Rapid Down-regulation of Thyroid Hormones in Acute Myocardial Infarction

Is It Cardioprotective in Patients With Angina?

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Background: In severe illness of any cause, down-regulation of the thyroid hormone system may occur. How this affects patients with acute myocardial infarction (AMI) is largely unknown.

Objective: To investigate changes in serum levels of the thyroid hormones during AMI and their association with cardiac function and outcome.

Methods: Forty-seven consecutive euthyroid patients with AMI were studied prospectively during the first 5 days and again 6 and 12 weeks later. Time from pain onset was used in all analyses.

Results: The thyroid hormone system was rapidly down-regulated with maximal changes 24 to 36 hours after onset of symptoms. The mean level of the hormone total triiodothyronine (T₃) decreased 19% (P= .02), the inactive metabolite reverse T₃ (rT₃) levels increased 22% (P=.01), and thyrotropin levels declined 51% (P<.001) between the first 6-hour and the 24- to 36-hour period. The prohormone free thyroxine was largely unchanged. Patients with poor heart function or more intense inflammatory reaction showed more pronounced down-regulation of the thyroid system. No correlation was found with cardiac enzymes. Patients with prior angina pectoris had lower T₃ levels in early samples, smaller infarctions, and higher levels of C-reactive protein and the proinflammatory cytokine interleukin 6 on admittance. Peak levels of interleukin 6 correlated negatively with T₃ (P= .005) and positively with rT₃ (P<.05), suggesting that down-regulation before AMI may be cardioprotective. However, mortality was high among patients with the most pronounced thyroid level depression, indicating that down-regulation after AMI may be maladaptive.

Conclusions: The thyroid hormone system is rapidly down-regulated in AMI. This may be beneficial during acute ischemia. Patients with angina had higher levels of interleukin 6 and C-reactive protein and more depressed thyroid hormone system in early samples. Thyroid level depression in patients with angina may possibly have been present before the infarction process started. This novel finding needs further evaluation in large studies to sort out cause-and-effect relationships.

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In severe illness of any cause, depression of thyroid hormone system may occur in otherwise euthyroid patients. In this condition, called the euthyroid sick syndrome, the normal feedback control of the thyroid homeostasis is changed.1-3 Levels of thyrotropin do not increase, although levels of the active hormone triiodothyronine (T₃) become low. The conversion of the prohormone free thyroxine (T₄) into T₃ is hampered, and there is an accumulation of the inactive metabolite reverse T₃ (rT₃).

This syndrome has been found in severe chronic heart failure,4 in acute myocardial infarction (AMI),5,6 and as a rapidly emerging phenomenon during open-heart surgery.7 The more profound the changes in hormone pattern, the poorer the prognosis.8,9 Triiodothyronine has profound effects on the cardiovascular system. It increases cardiac contractility and reduces systemic vascular resistance.10,11 These properties have made investigators explore potential benefits of thyroid hormone supplementation in conditions with poor heart function and low T₃ levels. The usefulness of T₃ as an inotropic agent has been studied in patients during open-heart surgery. Results have been promising, and few adverse reactions have been reported.12-15 Experimental animal studies indicate that treatment with thyroid hormone may be beneficial in heart failure after AMI.15-18 The aims of the present investigation were to study changes in the thyroid hormone system in patients with AMI and to evaluate whether such changes are important for the outcome.
PATIENTS AND METHODS

STUDY POPULATION

Blood samples were obtained from 54 consecutive patients presenting with chest pain and subsequently proven AMI on admission to the coronary care unit. Patients with known or suspected thyroid disease and patients taking medication that affected the thyroid hormone system (T\textsubscript{3}, glucocorticoids, amiodarone, heparin sodium) were excluded from further studies. Forty-seven patients remained for evaluation (mean±SD age, 69±13 years; range, 31-93 years; 16 women). Patient characteristics are given in Table 1. As a control group, we used 123 healthy individuals (mean±SD age, 59±14 years; range, 31-86 years), none of whom were taking any medications. Regarding levels of rT\textsubscript{3}, another control group, consisting of 109 healthy, 70-year-old individuals taking no medications, was used (Table 2).

Median delay from pain onset until the first sample was obtained was 7 hours 20 minutes. Only 4 patients arrived later than 24 hours and none later than 48 hours after onset of symptoms. For each patient, the time from pain onset, rather than the time from admission, was used in the analysis. Six patients died within the first year of AMI. After 2 years, 11 patients had died (Table 3).

BIOCHEMICAL ASSAYS

Blood samples were obtained on admittance to the coronary care unit and 4 times daily for 2 days, once daily for another 3 days, and during convalescence 6 and 12 weeks later. Samples were centrifuged for 10 minutes, and serum was aspirated and frozen at −20°C. Serum concentrations of total T\textsubscript{3} (T\textsubscript{3}), free T\textsubscript{4} (FT\textsubscript{4}), and thyrotropin were determined in a DELFIA system by dissociation-entranced lanthanid pfluoro-assay (Auto DELFIA; Wallac OY, Turku, Finland). The rT\textsubscript{3} was determined by Radioimmuno Assay (Biodata Diagnostic, Rome, Italy). Infarction size was estimated by serum levels of the isoenzyme creatine kinase–MB fraction (CK-MB). Peak levels of samples obtained every 6 hours until values had returned to normal were used. In addition, levels of troponin T obtained 18±6 hours (mean±SD) from the onset of symptoms were evaluated. The proinflammatory cytokine interleukin 6 (IL-6), which was determined in 28 patients only, was analyzed by enzyme immunoassay (IL-6 high-sensitivity kit; R&D Systems, Abingdon, England). Standard hospital procedures were applied for quantification of C-reactive protein (CRP) and fasting morning samples of cortisol.

ECHOCARDIOGRAPHY

Examinations were performed the third day and after 6 weeks by the same observer. Systolic left ventricular function was evaluated by the mean displacement of the mitral annulus (atrioventricular [AV] plane) from the apical position. This method was chosen because of its relative insensitivity to regional wall motion disturbances. In addition, it is a structure that is generally easily identified in patients with poor echocardiographic windows.

STATISTICAL ANALYSIS

Values concerning the entire study population are presented as mean±SD. When groups are compared, SEM is used. A consequence of the differences in delay between pain onset and the first sample is that in the early intervals, before all of the patients had arrived, the number of patients presented does not include all 47 patients. (The number of patients presented in these intervals are as follows: 19 patients in the 0- to 6-hour period, 31 patients in the 6- to 12-hour period, 32 patients in the 12- to 18-hour period, and 38 patients in the 18- to 24-hour period). When more than 1 sample was acquired during the same period, mean values are presented. Nonparametric tests (Mann-Whitney U test, Wilcoxon signed rank test, and Spearman rank correlation) were used because of the limited number of patients. A 2-tailed P <.05 was regarded as significant. Informed consent was obtained, and the study was approved by the ethics committee of Karolinska Institute at Huddinge University Hospital, Stockholm, Sweden.
The mean concentration of T3 decreased successively after admission, reaching the lowest mean level 24 to 36 hours after pain onset. This level was 19% lower than during the first 6 hours (P = .02). The decrease from the first sample obtained to the lowest value for each patient was 23% ± 12% (P = .001). Compared with controls, levels of T3 were depressed already within the first 6 hours (P = .001) (Table 2). Longitudinal serum profiles for thyroid hormones are shown in Figure 1.

Reverse T3

The serum profile of rT3 was reciprocal to T3; values increased successively, reaching maximal levels 24 to 36 hours after pain onset, which were 22% higher than during the first 6 hours (P = .01) (Figure 1). The mean increase from the first sample to the highest value was 37% ± 32% (P < .001). There was no difference in mean rT3 levels during the first 6 hours between patients and controls. In the 24- to 36-hour interval, the mean level in the patient group was significantly higher: 29 ± 1 ng/dL (0.45 ± 0.02 nmol/L) vs 24 ± 1 ng/dL (0.37 ± 0.01 nmol/L) in controls (P = .005).

Free T4

The mean concentration of the precursor hormone FT4 was slightly higher during the first 18 hours than during the rest of the study period when the mean FT4 level remained unchanged. Patient values fluctuated during the first 5 days without relation to the time for pain onset. Mean values for the whole group of patients did not differ significantly from the control group on any occasion.

Thyrotropin

Mean concentration of thyrotropin declined by 51% between the first 6-hour period and the 24- to 36-hour period (from 2.6 ± 0.5 µIU/L to 1.3 ± 0.1 µIU/L, P < .001). The mean thyrotropin level during the first 6 hours did not differ from the control group. In the 24- to 36-hour interval, patients had significantly lower values than controls (1.3 ± 0.1 µIU/L vs 1.9 ± 0.1 µIU/L, P < .001).

AGE AND SEX

In the patient group, negative correlation was found between age and T3 levels during the first 5 days (r = −0.32, P = .005). Elderly patients tended to have higher FT4 levels, although this was not significant (r = 0.24, P = .11). In the control group, FT4 but not T3 correlated with age (r = 0.29, P = .001). Levels of rT3 and thyrotropin did not correlate with age among patients and controls. The thyroid hormones were not related to sex differences.

SEVERITY OF MYOCARDIAL DAMAGE

No relation was found between the occurrence of new Q waves on the electrocardiogram or whether patients had their first infarction and levels of any of the thyroid hormones during the first 5 days. Serum concentrations of cardiac enzymes did not correlate with mean levels of the thyroid hormones during the first 5 days.

Table 2. Thyroid Hormone Levels in Patients With Myocardial Infarction and Controls

<table>
<thead>
<tr>
<th>Thyroid Hormone</th>
<th>&lt;6 h After Pain Onset</th>
<th>24-36 h After Pain Onset</th>
<th>P Value</th>
<th>First Sample</th>
<th>Maximum Change</th>
<th>P Value</th>
<th>Controls‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3, ng/dL</td>
<td>97 ± 6</td>
<td>67 ± 6</td>
<td>.02</td>
<td>97 ± 6</td>
<td>67 ± 6</td>
<td>&lt;.001</td>
<td>142 ± 2</td>
</tr>
<tr>
<td>rT3, ng/dL</td>
<td>24 ± 2</td>
<td>29 ± 1</td>
<td>.02</td>
<td>25 ± 1</td>
<td>32 ± 1</td>
<td>&lt;.001</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>FT4, ng/dL</td>
<td>1.2 ± 0.1</td>
<td>1.1 ± 0.04</td>
<td>.02</td>
<td>1.2 ± 0.04</td>
<td>Fluctuating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyrotropin, µIU/mL</td>
<td>2.6 ± 0.5</td>
<td>1.3 ± 0.1</td>
<td>&lt;.001</td>
<td>2.0 ± 0.2</td>
<td>0.9 ± 0.1</td>
<td>&lt;.001</td>
<td>2.0 ± 0.1</td>
</tr>
</tbody>
</table>

* indicates total triiodothyronine; † indicates reverse triiodothyronine; and ‡ indicates free thyroxine. To convert nanograms per deciliter to nanomoles per liter (T3 and rT3), multiply by 0.0154. To convert nanograms per deciliter to picomoles per liter (FT4), multiply by 12.87.

Table 3. History of Angina Related to Thyroid Hormones, Inflammation, and Myocardial Damage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Angina (n = 21)</th>
<th>No Angina (n = 26)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3 ng/dL (6 h)</td>
<td>97 ± 6</td>
<td>130 ± 13</td>
<td>.03</td>
</tr>
<tr>
<td>T3 ng/dL (24 h)</td>
<td>97 ± 6</td>
<td>117 ± 6</td>
<td>.008</td>
</tr>
<tr>
<td>FT4 ng/dL (24 h)</td>
<td>1.2 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>.01</td>
</tr>
<tr>
<td>CRP, mg/L (24 h)</td>
<td>33 ± 10</td>
<td>13 ± 5</td>
<td>.04</td>
</tr>
<tr>
<td>IL-6, ng/L (24 h)</td>
<td>64 ± 37</td>
<td>23 ± 7</td>
<td>.21</td>
</tr>
<tr>
<td>Peak CK-MB, µg/L</td>
<td>83 ± 17</td>
<td>176 ± 21</td>
<td>.002</td>
</tr>
<tr>
<td>Tropinon T, µg/L</td>
<td>4.7 ± 0.5</td>
<td>8.2 ± 1.0</td>
<td>.01</td>
</tr>
</tbody>
</table>

* indicates total triiodothyronine; † indicates free thyroxine; and ‡ indicates creatine kinase–MB fraction. To convert nanograms per deciliter to nanomoles per liter (T3), multiply by 0.0154. To convert nanograms per deciliter to picomoles per liter (FT4), multiply by 12.87.

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When subgroup analysis was performed, correlation with cardiac enzymes was found in patients without history of angina pectoris preceding the AMI (n = 26). In patients without angina, peak CK-MB levels correlated negatively with T3 levels on the second day when changes were maximal (r = -0.52, P = .007) and positively with rT3 levels (r = 0.45, P = .02). Similar correlations were found between levels of troponin T and T3 (r = -0.53, P = .009) and between troponin T and rT3 (r = 0.48, P = .02). Levels of FT4, and thyrotropin did not correlate with the cardiac enzymes. No such correlations were found among patients with angina pectoris. Patients without preceding angina pectoris experienced AMIs with enzyme levels twice as high as in patients with angina (peak CK-MB levels, 176 ± 21 μg/L vs 83 ± 17 μg/L, P = .002; troponin T levels, 8.2 ± 1.0 μg/L vs 4.7 ± 0.5 μg/L, P = .01).

VENTRICULAR FUNCTION

Echocardiography during the hospital period showed correlations between the displacement of the AV plane and mean levels of the thyroid hormones during the whole hospital period. Thus, the displacement of the AV plane correlated with levels of T3 (r = 0.36, P = .02), rT3 (r = -0.44, P = .02), and FT4 (r = -0.57, P < .001). No significant correlation with thyrotropin levels was found. Eleven patients with AV plane displacement less than 8 mm, corresponding to a left ventricular ejection fraction of approximately 35%, had a mean concentration of T3 of 84 ± 6 ng/dL (1.3 ± 0.1 nmol/L) compared to 104 ± 6 ng/dL (1.6 ± 0.1 nmol) in other patients (P = .03).

On reexamination 6 weeks later, the displacement of the AV plane for the whole group of patients had increased 0.7 ± 0.2 mm (P = .006). No correlation was found between changes in AV displacement and levels of T3, rT3, or thyrotropin. A modest negative correlation was found with FT4 levels during the hospital period (r = -0.33, P = .045).

ANGINA PECTORIS

Patients with angina pectoris preceding AMI (n = 21) had lower levels of T3 during the first 24 hours than those without angina: 97 ± 6 ng/dL (1.5 ± 0.1 nmol/L) vs 117 ± 6 ng/dL (1.8 ± 0.1 nmol/L) (P = .008) (Table 3 and Figure 2). The lowest values were found in 4 patients with unstable angina (78 ± 13 ng/dL [1.2 ± 0.2 nmol/L]). The differences in T3 levels between those with and those without angina were more pronounced the earlier the samples were obtained. Thus, during the first 6 hours, patients with angina had T3 levels of 97 ± 6 ng/dL (1.5 ± 0.1 nmol/L) vs 130 ± 13 ng/dL (2.0 ± 0.2 nmol/L) in those without angina (P = .002) (Table 3). No differences between the groups were seen regarding rT3 levels. Patients with a history of angina pectoris had higher FT4 levels during the first 24 hours than others: 1.24 ± 0.08 ng/dL (16 ± 1 pmol/L) vs 1.2 ± 0.1 ng/dL (14 ± 1 pmol/L) (P = .01) (Table 3). The highest levels of FT4 were found in patients with unstable angina pectoris (1.5 ± 0.2 ng/dL [20 ± 3 pmol/L]). Levels of thyrotropin did not differ between the groups.

STRESS AND INFLAMMATION

The inflammatory markers IL-6 and CRP increased successively after AMI, with peaks occurring on the second and third days, respectively. On the second day, the mean IL-6 level correlated with peak levels of CK-MB (r = 0.48, P = .009) (Figure 3) and troponin T levels (r = 0.59, P = .002). The mean CRP level on the third day correlated with peak CK-MB levels (r = 0.34, P = .02) and troponin T levels (r = 0.57, P < .001) (Figure 3). Patients with a history of angina pectoris had higher levels of CRP within the first 24 hours (33 ± 10 mg/L vs 13 ± 5 mg/L, P = .04) and
tended to have higher levels of IL-6, although this finding was not significant (64±37 ng/L vs 23±7 ng/L, \( P = .21 \)) (Table 3).

Figure 3 shows correlations on the second day between the mean levels of IL-6 vs T3 and rT3, respectively. Peak levels of IL-6 correlated negatively with T3 levels 24 to 36 hours after pain onset (\( r = -0.49, P = .005 \)) and positively with rT3 levels (\( r = 0.41, P < .05 \)) but not with levels of FT4 or thyrotropin. There were tendencies to similar correlations between peak levels of CRP and levels of T3 (\( r = -0.26, P = .07 \)) and rT3 (\( r = 0.22, P = .15 \)) in the 24- to 36-hour interval, but this was not significant. A significant correlation between CRP and T3 levels was found when mean levels during all 5 days were used (\( r = -0.37, P = .01 \)).

Fasting morning samples of cortisol were higher during the first days after AMI and declined successively. The maximum level was reached on the second day at 17±7 µg/dL (46±190 nmol/L). No correlation was found with levels of cardiac enzymes. Mean levels of cortisol during the first 5 days correlated with levels of rT3 (\( r = 0.45, P = .002 \)) and FT4 (\( r = 0.29, P = .048 \)) but not with levels of T3 or thyrotropin.

**MORTALITY**

Thyroid hormone levels differed between patients who died and the survivors. This was most obvious for T3 (Figure 4). Patients who died within the first year of AMI (n=6) had lower mean levels of T3 and higher levels of rT3 during the hospital period. Their FT4 levels tended to be higher (\( P = .07 \)), whereas their thyrotropin levels were lower. Values are given in Table 4. The dif-

![Figure 3. Scatterplots showing relation between interleukin 6 (IL-6) on day 2 and total triiodothyronine (T3) on day 2, reverse T3 (rT3) on day 2, peak creatine kinase-MB fraction (CK-MB), troponin T, and C-reactive protein (CRP) on day 3 vs peak CK-MB and troponin T, respectively. Solid lines indicate regression lines; dotted lines, 95% confidence intervals; and open circles, values for each patient. To convert nanograms per deciliter to nanomoles per liter (T3 and rT3), multiply by 0.0154.](http://archinte.jamanetwork.com/pdfaccess.ashx?url=/data/journals/medic/6329/)
ference in T₃ levels during the hospital period was significant between those who had died within 2 years following AMI (n = 11) and survivors.

The thyroid hormone system was transiently down-regulated in otherwise euthyroid individuals during the acute phase of myocardial infarction. The changes in hormone levels were rapid during the first 24 hours after pain onset. Maximal changes were found in the 24- to 36-hour period. Compared with healthy controls, significant down-regulation was already evident on admission, indicating that the reaction may have started directly before or after coronary occlusion.

The suppression of T₃ was more pronounced in patients who were old, had poor heart function, or had intense inflammatory reaction. Patients who died during follow-up had the most pronounced T₃ level depression. The finding of lower T₃ levels in the older patients was probably not due to age. In the control group, there was no correlation between age and T₃ levels. In the literature, opinions are conflicting on whether there is an age-dependent reduction in T₃ levels in healthy individuals.²⁰⁻²² In a study of 7248 healthy euthyroid individuals aged 3 months to 106 years, it was concluded that little change occurred after age 25 years.²³ The degree of hormone level depression did not seem to be related to the severity of AMI, as estimated by levels of cardiac enzymes, or by the occurrence of new Q waves on the electrocardiogram. This lack of relation has previously been reported but not explained.³

The cause of the euthyroid sick syndrome is still poorly understood. The pathogenesis is probably multifactorial. The role of cytokines has recently been put into focus by studies demonstrating that administration of interferon alfa and IL-6 can induce changes in the thyroid hormone system, mimicking the euthyroid sick syndrome.²⁴,²⁵ In our study, we found negative correlations between levels of IL-6 and T₃, and between levels of CRP and T₃, supporting this hypothesis. The increases in IL-6 and CRP levels were apparently related to the extent of myocardial damage and necrosis, since relatively strong correlations were found with cardiac enzymes.

Differences in levels of inflammatory mediators in patients with and without angina pectoris before the AMI may help explain why there was no correlation between cardiac enzymes and thyroid hormones. Patients with angina pectoris had higher levels of IL-6 and CRP and also more depressed thyroid hormone systems in early samples than others. Possibly, thyroid level depression was present before the infarction process started. Since patients with angina had infarctions that were much smaller than those in patients without angina, the relative rise in IL-6 and CRP levels after AMI was modest. When patients with and without angina were analyzed separately, correlation between cardiac enzymes and thyroid hormones was indeed found in patients without angina, but not in patients with angina, which seems to support this reasoning. To validate this hypothesis, it is necessary to study the thyroid hormones prospectively in patients with angina pectoris. Little has been done yet in this field of interest. The only publication, to our knowledge, is a report on 187 patients with coronary heart disease in whom signs of subclinical hypothyroidism was demonstrated in 60% of the patients.²⁶

The fact that patients with preceding angina had more depressed thyroid hormone systems on admission...
and subsequently developed smaller infarctions does not prove that there is a causal relationship. It is, however, plausible that down-regulation of the thyroid hormone system may be an advantage if it is present when AMI strikes because the oxygen demand of the myocardium may be reduced when the metabolic rate is diminished.

Whether the euthyroid sick syndrome is an advantage after AMI when damage has occurred and heart failure might be emerging may be questioned. Circumstances make it adequate to hypothesize that it may be deleterious. Thyroid hormones affect ventricular function through stimulation of sarcoplasmatic calcium adenosinetriphosphatase activity and expression. 27 This adenosinetriphosphatase is responsible for the removal of calcium from the cytosol during diastole, thereby allowing for uncoupling of actin-myosin cross-bridging. It is therefore of major importance for diastolic heart function. It also regulates the quantity of calcium in the sarcoplasmatic reticulum available for systolic contraction and is thus hereby also important for the systolic function of the heart. 28 When the thyroid hormone system is down-regulated in the short term in AMI, intracellular calcium handling is affected in a way that may contribute to myocardial stunning and reperfusion injury due to calcium overload. 29 Furthermore, down-regulation of the thyroid hormone system leads to increase in systemic vascular resistance and increased cardiac afterload. If the heart is unable to cope with this, cardiac output will be reduced.

If these seemingly disadvantageous effects of decreased production of biologically active T3 were important, patients with more marked hormone derangement would have a worse prognosis regarding heart function and survival. In our study, we found no indications of such deleterious effects on the recovery of systolic function as measured by echocardiographic reexamination 6 weeks after AMI. However, we did find an association between the degree of thyroid hormone level depression and mortality.

Triiodothyronine has profound effects on the cardiovascular system, and it is likely that a short-term down-regulation does affect outcome of AMI. With prospective studies on larger patient materials, evaluating stringent clinical end points and taking into consideration confounding factors such as age and infarction size, the cause and consequences of the euthyroid sick syndrome in AMI can be further clarified. Maybe this biochemical marker, in addition to others, can be helpful in predicting the outcome of our patients with coronary artery disease. 30 If this marker can be verified to be of significant importance for outcome in several prospective investigations, intervention studies on the thyroid hormone system may be initiated.

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