Physiological effects of nonthyroidal illness syndrome in patients after cardiac surgery

D. I. Spratt,1,2 M. Frohnauer,3 H. Cyr-Alves,1 R. S. Kramer,5 F. L. Lucas,4 J. R. Morton,5 D. F. Cox,6 K. Becker,1 and J. T. Devlin3
1Endocrine Research Program, Maine Medical Center Research Institute, and 3Maine Center for Endocrinology and Diabetes, Scarborough; 2Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, 4Center for Outcomes Research, and Departments of 5Cardiac Services and 6Pediatrics, Maine Medical Center, Portland, Maine

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Spratt DI, Frohnauer M, Cyr-Alves H, Kramer RS, Lucas FL, Morton JR, Cox DF, Becker K, Devlin JT. Physiological effects of nonthyroidal illness syndrome in patients after cardiac surgery. Am J Physiol Endocrinol Metab 293:E310–E315, 2007. First published April 10, 2007; doi:10.1152/ajpendo.00687.2006.—In a prospective randomized placebo-controlled study, we assessed potential physiological effects of nonthyroidal illness syndrome (NTIS) in acute illness. Coronary artery bypass graft surgery was employed as a prospective model of acute illness and NTIS. Triiodothyronine (T3) or placebo was infused for 24 h after surgery, with a T3 dose selected to maintain postoperative serum T3 concentrations at preoperative levels. Patients were evaluated before coronary artery bypass graft and during the postoperative period. Cardiovascular function was monitored with Swan-Ganz catheter measurements and ECG. Urinary nitrogen excretion and 1/[1-13C]leucine flux were used to evaluate protein metabolism. Serum measurements of relevant hormones, iron, and total iron-binding capacity were used to assess effects on sex steroid, growth hormone axis, and iron responses to illness. Cardiovascular function was not affected by T3 infusion, except for a transient higher cardiac index in the T3 group 6 h after surgery (3.04 ± 0.12 for T3 and 2.53 ± 0.08 for placebo, P = 0.0016). Protein metabolism was not affected; changes in urinary nitrogen excretion and 1/[1-13C]leucine flux were equivalent in the two groups (P = 0.35 and P = 0.95, respectively). No differences were observed in changes in testosterone, estrogens, growth hormone, insulin-like growth hormone I, iron, or total iron-binding capacity between T3 and placebo groups. We conclude that, in the early stages of major illness, the decrease in circulating T3 concentrations in NTIS has only a minimal transient physiological impact on cardiac function and plays no significant role in protecting against protein catabolism or modulating other endocrine responses or iron responses to illness.

euthyroid sick syndrome was first described nearly three decades ago. Its most prominent feature is a marked decrease in circulating triiodothyronine (T3) levels with the onset of illness or fasting (19). Recently, a change in terminology from euthyroid sick syndrome to “nonthyroidal illness syndrome” (NTIS) has been adopted by many (8). This change in nomenclature reflects an underlying controversy as to whether NTIS is truly a euthyroid state or deserves therapy with thyroid hormone, amiodarone, glucocorticoids, or sex steroids within the past year. Body mass index of patients ranged from 22 to 42. Baseline characteristics of patients are displayed in Table 1. A single group of five cardiovascular surgeons was involved with similar strategies for postoperative management of patients. The study was approved by the Internal Review Board of the Maine Medical Center.

METHODS

Patient Population

Fifty-nine patients (7 women and 52 men) undergoing elective CABG were included in the study. Because the primary aim of this study was to evaluate physiological effects of NTIS, volunteers were selected to provide a relatively healthy baseline (with no evidence of NTIS before surgery). We did not intend to answer clinical questions regarding the use of T3 in patients with markedly compromised preoperative cardiac function. Inclusion criteria were as follows: ≤80 yr of age, ambulatory before surgery with New York Heart Association classification I or II, preoperative ejection fraction ≥40%, no active endocrine illness as assessed by history and by serum levels of thyroxine (T4), T3, thyroid-stimulating hormone (TSH), testosterone (T), GH, and IGF-I within the normal range before surgery, no major illness other than cardiac disease, and no therapy with thyroid hormone, amiodarone, glucocorticoids, or sex steroids within the past year. Body mass index of patients ranged from 22 to 42. Baseline characteristics of patients are displayed in Table 1. A single group of five cardiovascular surgeons was involved with similar strategies for postoperative management of patients. The study was approved by the Internal Review Board of the Maine Medical Center.

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Address for reprint requests and other correspondence: D. I. Spratt, Division of Reproductive Endocrinology, Dept. of Ob/Gyn, Maine Medical Center, Portland, ME 04102 (e-mail: spratd@mmc.org).
collections were initiated for determination of UN. UN was determined by measurement of urinary nitrogen for the larger study. Inclusion criteria were as stated above.

**Cardiac Index (CI)**

Cardiac output (CO), mean arterial pressure (MAP), central venous pressure (CVP), and mixed venous O₂ saturation were measured via an indwelling Swan-Ganz catheter upon insertion of the catheter and 1, 6, 12, and 18 h after CC removal. Derivative measurements were cardiac index (CI; calculated as CO ÷ body surface area) and systemic vascular resistance [calculated as (MAP - CVP) ÷ CO].

ECGs were performed just before admission and 36 h after CC removal to monitor heart rate (HR) and evidence of ischemia or myocardial damage. Arrhythmias as recorded by telemetry were monitored for 24 h after CC removal. In addition, in the first 20 patients, cardiac activity was recorded by Holter monitor for the 6 h before CABG and for 24 h after CABG.

**Evaluation of Protein Catabolism**

Protein metabolism was evaluated in a subset of 20 patients (10 each in placebo and T₃-treated groups). These 20 patients were entered consecutively into the protein protocol during routine recruitment for the larger study. Inclusion criteria were as stated above. Evaluation was accomplished by measurement of urinary nitrogen excretion (UN) and L-[1-¹³C]leucine flux.

**Iron-Handling Parameters**

Concentrations of T₃, TSH, total T, GH, IGF-I, and iron, as well as total iron-binding capacity (TIBC), were measured on serum samples obtained from patients within the week before surgery and then following CC removal after surgery (Table 2). We did not monitor serum levels of T₄, because we and other groups previously reported that serum levels of T₄ declined in parallel with T₃ (but to a lesser degree) after CABG (7, 14, 33). We also did not measure serum concentrations of free T or sex hormone-binding globulin, because we and others previously reported that serum levels of free T decreased in parallel with total T after CABG (22, 33).

**Statistics**

Repeated-measures ANOVA was used to assess treatment and time effects and the time-treatment interaction. We used the time-treatment interaction as the major test of our hypothesis. Mean TSH values from T₃ and placebo groups were compared using a two-tailed unpaired t-test. In addition, because a post hoc examination of confidence intervals suggested a difference between values in the placebo and T₃ groups, we also did a pairwise comparison using a two-tailed unpaired t-test.

### Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>Women/Men</th>
<th>EF, %</th>
<th>CI, l·min⁻¹·m⁻²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>59.4 ± 2.4</td>
<td>29.3 ± 0.9</td>
<td>3/30</td>
<td>55.7 ± 2.7</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>T₃</td>
<td>63.7 ± 1.7</td>
<td>27.8 ± 0.6</td>
<td>4/28</td>
<td>55.0 ± 2.7</td>
<td>2.6 ± 0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. BMI, body mass index; EF, ejection fraction; CI, cardiac index; T₃, triiodothyronine.
are means infused from the time of cross-clamp removal until 24 h after CABG. Values are means ± SE.

RESULTS

Serum T3 and TSH Concentrations

Figure 1 displays serum T3 concentrations throughout the study in the placebo and T3 groups. As anticipated, serum T3 levels decreased markedly in the placebo group but remained at baseline levels in the T3 group until discontinuation of the infusion at 24 h. TSH remained within the normal range in all patients in the placebo group at 24 h after surgery (1.81 ± 0.22 (0.43–3.84) μU/ml). TSH in the T3 group was 0.57 ± 0.07 (0.19–1.18) μU/ml, with values slightly below the lower limit of normal (0.4 μU/ml) in seven patients. TSH was significantly lower in the T3 than in the placebo group (P < 0.0001).

Hemodynamic Parameters

CI was increased over baseline values by 1 h after CC removal in the placebo and T3 groups (Fig. 2; P < 0.001). No significant difference in mean CI values was observed between the two groups, except at 6 h after CC removal, when CI in the placebo group fell below CI in the T3 group (2.53 ± 0.08 vs. 3.04 ± 0.12 l·min⁻¹·m⁻², P = 0.0016). Values for systemic vascular resistance and mixed venous O₂ saturation were also equivalent in the placebo and T3 groups (Table 3). ECG data demonstrated similar increases in HR after CABG in the placebo (19.2 ± 2.9 beats/min) and T3 (22.4 ± 2.1 beats/min) groups. Holter monitor data confirmed this finding, with increases in HR of 24.8 ± 2.3 and 27.6 ± 2.5 beats/min in the placebo and T3 groups (P = 0.43). ECG data also demonstrated no ischemic damage in either group.

Arrhythmias and Drug Administration

No differences in the incidence of arrhythmias were noted postoperatively between the placebo and T3 groups. Particularly, no decrease in the incidence of atrial fibrillation was observed in the T3 group.

Very few patients in these populations received dopamine. T3 and placebo patients were equally likely to receive dopamine, and only small “renal” doses (≤5 μg·kg⁻¹·h⁻¹) were administered. Placebo and T3 patients were also equally likely to receive 1) vasodilators, 2) inotropes, 3) cardiac glycosides, 4) antihypertensives (primarily nitroprusside), 5) β-blockers, 6) calcium channel blockers, 7) angiotensin-converting enzyme inhibitors, 8) antiarrhythmics, and 9) diuretics.

Protein Catabolism

UN values were not significantly increased postoperatively in the placebo or T3 group. Pre- and postoperative UN values were 6.27 ± 0.19 and 7.25 ± 1.13 g/24 h (P = 0.19) in the placebo group and 5.36 ± 0.58 and 5.46 ± 0.50 g/24 h (P = 0.86) in the T3 group. No significant difference was observed in the pre- to postoperative change in UN excre-
TABLE 5. GH and IGF-I in placebo and T3 groups

<table>
<thead>
<tr>
<th></th>
<th>PreOp</th>
<th>1 h</th>
<th>24 h</th>
<th>36 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH, µg/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.6±0.4</td>
<td>4.1±0.9</td>
<td>1.4±0.3</td>
<td>1.6±0.5</td>
</tr>
<tr>
<td>T3</td>
<td>2.0±0.4</td>
<td>4.6±1.0</td>
<td>2.3±0.6</td>
<td>1.1±0.2</td>
</tr>
<tr>
<td>IGF-I, µg/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>121.7±16.2</td>
<td>60.6±13.1</td>
<td>67.7±6.4</td>
<td>62.7±2.7</td>
</tr>
<tr>
<td>T3</td>
<td>127.8±17.0</td>
<td>66.7±11.3</td>
<td>80.1±7.8</td>
<td>75.2±3.1</td>
</tr>
<tr>
<td>IGF-I/IGF ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>102.6±16.7</td>
<td>28.5±7.5</td>
<td>83.7±26.2</td>
<td>62.2±21.8</td>
</tr>
<tr>
<td>T3</td>
<td>97.8±19.5</td>
<td>28.0±7.6</td>
<td>86.7±39.9</td>
<td>74.8±9.4</td>
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</table>

Values are means ± SE.

measures ANOVA showed no difference between time points within each group.

L-[1-13C]leucine flux (µmol·kg⁻¹·min⁻¹) increased slightly postoperatively in the placebo group: from 121±4 to 139±8 (P = 0.05; Fig. 3). In the T3 group, the difference between pre- and postoperative values (126±9 and 145±8, respectively) was not significant (P = 0.13). Postoperative changes in L-[1-13C]leucine flux in the placebo group were not significantly different from those in the T3 group (18.2±17.7 and 19.0±31.1, respectively, P = 0.95).

Sex Steroids

T decreased profoundly in the placebo and T3 groups to similar nadir levels within the range of prepubertal values (Fig. 4A). In the placebo group, serum T decreased from a preoperative value of 3.5±0.9 ng/ml to a nadir postoperative value of 0.9±0.4 ng/ml (P < 0.0001) and in the T3 group from 4.0±1.4 to 0.8±0.3 ng/ml (P < 0.0001). These decreases were statistically the same for both groups (P = 0.11).

In contrast to T, serum E1 levels rose in the placebo and T3 groups (Fig. 4B). The increase in the T3 group (from 34.7±2.6 to 90.9±9.0 pg/ml) was not significantly greater than the increase in the placebo group (from 35.3±3.0 to 70.2±9.1 pg/ml; P = 0.31). Serum levels of E2 did not rise significantly in either group, with similar values observed in both groups (Table 4).

**GH Axis and Serum Iron and TIBC**

Serum GH levels increased and IGF-I levels decreased in placebo and T3 patients (Table 5). No significant differences between these changes were observed between the two groups.

<table>
<thead>
<tr>
<th></th>
<th>PreOp</th>
<th>1 h</th>
<th>24 h</th>
<th>36 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron, µg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>73.6±11.3</td>
<td>57.8±10.4</td>
<td>17.4±5.7</td>
<td>12.5±2.1</td>
</tr>
<tr>
<td>T3</td>
<td>100.9±12.4</td>
<td>62.0±12.0</td>
<td>17.9±3.3</td>
<td>15.2±2.9</td>
</tr>
<tr>
<td>TIBC, µg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>296±22</td>
<td>105±26</td>
<td>135±21</td>
<td>172±15</td>
</tr>
<tr>
<td>T3</td>
<td>312±23</td>
<td>82±18</td>
<td>156±15</td>
<td>173±7</td>
</tr>
</tbody>
</table>

Values are means ± SE.

Table 6. Serum iron concentrations and TIBC in placebo and T3 groups
Expression of an intronic splicing regulatory element is associated with hyperandrogenaemia in women with polycystic ovary syndrome.


REFERENCES


