodynamic parameters after coronary surgery.

Acknowledgements

We thank Dr Annalisa Iervasi, Miss Chiara Taddei and Mr Stefano Turchi for excellent technical support and Mrs Laura Mazza for skillful secretarial assistance.

References


Figure 5 Graphical representation of the correlation between post-operative days and slopes measured in the T3 curve in the time range 12–144 h. OPCAB patients (△); CPB patients (▲).


Received 5 July 2002
Accepted 20 August 2002