Thyroid hormone and recovery of cardiac function in patients with acute myocardial infarction: a strong association?

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Abstract

Objective: This study investigated whether changes in thyroid hormone (TH) in plasma are associated with the recovery of cardiac function in patients with acute myocardial infarction (AMI). Previous experimental studies have provided evidence of potential implication of TH signaling in post-ischemic recovery of cardiac function.

Methods: A total of 47 patients with AMI and early reperfusion therapy were included in this study. Myocardial injury was analyzed by peak creatinine kinase–MB (CKMB) and cardiac function was assessed by echocardiographic left ventricular ejection fraction (LVEF%). Recovery of function (ΔEF%) was estimated as the difference of LVEF% between 48 h and 6 months (6 mo) after AMI. Total triiodothyronine (T3), thyroxine (T4), and TSH were measured in plasma at different time points (24 h, 48 h, 5 d, and 6 mo).

Results: A significant correlation between LVEF% and T3 (r=0.5, P=0.0004) was found early after AMI (48 h), whereas no correlation was observed between CKMB and T3 (r=0.04, P=0.81). A strong correlation was found between ΔEF% and total T3 (r=0.64, P=10−6) at 6 mo after AMI. Furthermore, multivariate regression analysis revealed that T3 at 6 mo (r=0.64, r2=0.41, P=10−6) was an independent determinant of ΔEF%.

Conclusion: Changes in T3 levels in plasma are closely correlated with the early and late recovery of cardiac function after AMI. T3 levels at 6 mo appear to be an independent predictor of late functional recovery.

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Introduction

Acute and chronic illnesses can cause changes in thyroid hormone (TH) profile, a condition known as ‘non-thyroidal illness syndrome’ (1–3). This syndrome affects nearly 70% of patients hospitalized with diseases of various etiologies (4). The physiological significance of this response is not fully understood, and there is a long-lasting dilemma whether this abnormality needs correction (1, 2).

Low triiodothyronine (T3) state is common in severe chronic heart failure (5), acute myocardial infarction (AMI) (6–8), and cardiac surgery (9). Furthermore, changes in TH in plasma are linked to high mortality both in patients with heart failure (5) and those with AMI (8), indicating potential implication of TH signaling in the post-ischemic cardiac recovery. Interestingly, this hypothesis has recently been addressed in experimental models of ischemia–reperfusion and myocardial infarction in animals and accumulating evidence reveals that TH is critical for the response of the myocardium to ischemic stress and TH may possess cytoprotective properties that are ‘silent’ in healthy tissue, manifesting only during stress (10–13).

Based on this evidence, this study investigated whether changes in TH in plasma are associated with early and late recovery of cardiac function in patients with AMI. This issue has not been previously addressed and may be of clinical relevance. AMI results in loss of cardiac function due to tissue necrosis, reperfusion injury, and cardiac remodeling, causing significant morbidity and mortality with a high risk (30–75%) of developing heart failure despite modern reperfusion and pharmacological therapy (14–17).

Methods

Patients and measurements

A total of 47 patients (61.7% male, mean age 62.3 ± 10.2 years) admitted to the emergency cardiac care and diagnosed with ST elevation AMI (STEMI) were included in this study. AMI diagnosis and treatment was based on the guidelines of the European Society of
Cardiology 2008 (18). All patients with AMI underwent coronary angiography and primary percutaneous coronary intervention (PCI) within 120 min after first medical contact.

Of the 67 patients in total, 12 had a history of coronary artery disease (CAD), thyroid dysfunction (based on medical history and treatment), amiodarone treatment, clinical evidence of sepsis, cachexia, or other severe systemic disease (e.g., cancer, autoimmune disease, and chronic renal disease) were not included in the study. Furthermore, eight patients with acute pulmonary edema, stent thrombosis, new AMI, death, or need for coronary artery bypass graft surgery (CABG) during the 6-month follow-up period were also excluded. Thus, of the 67 patients with STEMI that remained unchanged during the following 6 mo.

All patients were given standard therapeutic treatment to acute coronary syndrome protocol and subjected to echocardiographic evaluation within 48 h from admission and 6 months (6 mo) later. At hospital discharge, all patients were given standard therapeutic treatment that remained unchanged during the following 6 mo.

The local ethics review committee approved the study. Declaration of Helsinki. All the enrolled patients signed an informed consent.

Measurement of myocardial injury

Myocardial injury was measured from peak value of CKMB after serial measurements of CKMB on admission and at 6, 12, 24, and 48 h. CKMB normal values were <25 U/l. Diagnosis of AMI was also based on qualitative troponin assessment.

Measurement of left ventricular ejection fraction

Left ventricular ejection fraction (LVEF) was measured with transthoracic echocardiography (General Electric Vigitum Ultrasound System, with a 3.5 MHz transducer, Pollards Wood, Chalfont St. Giles, UK) according to the guidelines set by the American Society of Echocardiography. Left ventricular end-diastolic diameter (mm), left ventricular end-systolic diameter (mm), and fractional shortening were also determined. Patients were divided into two groups according to the change of LVEF (ΔEF%) between 6 mo and 48 h after AMI. The analysis of the distribution of ΔEF% values showed a median value of 5.0, a mean value of 5.7, and a s.d. of 5.5. Thus, on the basis of this analysis, patients were divided into two groups: group A (ΔEF% < 5%) and group B (ΔEF% ≥ 5%).

Measurement of TH in plasma

Changes in TH profile were assessed in all patients at 24 h, 48 h, 5 d, and 6 mo after myocardial infarction. Blood samples were collected from an antecubital vein, and after centrifugation, serum was collected and total T₁ and thyroxine (T₄) were determined using a Hitachi Modular E170 Chemistry Analyzer, whereas TSH was measured using ADVIA Centaur Immunoassay System (Siemens, Athens, Greece). The reference intervals for our laboratory were as follows: T₁, 1.2–2.5 nmol/l; T₄, 66–181 nmol/l; and TSH, 0.40–4.2 μIU/ml.

Statistical analysis

Continuous variables are expressed as mean ± s.d., whereas categorical variables are expressed as numbers or percentages. Potential correlations between continuous variables were evaluated by Pearson’s product-moment (Pearson r) or by Spearman’s rank correlation coefficient (Spearman r) as appropriate. Independent sample t-test or non-parametric Mann–Whitney U test (for continuous variables) and χ² test (for dichotomized variables) were used to assess differences in parameters between groups. All tests were two-sided. A P value <0.05 was considered statistically significant. Continuous variables (T₁, T₄, TSH, and creatinine) and dichotomized variables (gender, Killip class) were entered in the linear multiple logistic regression model using a
stepwise method to identify potential independent determinants of EF% change (ΔEF%). Statistical analysis was performed using statistical software package (SPSS 17.0, IBM SPSS Chicago, IL, USA).

Results

Patients’ baseline characteristics

Patients’ baseline characteristics are shown in Table 1. All patients were subjected to optimal reperfusion strategy consisting of primary PCI. Post-intervention medical therapy was maximal according to current recommendations including β-blockers, angiotensin converting enzyme inhibitors, statins, and anti-platelet therapy. Aldosterone antagonists were administered in patients with EF% <40% whereas diuretics were administered depending on the symptoms and clinical evaluation. A small percentage of patients (12.8%) were on nitrate treatment (Table 1). Functional and standard laboratory data of all patients early and late after AMI are shown in Table 2.

TH and early functional recovery

Total T₃ levels in plasma at 48 h were found to be significantly correlated to EF% at 48 h (r = 0.50, P = 0.0004; Fig. 1A), although no correlation was shown between T₃ levels and the peak value of CKMB (r = −0.04, P = 0.81; Fig. 1B).

No significant correlations between EF% at 48 h and T₄ or TSH at 48 h were observed.
Table 3 Group characteristics. Data are presented as percent (%)

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=22; ΔEF% &lt;5%)</th>
<th>Group B (n=25; ΔEF% ≥5%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean)</td>
<td>64.6 ± 9.9</td>
<td>60.3 ± 10.4</td>
<td>0.16</td>
</tr>
<tr>
<td>± (s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>45.5/54.5</td>
<td>76/24</td>
<td>0.032</td>
</tr>
<tr>
<td>Smoking</td>
<td>86.4</td>
<td>88</td>
<td>0.87</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>63.6</td>
<td>72</td>
<td>0.54</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31.8</td>
<td>28</td>
<td>0.78</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80.8</td>
<td>89.7</td>
<td>0.36</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>81.8</td>
<td>88</td>
<td>0.55</td>
</tr>
<tr>
<td>Culprit vessel (LAD/LCX/RCA)</td>
<td>86.3/4.6/9.1</td>
<td>64/20/16</td>
<td>0.18</td>
</tr>
<tr>
<td>No. of diseased vessels (1/2/3; mean ± s.d.)</td>
<td>36.4/63.6/0</td>
<td>56.36/8</td>
<td>0.10</td>
</tr>
<tr>
<td>Peak CKMB (U/l)</td>
<td>332 ± 253</td>
<td>220 ± 256</td>
<td>0.14</td>
</tr>
<tr>
<td>Killip class (I/II/III)</td>
<td>22.7/40.9/36.3</td>
<td>48/48/4</td>
<td>0.014</td>
</tr>
</tbody>
</table>

P<0.05 is presented in boldface.

ΔEF% < 5% (groups B and A respectively). Similarities and differences regarding the characteristics of both groups are shown in Tables 3 and 4.

T₃ levels were found to be low in most of the patients at 24 h from admission and were significantly different between the two groups at 24 h (1.12 ± 0.05 in group A versus 1.27 ± 0.05 in group B, P < 0.05). In addition, T₃ levels at 48 h, 5 d, and 6 mo were significantly lower in group A compared with group B (1.16 ± 0.04, 1.23 ± 0.04, and 1.23 ± 0.04 vs 1.37 ± 0.05, 1.51 ± 0.05, and 1.77 ± 0.07, respectively, P < 0.05). Thus, T₃ levels remained nearly unchanged from baseline values measured at 24 h in group A, whereas in group B, T₃ levels progressively restored to normal values after 6 mo (Fig. 2A).

T₄ levels were not significantly different between the two groups during the acute phase of myocardial infarction. In fact, T₄ levels at 24 h, 48 h, and 5 d were 87.9 ± 5.0, 89.7 ± 4.4, and 91.3 ± 4.3 in group A versus 95.8 ± 2.8, 98.6 ± 2.8, and 95.1 ± 5.3 in group B, respectively, P > 0.05. At 6 mo, T₄ levels were significantly lower in group A compared with group B (89.4 ± 4.6 vs 107.2 ± 4.7, P < 0.05; Fig. 2B).

TSH levels were not significantly different between the two groups during the acute phase of myocardial infarction. In fact, TSH levels at 24 h, 48 h, and 5 d were 2.2 ± 0.4, 2.6 ± 0.6, and 3.0 ± 0.84 in group A versus 1.6 ± 0.2, 1.7 ± 0.14, and 1.8 ± 0.15 in group B, respectively, P > 0.05. At 6 mo, TSH levels were significantly higher in group A compared with group B (2.9 ± 0.55 vs 1.46 ± 0.16, P < 0.05; Fig. 2C).

Determinants of late cardiac recovery after AMI

A linear multiple logistic regression model with a stepwise method was used to identify potential independent determinants of EF% change (ΔEF%). Thus, total T₃ at 6 mo, gender and high-density lipoprotein (HDL) at early phase were found to be independent determinants of ΔEF% (Table 5). The variables, which were entered into the statistical model and found not to be independent predictors of ΔEF%, included age, smoking, family history of CAD, diabetes, hypertension, dyslipidemia, Killip score, culprit vessel, number of diseased vessels, peak CKMB, THs (T₃ 24 h, T₄ 24 h, TSH 24 h, T₃ 48 h, T₄ 48 h, TSH 48 h, T₃ 5 d, T₄ 5 d, TSH 5 d, T₄ 6 mo, and TSH 6 mo), Hct, low-density lipoprotein (LDL), and creatinine early after AMI and Hct, LDL, HDL, and creatinine late after AMI. The regression equation, which predicted recovery of EF% according to T₃ values at 6 mo for male, was as follows: ΔEF% = −12.8 + (9.2 × (T₃ at 6 mo)) + (0.15 × HDL) with ΔEF% to be lesser by 4.3% in female group for any given value of T₃ and HDL (Fig. 3).

Discussion

Although it has been long recognized that changes in TH profile occur in patients with AMI, the physiological significance of this response has not been extensively

Table 4 Functional and laboratory data, early (during hospital stay) and late (6 mo), after AMI. Data are presented as percent (%) or mean ± s.d.

<table>
<thead>
<tr>
<th></th>
<th>Early after AMI</th>
<th>Late after AMI</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>38.1 ± 8.3</td>
<td>44.4 ± 10.2</td>
<td>0.022</td>
</tr>
<tr>
<td>LVFS%</td>
<td>24.5 ± 7.7</td>
<td>31.6 ± 6.6</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>49.9 ± 5.5</td>
<td>49.2 ± 5.3</td>
<td>0.63</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>37.6 ± 5.7</td>
<td>33.6 ± 4.6</td>
<td>0.011</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>41.0 ± 4.3</td>
<td>42.3 ± 3.4</td>
<td>0.25</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.07 ± 0.36</td>
<td>0.92 ± 0.17</td>
<td>0.07</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>148 ± 38</td>
<td>150 ± 43</td>
<td>0.91</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>43.1 ± 10.7</td>
<td>40.9 ± 10.7</td>
<td>0.47</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

P<0.05 is presented in boldface.
TH and early functional recovery

Early after myocardial infarction, cardiac function is compromised due to ischemic injury and also to reperfusion injury in the case of early reperfusion therapies (23). During the acute event, a number of changes in the neurohormonal and inflammatory systems occur with potential physiological consequences. Decrease in TH levels is a frequent observation and is considered as an energy adaptation to acute stress, which may lead to cardioprotection. However, TH can control contractile function via the regulation of contractile proteins, calcium handling, and ion channels (24). Thus, TH changes early after AMI may affect cardiac function with potential hemodynamic consequences. This issue, although of clinical relevance, has not been previously addressed. However, in this study, we provide some evidence showing that T₃ levels in plasma early after AMI were strongly correlated with LVEF, whereas no correlation was seen with T₄ and TSH. These data probably indicate that TH may be implicated in post-ischemic functional recovery. Several lines of evidence support this assumption. T₃ treatment at reperfusion was shown to improve post-ischemic recovery of function while limiting apoptosis in experimental models of ischemia–reperfusion (25). This response was contrary to detrimental effect caused by dobutamine, which is often used to improve post-ischemic hemodynamics (26). Furthermore, T₃ cardioprotection was shown to be mediated via the suppression of the pro-apoptotic p38MAPK signaling pathway and be TRa₁ receptor dependent (13, 25).

More importantly, in accordance with this experimental evidence, T₃ treatment resulted in marked increase of post-surgery cardiac function in patients undergoing cardiac bypass operations (27, 28).

Table 5 Multivariate linear regression analysis revealed that T₃ at 6 mo and gender and high-density lipoprotein (HDL) at early phase were independent predictors of myocardial function recovery (ΔEF%) after acute myocardial infarction.

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>r</th>
<th>r²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₃</td>
<td>0.64</td>
<td>0.41</td>
<td>0.000001</td>
</tr>
<tr>
<td>T₃ + gender</td>
<td>0.71</td>
<td>0.50</td>
<td>0.006</td>
</tr>
<tr>
<td>T₃ + gender + HDL</td>
<td>0.76</td>
<td>0.58</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Figure 2 Time course analysis of T₃ (A), T₄ (B), and TSH (C) after myocardial infarction in patients with poor recovery of function (group A, ΔEF% <5%) and patients with better recovery of function (group B, ΔEF% ≥5%). A different pattern of T₃ recovery is observed between the two groups. *P<0.05 versus group A.

explored (6–8). Thus, this study provides some evidence showing a potential link of changes in TH in plasma to early and late functional recovery in patients with AMI.

Patients with AMI and early reperfusion therapy were included in this study. Myocardial injury was estimated by peak CKMB and cardiac function was assessed by echocardiographic LVEF (LVEF%). LVEF% seems to be a suitable indicator of cardiac performance and thus it has been used in several studies for the assessment of functional recovery after myocardial infarction, testing the efficacy of applied treatments and as a marker of prognosis (19–21). Changes in TH profile were assessed by measuring T₃, T₄, and TSH in plasma at different time points after AMI. In particular, total T₃ has previously been shown to be correlated to functional status and an index of the disease outcome (5, 8, 22).
Non-ischemic viable myocardium after myocardial infarction undergoes a series of structural and functional changes, known as cardiac remodeling (15). Thus, nearly half of the patients with AMI show small or absence of left ventricular functional recovery at 6 mo, despite early reperfusion treatments and intense anti-remodeling treatments (20). According to these data, nearly half of our patients showed <5% difference in the recovery of LVEF (ΔEF%). Interestingly, time course analysis of TH changes in plasma revealed poor recovery of T3 levels in this group of patients, indicating a potential association of T3 to cardiac function late after AMI. In fact, further analysis revealed that T3 levels at 6 mo were an independent predictor of ΔEF%. In addition, ΔEF% was strongly correlated to 6 mo T3 levels in plasma.

The potential implication of TH in post-ischemic recovery of function has been recently demonstrated in animal and cell-based models. Thus, induction of myocardial infarction in animals resulted in a series of changes in TH signaling including alterations in T3 tissue levels, enzyme type 3 deiodinase activity, and in the expression of TH receptors all resulting in changes in T3-dependent transcription activity (12, 29, 30). Interestingly, TRα1 receptor, which is predominantly expressed in the myocardium and regulates important structural and functional genes, was shown to be an important component of the growth kinase signaling pathways that are activated early after AMI and promote pathological growth (29, 31). In accordance with this evidence, induction of hypothyroidism resulted in exacerbation of cardiac remodeling (32, 33), whereas TH treatment improved post-ischemic cardiac hemodynamics in animal models of myocardial infarction (10, 34–38). Here, it should be noted that low T3 levels have also been associated with worse neurological outcome and T3 appears to be a predictor of functional improvement in acute ischemic stroke (39). This is in accordance with recent experimental evidence showing the reparative effect of TH after neuronal injury (40).

**Limitations of the study**

To our knowledge, this study is the first to show potential association of early and late recovery of function in patients with AMI. However, this study has not included a large number of patients, which would allow the investigation of possible association of TH with mortality after AMI. Interestingly, this issue has been addressed by a previous study (8). Furthermore, assessment of cardiac function was performed with echocardiography, which does not allow accurate measurement of specific indices of cardiac remodeling. Finally, the patients included in this study were urgently admitted to the hospital so that TH disorders were excluded on the basis of the medical history and treatment, but silent thyroid dysfunction cannot be excluded.

In conclusion, changes in T3 levels in plasma are closely correlated with the early and late recovery of cardiac function after AMI. T3 levels at 6 mo appear to be an independent predictor of late functional recovery.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**References**


**Figure 3** Scatterplot showing a strong correlation between ΔEF% and T3 at 6 mo in both females and males. Regression equation that estimates recovery of function is as follows: ΔEF% = −12.8 + (9.2 × (T3 at 6 mo)) + (0.15 × HDL) with ΔEF% to be lesser by 4.3% in female group for any given value of T3 at 6 mo and HDL at early phase.


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