**Thyroid hormone is a critical determinant of myocardial performance in patients with heart failure: potential therapeutic implications**

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**Abstract**

**Objective**: Previous experimental studies have provided evidence showing that changes in thyroid hormone signaling correspond to alterations in myocardial function in animal models of heart failure. The present study further explores whether thyroid hormone alterations are correlated with the functional status of the myocardium in patients with heart failure.

**Methods**: In this study, 37 patients with mean ejection fraction (EF%) of 26.2 (8.2) were included. Myocardial performance was assessed by echocardiography and cardiopulmonary exercise testing. Total tri-iodothyronine (T3), thyroxine, and TSH levels were measured in plasma.

**Results**: Total T3 was strongly correlated with VO2max ($r=0.78$, $P<2 \times 10^{-8}$). Furthermore, multivariate analysis revealed that total T3 was an independent predictor of VO2max ($P=0.000 005$). A weaker but significant correlation was also found between total T3 and EF% ($r=0.56$, $P=0.0004$), systolic ($r=0.43$, $P=0.009$) and diastolic ($r=0.46$, $P=0.004$) blood pressure.

**Conclusions**: Changes in thyroid hormone were closely correlated to myocardial functional status in patients with heart failure. These data probably indicate a possible role of thyroid hormone in the pathophysiology of heart failure and confirm previous experimental reports.

**Introduction**

Although several genes encoding the expression of important regulatory and structural proteins in the myocardium are thyroid hormone responsive (1, 2), the role of thyroid hormone in the pathophysiology of heart failure has not been adequately explored. Initial studies demonstrated that reduction in plasma tri-iodothyronine (T3) without significant changes in thyroxine (T4) can occur in patients with cardiac or non-cardiac illnesses (1, 3). This is known as the ‘low T3 state’ and has been considered as an adaptive response, which needs no treatment (4). However, it is now recognized that low total T3 levels in plasma may be an independent factor for mortality in patients with heart failure (5, 6), indicating that thyroid hormone probably has an important role in the pathophysiology of heart failure. Such a possibility is further supported by recent experimental studies which clearly demonstrate that changes in thyroid hormone–thyroid nuclear receptor axis occur in the failing myocardium and correlate to cardiac dysfunction (7–10). Based on this evidence, the present study has further explored whether thyroid hormone can be correlated to functional myocardial status in patients with dilated cardiomyopathy of ischemic or non-ischemic origin.

**Methods**

**Patients and measurements**

Thirty-seven consecutive patients with mean left ventricular ejection fraction (EF) of 26.2 (8.2) were studied; 25 (67.6%) had non-ischemic dilated cardiomyopathy and 12 (32.4%) had post-ischemic dilated cardiomyopathy. The diagnosis of the dilated cardiomyopathy was established in all patients at least 6 months prior to the study. All patients were in stable clinical condition (no change in clinical symptoms, no hospitalization and i.v. inotropic treatment for 3 weeks prior to hospital admission and during the study) and on conventional medical treatment for heart failure with diuretics, angiotensin–converting enzyme inhibitors, and ß-blockers. Treatment was unchanged for at least 2 months prior to admission and remained unchanged during the study. All patients were admitted to the hospital for scheduled follow-up. Baseline characteristics of these
patients are shown in Table 1. The investigation conformed to the principles outlined in the Declaration of Helsinki. Post-ischemic dilated cardiomyopathy was diagnosed by coronary artery disease found on coronary angiography or by documented myocardial infarction. Non-ischemic dilated cardiomyopathy was diagnosed based on the absence of coronary artery disease on coronary angiography. Coronary angiography was performed at the time of diagnosis of the disease. Patients with clinical evidence of sepsis, cachexia, other severe systemic disease or primary thyroid disorder were not included in this study. All patients had standard laboratory tests (T3, T4, thyrotropin (TSH), hematocrit (Hct), creatinine, etc.) and subjected to echo-cardiographic evaluation and cardiopulmonary exercise testing. The laboratory tests and echo-cardiographic evaluation were initially performed during the first hospital admission, while cardiopulmonary exercise testing was performed within 2 weeks thereafter. In a subgroup of patients (n = 8), we performed sequential measurements of T3, T4, and TSH within 2 weeks to check for variation in thyroid hormone levels were highly reproducible.

### Thyroid hormone measurements

Total T3 and T4, and TSH were measured in plasma. The normal values of thyroid hormones and TSH were ranged from 0.6 to 1.6 ng/ml for total T3, 58 to 156 nmol/l (4.5 to 12 µg/dl) for total T4, and 0.3 to 3.8 mIU/l for TSH.

### Echocardiographic study

Transthoracic echocardiography recordings were taken with General Electric Vivid 7 system using a 2–4 MHz probe. Images at parasternal long-axis, short-axis, and four-chamber view were obtained. Left ventricular end-diastolic diameter, left ventricular end-systolic diameter, fractional shortening, and left ventricular EF (LVEF) were measured according to the guidelines set by the American Society of Echocardiography.

### Cardiopulmonary exercise testing

Patients performed a cardiopulmonary exercise stress test to evaluate their exercise capacity by measuring peak oxygen consumption (VO2max, ml/kg per min). Exercise testing with respiratory gas exchange measurements was performed using the MedGraphics CPX/MAX (Medical Graphics Corp., St Paul, MN, USA) measuring system, while patients exercised on a treadmill according to the Dargie protocol (11). Peak oxygen consumption during exercise was recorded as the mean value during the last minute of exercise.

### Statistical analysis

All data are expressed as mean (s.d.). Potential correlations between continuous variables were evaluated by the Pearson product–moment (Pearson r) or by the Spearman 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. A P value of 0.05 was considered statistically significant. Continuous variables (age, systolic and diastolic blood pressure, T3, T4, TSH, LVEF, and Hct) were entered in the linear multiple logistic regression model using a stepwise method to identify potential independent determinants of VO2max.

### Results

#### Left ventricular performance and thyroid hormone levels in plasma

T3 levels in plasma were significantly correlated to the functional indices measured in the study. In fact, T3 levels were strongly correlated with VO2max (r = 0.78, P = 2 × 10-8), while no significant correlations were found between VO2max and T4 or TSH (Fig. 1).

A weaker but significant correlation between T3 and LVEF% (r = 0.56, P = 0.0004), systolic (SBP, r = 0.43, P = 0.009) and diastolic (DBP, r = 0.46, P = 0.004) blood pressure was also observed (Fig. 2). No significant correlations were found between LVEF% or SBP or DBP and T4 or TSH.

In a multivariate linear logistic regression analysis that included T3, T4, TSH, age, LVEF%, SBP, DBP, and Hct as possible predictors of VO2max values, only total T3 and LVEF% were found to be associated with VO2max.
Furthermore, total T₃ was the strongest independent determinant of VO₂max (Table 2).

**Amiodarone and thyroid hormone levels in plasma and left ventricular performance**

Patients with amiodarone treatment had a small but non-significant decrease in T₃ and a trend towards an increase in T₄. In addition, TSH was found to be significantly increased in patients receiving amiodarone (Table 3). However, VO₂max, LVEF%, SBP, and DBP were not different between patients with and without amiodarone treatment (Table 3). These results are consistent with previous reports (12).

Since amiodarone treatment could have influenced the correlation of thyroid hormone values with left ventricular performance, we performed a separate analysis in heart failure patients not treated with amiodarone. T₃...
levels were also strongly correlated with VO2max \( (r=0.84, P=10^{-6}) \), while no significant correlation was found between VO2max and T4 (Fig. 3). Interestingly, in this subgroup of patients, TSH showed a significant negative correlation with VO2max values \( (r=-0.62, P=0.002; \text{Fig. 3}) \). A significant correlation between T3 and LVEF% \( (r=0.53, P=0.009) \), SBP \( (r=0.46, P=0.03) \) and DBP \( (r=0.49, P=0.02) \) was also observed.

Discussion

There is accumulating experimental evidence showing that changes in thyroid hormone and/or thyroid hormone receptors (TRs) can occur in cardiac hypertrophy and myocardial infarction, and this seems to be of physiological relevance \((7–10)\). More importantly, after myocardial infarction in rats, changes in myosin isoform expression in the myocardium are evident, corresponding to exacerbation of cardiac dysfunction. This response is thought to be due to the TRalpha1 apo-receptor repressive activity \((10)\). Interestingly, this type of TR appears to be overexpressed in human myocardium in patients with dilated cardiomyopathy \((13)\). Thus, it is likely that thyroid hormone signaling may have a critical role in the pathophysiology of heart failure.

As a ‘proof of concept’, the present study shows a close correlation between changes in thyroid hormone in plasma and myocardial performance as that assessed by blood pressure measurements, left ventricular EF and peak oxygen consumption on cardio-respiratory exercise testing. In fact, total T3 levels in plasma were significantly correlated with LVEF\% in accordance with previous reports \((14)\). A weak positive correlation between T3, and systolic and diastolic blood pressure

Table 2  Tri-iodothyronine (T3) and left ventricular ejection fraction % (LVEF\%) are independent predictors of VO2max in patients with dilated cardiomyopathy (multivariate linear regression analysis).

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>r</th>
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<th>P value</th>
</tr>
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<tr>
<td>T3</td>
<td>0.78</td>
<td>0.61</td>
<td>0.000 005</td>
</tr>
<tr>
<td>LVEF%</td>
<td>0.84</td>
<td>0.70</td>
<td>0.006</td>
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<table>
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<tr>
<th>Excluded variables</th>
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<tr>
<td>DBP</td>
<td>0.11</td>
<td>0.71</td>
</tr>
<tr>
<td>SBP</td>
<td>0.14</td>
<td>0.77</td>
</tr>
<tr>
<td>Age</td>
<td>0.02</td>
<td>0.94</td>
</tr>
<tr>
<td>Hct</td>
<td>0.09</td>
<td>0.80</td>
</tr>
<tr>
<td>T4</td>
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</tr>
<tr>
<td>TSH</td>
<td>-0.22</td>
<td>0.96</td>
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Table 3  Left ventricular performance and thyroid hormone levels in patients with and without amiodarone treatment. Data are presented as mean (s.d.).

<table>
<thead>
<tr>
<th>Patients without amiodarone treatment</th>
<th>Patients with amiodarone treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>Total T3 (ng/ml)</td>
<td>0.86 (0.2)</td>
<td>0.80 (0.21)</td>
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<tr>
<td>Total T4 (\mu g/dl)</td>
<td>7.7 (1.1)</td>
<td>8.8 (1.8)</td>
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<tr>
<td>TSH (mIU/l)</td>
<td>2.1 (1.9)</td>
<td>4.8 (3.8)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>28 (9.0)</td>
<td>25 (6.1)</td>
</tr>
<tr>
<td>VO2max (ml/min per kg)</td>
<td>18.0 (5.7)</td>
<td>16.3 (6.0)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>105 (17)</td>
<td>106 (16)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>68.0 (9.5)</td>
<td>67.8 (8.7)</td>
</tr>
</tbody>
</table>

Figure 3  Scatterplots showing correlation of T3 (A), T4 (B), and TSH (C) with maximal oxygen consumption (VO2max) in patients with dilated cardiomyopathy without amiodarone treatment.
was also observed. It is interesting to note that lower T3 levels in the setting of heart failure were not associated with increased diastolic pressure, as has been observed in hypothyroid and subclinical hypothyroid patients (15, 16). This probably reflects different pathophysiological mechanisms underlying these two conditions.

The present study provides additional evidence of the importance of T3 on the cardio-respiratory exercise testing response in patients with heart failure: a strong correlation between total T3 and the peak oxygen consumption was observed and the variability in VO2max could be explained by almost 61% by changes in T3 values. Furthermore, multivariate analysis showed that total T3 was the strongest independent determinant of VO2max. At this point, it should be noted that the present study included a number of patients treated with amiodarone, which can interfere with thyroid hormone signaling and potentially influence our results. However, a persistent correlation between triiodothyronine and myocardial performance was still observed in the absence of amiodarone treatment. Furthermore, no significant differences in T3 levels and functional indices were found between the amiodarone treated and non-treated patients. It is interesting to note that abnormal thyroid hormone function has previously been shown to correlate to NYHA classification regardless of amiodarone treatment (3). Taken together, these data appear to be of important clinical significance. Peak oxygen consumption provides a precise estimate of aerobic capacity and is considered to be a sensitive index to assess functional status in patients with heart failure (17). Moreover, peak oxygen consumption independently predicts mortality (18, 19). In fact, the freedom from death or urgent cardiac transplantation was found to be only 48% in 1 year in patients with peak oxygen consumption of <14 ml/min per kg. In contrast, patients without significant comorbidities and peak oxygen consumption >14 ml/min per kg had 1-year survival of 94% (20).

Limitations of the study
The present study is the first to provide evidence on the importance of total T3 on the cardio-respiratory testing response in patients with heart failure. Although the study has not included a large number of patients, this may be the basis for further investigation in this new field of research. Furthermore, it should be noted that free fractions of thyroid hormones in plasma were not measured. We measured only the total T3, which in previous experimental and clinical studies has been mostly associated with increased mortality and impaired cardiac function (5, 10).

In conclusion, changes in thyroid hormone are closely correlated to myocardial functional status in patients with heart failure. These data are in accordance with experimental observations that strongly support a potential role of thyroid hormone in the pathophysiology of heart failure. This may be of physiological and therapeutic relevance.

Acknowledgements
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