CLINICAL STUDY

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

Constantinos Pantos, Athanasios Dritsas¹, Iordanis Mourouzis, Antonios Dimopoulos, Georgios Karatasakis¹, Georgios Athanassopoulos¹, Sofia Mavrogeni¹, Athanasios Manginas¹ and Dennis V Cokkinos¹

Department of Pharmacology, University of Athens, 75 Mikras Asias Avenue, 11527 Goudi, Athens, Greece and ¹1st Cardiology Department, Onassis Cardiac Surgery Center, 356 Sygrou Avenue, 176 74 Kallithea, Athens, Greece

(Correspondence should be addressed to C Pantos; Email: cpantos@cc.uoa.gr)

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 VO_{2max} ($r=0.78$, $P=2\times 10^{-8}$). Furthermore, multivariate analysis revealed that total T₃ was an independent predictor of VO_{2max} ($P=0.000\ 005$). 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.

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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 β -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

Table 1 Baseline characteristics of patients.

	Number (%) or mean (s.d.)
Gender (male/female)	30 (81%)/7 (19%)
Age (years)	45 (15.4)
Systolic blood pressure (mmHg)	105.5 (16.2)
Diastolic blood pressure (mmHg)	68.0 (9.1)
Resting heart rate (bpm)	81 (13.3)
Diuretics	33 (89.2%)
β-Blockers	30 (81.1%)
Angiotensin-converting enzyme inhibitors	26 (70.3%)
Angiotensin receptor type-1 blockers	3 (8.1%)
Amiodarone	14 (37.8%)
LV ejection fraction (%)	26.2 (8.3)
LV end-diastolic diameter (mm)	68.3 (10.5)
VO _{2max} (ml/min per kg)	17.4 (5.8)
TSH (mIU/l)	3.1 (3.0)
Total T ₃ (ng/ml)	0.84 (0.2)
Total T ₄ (μg/dl)	8.1 (1.5)
Hct (%)	41.6 (4.6)
Creatinine (mg/dl)	1.24 (0.56)

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 values. T₃, T₄, and TSH values within the same patient 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 (VO_{2max}, 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 VO_{2max}.

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 VO_{2max} (*r*=0.78, *P*=2×10^{−8}), while no significant correlations were found between VO_{2max} 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 VO_{2max} values, only total T₃ and LVEF% were found to be associated with VO_{2max}.

Figure 1 Scatterplots showing correlation of T_3 (A), T_4 (B), and TSH (C) with maximal oxygen consumption (VO_{2max}) in patients with dilated cardiomyopathy.

Furthermore, total T_3 was the strongest independent determinant of VO_{2max} (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 T_3 and a trend towards an

Figure 2 Scatterplots showing correlation of LVEF% (A), SBP (B), and DBP (C) with T_3 in patients with dilated cardiomyopathy.

increase in T_4 . In addition, TSH was found to be significantly increased in patients receiving amiodarone (Table 3). However, VO_{2max} , 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. T_3

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

	<i>r</i>	<i>r</i> ²	<i>P</i> value
Independent variables			
T ₃	0.78	0.61	0.000 005
LVEF%	0.84	0.70	0.006
Excluded variables			
DBP	0.11	—	0.71
SBP	0.14	—	0.77
Age	0.02	—	0.94
Hct	0.09	—	0.80
T ₄	−0.14	—	0.94
TSH	−0.22	—	0.96

levels were also strongly correlated with VO_{2max} ($r=0.84$, $P=10^{-6}$), while no significant correlation was found between VO_{2max} and T₄ (Fig. 3). Interestingly, in this subgroup of patients, TSH showed a significant negative correlation with VO_{2max} values ($r=-0.62$, $P=0.002$; 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 TRα1 aporeceptor 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.

Table 3 Left ventricular performance and thyroid hormone levels in patients with and without amiodarone treatment. Data are presented as mean (S.D.).

	Patients without amiodarone treatment	Patients with amiodarone treatment	<i>P</i> value
<i>N</i>	23	14	
Total T ₃ (ng/ml)	0.86 (0.2)	0.80 (0.21)	0.46
Total T ₄ (μg/dl)	7.7 (1.1)	8.8 (1.8)	0.06
TSH (mIU/l)	2.1 (1.9)	4.8 (3.8)	0.02
LV ejection fraction (%)	28 (9.0)	25 (6.1)	0.3
VO _{2max} (ml/min per kg)	18.0 (5.7)	16.3 (6.0)	0.38
Systolic blood pressure (mmHg)	105 (17)	106 (16)	0.96
Diastolic blood pressure (mmHg)	68.0 (9.5)	67.8 (8.7)	0.95

Figure 3 Scatterplots showing correlation of T₃ (A), T₄ (B), and TSH (C) with maximal oxygen consumption (VO_{2max}) in patients with dilated cardiomyopathy without amiodarone treatment.

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

was also observed. It is interesting to note that lower T_3 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 T_3 on the cardio-respiratory exercise testing response in patients with heart failure; a strong correlation between total T_3 and the peak oxygen consumption was observed and the variability in VO_{2max} could be explained by almost 61% by changes in T_3 values. Furthermore, multivariate analysis showed that total T_3 was the strongest independent determinant of VO_{2max} . 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 T_3 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 T_3 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 T_3 , 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.

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