

Altered Thyroid Hormone Metabolism in Advanced Heart Failure

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To determine the prevalence and significance of abnormal thyroid hormone metabolism in congestive heart failure, free thyroxine (T_4) index, free triiodothyronine (T_3) index, reverse T_3 and thyrotropin levels were obtained in 84 hospitalized patients with chronic advanced heart failure. Free T_4 index was normal in all patients. Free T_3 index was reduced or reverse T_3 elevated, or both, leading to a low free T_3 index/reverse T_3 ratio in 49 (58%) of the 84 patients.

A low free T_3 index/reverse T_3 ratio was associated with higher right atrial, pulmonary artery and pulmonary capillary wedge pressures and lower ejection fraction, cardiac

index, serum sodium, albumin and total lymphocyte count. In multivariate analysis, the free T_3 index/reverse T_3 ratio was the only independent predictor of poor 6 week outcome ($p < 0.001$); the actuarial 1 year survival rate was 100% for patients with a normal ratio and only 37% for those with a low ratio ($p < 0.0001$).

A low free T_3 index/reverse T_3 ratio is associated with poor ventricular function and nutritional status and is the strongest predictor yet identified for short-term outcome in patients with advanced heart failure.

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Thyroid hormone metabolism has been shown to be abnormal in nonthyroidal illness manifested by low triiodothyronine (T_3), elevated reverse T_3 and normal thyroid-stimulating hormone (1). Thyroxine (T_4) levels can be normal, elevated or reduced (2) and in patients hospitalized in medical intensive care units, low thyroxine has been associated with a high mortality rate (3). Most studies (3-5) investigating thyroid function in nonthyroid illnesses have combined patients with a variety of illnesses and have not differentiated among the underlying diseases or compared patients with various degrees of severity of one illness. Levels of T_3 are known to be low during acute myocardial infarction (6,7) and cardiac arrest (8), but the prevalence and significance of abnormal thyroid metabolism in chronic congestive heart failure have not yet been determined. Therefore, we analyzed thyroid hormone levels in relation to hemodynamics, nutritional status and survival in a large cohort of patients with advanced heart failure.

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Methods

Study patients. Our study group consisted of 84 consecutive patients admitted to the coronary care unit for evaluation and treatment of advanced congestive heart failure, frequently in conjunction with evaluation for cardiac transplantation. An additional seven patients taking amiodarone, four patients with clinical hypothyroidism and one patient with hyperthyroidism were not included. The study group consisted of 70 men and 14 women, aged 17 to 71 years (mean 50), of whom 38 had ischemic, 24 idiopathic, 15 valvular, 5 alcoholic and 2 postpartum cardiomyopathy. These patients had an average left ventricular ejection fraction determined by two-dimensional echocardiography of $18 \pm 5\%$ and severe congestive symptoms despite previous medical therapy. No patient was receiving a beta-adrenergic blocking agent, steroids, aspirin, heparin or Dilantin (phenytoin sodium) (medications known to alter thyroid metabolism) (9-11) and none had received radiographic contrast medium within 2 weeks before measurement of thyroid hormone levels (12). Six patients were receiving intravenous dopamine at the time of transfer, but none had received any intravenous inotropic infusion for >48 h.

Study protocol. On the day of right heart catheterization, venous blood samples were obtained for measurement of electrolytes, bilirubin, serum glutamic oxaloacetic transaminase (SGOT), creatinine, thyroid-stimulating hormone (Celltech Diagnostics, normal 0.4 to 4.4 mU/liter, coeffi-

cients of variability: intraassay 5.5%, interassay 5.2%) (13), reverse T₃ (Serono-Baker Diagnostics, normal 5 to 29 ng/ml, intraassay 6%, interassay 9%) (14), T₄ (Organon Teknika, normal 5 to 11 μg/dl, intraassay 7.4%, interassay 5.9%) (15) and T₃ (Organon Teknika, normal 75 to 175 ng/dl, intraassay 9.6%, interassay 11%) (16). In this study, we used the free T₄ index and free T₃ index to correct for variations in serum-binding protein levels. These indexes are the product of the total serum hormone level and the amount of labeled hormone that binds to resin after being incubated with the patient's serum (17).

Total lymphocyte count, serum albumin and percent body fat (calculated from triceps, chest, supraileal and thigh skinfold thickness) (18) were also measured as indexes of nutritional status. A pulmonary artery flotation catheter was passed under fluoroscopic guidance and baseline hemodynamic measurements were obtained after a 2 h equilibration period. Cardiac output was determined as the average of three values obtained by the thermodilution technique.

Because nonthyroid illness is associated with both a decrease in free T₃ index and an increase in reverse T₃, the free T₃ index/reverse T₃ ratio was evaluated as a potentially sensitive index of metabolic derangement. A free T₃ index/reverse T₃ ratio of 4 was chosen to divide the study cohort into two groups because it represented the midpoint in the range of values (0 to 8) displayed by 95% of the patients, as well as the lower limit of normal as calculated from our laboratory normal values: (free T₃ index mean - 1 SD)/ (reverse T₃ mean + 1 SD). Therefore, the patients were classified into two groups—free T₃ index/reverse T₃ ratio >4 (35 patients) and free T₃ index/reverse T₃ ratio ≤4 (49 patients)—for comparative analysis of hemodynamics, ejection fraction, nutritional variables, hepatic and renal function, serum sodium and survival.

During hospitalization, all patients received intravenous afterload reduction therapy followed by institution of high dose oral vasodilating and diuretic drugs. Clinically stable patients were discharged on this regimen. Those with hemodynamic instability requiring continued inotropic support, intraaortic balloon counterpulsation or a left ventricular assist device were placed on the urgent cardiac transplantation list if they were eligible. Because this outcome reflects a dismal prognosis without transplantation, it was included along with death as the "poor outcome" end point. Outpatients awaiting elective heart transplantation were not considered with this group because the degree of illness in all of the study patients was severe enough to warrant transplantation if they were eligible (19) and we have shown the functional and hemodynamic status in the group with elective transplantation to be similar to that of the patients followed up on medical therapy and not accepted for transplantation (20). In addition, the average outpatient waiting period is >3 months, during which time the mortality rate is highest, so that those surviving to elective transplantation

Table 1. Relation of Free T₃ Index/Reverse T₃ Ratio to Hemodynamics and Ventricular Function

	Free T ₃ Index/ Reverse T ₃ Ratio	
	≤4	>4
Ejection fraction (%)	16 ± 5	19 ± 5*
Cardiac index (liters/min per m ²)	1.8 ± 0.6	2.1 ± 0.6*
Right atrial pressure (mm Hg)	15 ± 6	10 ± 6*
Mean pulmonary artery pressure (mm Hg)	39 ± 10	33 ± 13*
Pulmonary wedge pressure (mm Hg)	29 ± 8	23 ± 10*

*p < 0.05. Data are expressed as mean values ± SD.

reflect a better prognostic group than those who died or required urgent transplantation.

Data analysis. The normal (>4) and low (≤4) free T₃ index/reverse T₃ ratio groups were compared by using two-tailed Student's *t* tests. Univariate and multivariate regression analyses were performed with a BMDP statistical package (21) to assess the relative predictive value for poor 6 week outcome of measured hemodynamic values, serum sodium and thyroid function abnormalities. The 12 month actuarial survival rate was calculated with placement on the urgent transplantation list considered as death and elective transplantation considered to be the last day of the follow-up period. The actuarial survival curves were compared with the use of Breslow and Mantel-Cox statistical analyses.

Results

Thyroid function tests. Serum free T₄ index was normal in all 84 patients. Free T₃ index was low in 24 patients and reverse T₃ elevated in 31 patients. The free T₃ index/reverse T₃ ratio was ≤4 in 49 patients (58%). A slight increase in thyroid-stimulating hormone between 5 and 10 mU/liter was present in four patients (a value >15 mU/liter is believed to be present in patients with clinical and biochemical evidence of hypothyroidism) (2).

Comparison with hemodynamics, chemistry values and nutritional status. Comparisons of the normal and low free T₃ index/reverse T₃ ratio groups revealed that a ratio ≤4 was associated with a lower ejection fraction and cardiac index and a higher right atrial pressure, mean pulmonary artery pressure and pulmonary capillary wedge pressure (Table 1). Serum sodium was lower and bilirubin, SGOT and creatinine higher in the low ratio group, but free T₄ index and thyroid-stimulating hormone were similar in both groups (Table 2). The mean total lymphocyte count and serum albumin in the patients with a low free T₃ index/reverse T₃ ratio were below the normal range, significantly lower than in those with a normal ratio. There was no difference in percent body fat. The mean duration of symptoms before referral was 34 months in both groups.

Table 2. Relation of Free T₃ Index/Reverse T₃ Ratio to Serum Chemistry Values and Nutritional Variables

	Free T ₃ Index/Reverse T ₃ Ratio	
	≤4	>4
Free T ₄ index (5-11)	7.0 ± 2.8	8.0 ± 3.1
Free T ₃ index (75-175)	75 ± 21*	117 ± 22
Reverse T ₃ (5-29 ng/ml)	36 ± 15*	21 ± 7
TSH (0.4-4.4 mU/liter)	3.4 ± 2.7	2.5 ± 1.5
Serum sodium (136-146 mmol/liter)	133 ± 5*	138 ± 4
SGOT (5-40 U/liter)	56 ± 87*	24 ± 10
Bilirubin (0.3-1.2 mg/dl)	1.8 ± 1.3*	1.0 ± 0.6
Creatinine (0.7-1.3 mg/dl)	1.3 ± 0.4*	1.1 ± 0.2
Albumin (4.0-5.2 g/dl)	3.8 ± 0.5*	4.2 ± 0.4
Total lymphocyte count (>1,500/cm ³)	1,358 ± 577*	1,714 ± 642
% body fat (10%-22%)	13.4 ± 6.6	17.9 ± 6.4

*p < 0.05. Data are expressed as mean values ± SD. Numbers in parentheses refer to normal values. SGOT = serum glutamic oxaloacetic transaminase; TSH = thyroid-stimulating hormone.

Outcome. During the initial hospitalization, 8 patients (10%) died and 6 (7%) were placed on the urgent transplantation list; the condition of 70 patients (83%) was stabilized and they were discharged on oral medications. There were a total of 23 "poor outcomes" (17 deaths and 6 urgent transplantations) in the 84 patients within 1 year after initial referral; 14 of these outcomes occurred before hospital discharge. Elective cardiac transplantation was performed in 15 patients after a waiting period of 3.3 ± 3.2 months. These patients were not included in the poor outcome group because of the clinical similarity of patients undergoing transplantation electively and those remaining on medical therapy after referral for transplantation (20), as mentioned previously. The average length of follow-up study in patients without transplantation or death was 7.3 ± 6.6 months.

Low free T₃ index, high reverse T₃, low free T₃ index/reverse T₃ ratio and high right atrial pressure were each univariate predictors of poor outcome (death within 6 weeks or placement on the urgent transplantation list) (p < 0.01). Serum sodium was of borderline univariate significance (p = 0.08). In multivariate regression analysis, however, the free T₃ index/reverse T₃ ratio was the only independent prognostic indicator (p < 0.001). No patient with a free T₃ index/reverse T₃ ratio >4 died or required urgent transplantation in the follow-up period, leading to a predicted 1 year survival rate of 100%. The actuarial survival rate in the group with a free T₃ index/reverse T₃ ratio ≤4 was 37% at 12 months (Fig. 1), with 76% of the deaths and all of the urgent transplantations occurring within the first 6 weeks of referral. Further analysis of free T₃ index/reverse T₃ ratio groups revealed that even within the high risk group, the lowest free T₃ index/reverse T₃ ratios were associated with the poorest prognoses during this 6 week period (Fig. 2).

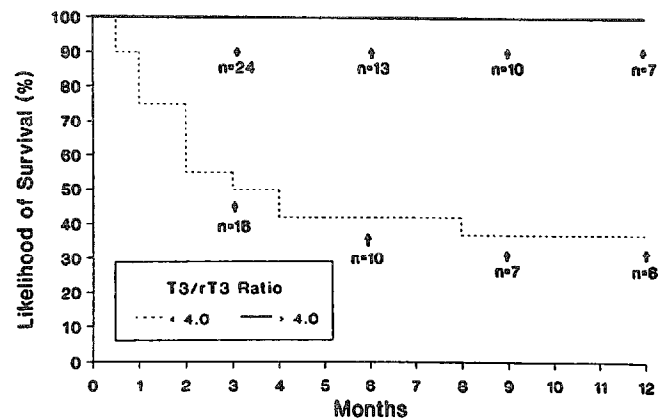
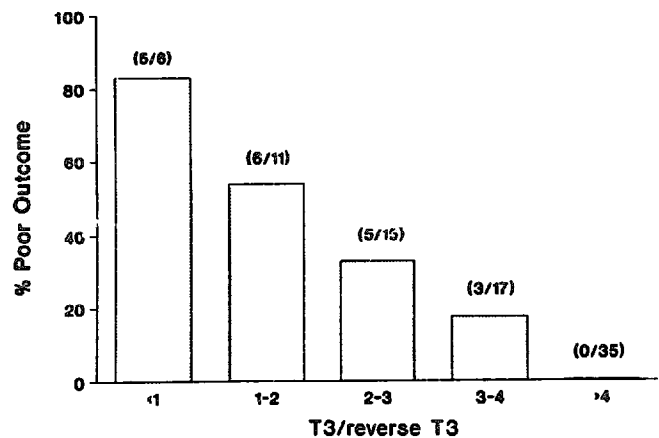


Figure 1. One year actuarial survival in 84 patients with heart failure in relation to the free T₃ index/reverse (r) T₃ ratio. The ratio was normal (>4) in 35 patients (top solid line) and abnormal (≤4) in 49 patients (dashed line). No patient in the normal ratio group died or underwent urgent cardiac transplantation during this period. Arrows indicate the number of patients followed up over each time interval.

Discussion

Thyroid function in heart failure. In this study, we have shown that thyroid hormone metabolism is frequently altered in patients with advanced heart failure. The most common abnormality in the patients studied was a reduction in free T₃ index or an increase in reverse T₃, or both, leading to a low free T₃ index/reverse T₃ ratio in >50% of the patients. Free T₄ index was normal in all patients studied, suggesting that the mechanism involved is different from that found in severely ill patients in a general medical intensive care unit (3); in that group, T₄ was found to be low in 22% and was the only thyroid test associated with a poor prog-

Figure 2. Short-term outcome in 84 patients with heart failure. Poor outcome includes death or urgent transplantation within 6 weeks after referral. Data in parentheses represent the number of patients with a poor outcome in each group. Logistic regression analysis revealed the free T₃ index/reverse T₃ ratio to be highly predictive of outcome (p < 0.0001).



nosis. Despite the low free T_3 index in our patients, thyroid-stimulating hormone was normal in 95% and only mildly elevated in the others, a finding consistent with previous reports (2). The degree of T_3 abnormality was clearly related to the hemodynamic severity of illness because the ejection fraction and all hemodynamic variables were significantly worse in the patients with a low free T_3 index/reverse T_3 ratio. However, thyroid function was not related to the duration of illness.

Potential mechanisms for alterations in thyroid hormone metabolism. The mechanism by which thyroid hormone metabolism is altered in nonthyroid illness is not known. The reduction in free T_3 index and increase in reverse T_3 levels are most likely due to an inhibition of iodothyronine 5'-deiodinase, the enzyme that both converts T_4 to T_3 and leads to reverse T_3 catabolism (22). There is evidence to support the existence of a thyroid-binding inhibitor that alters the availability of T_4 for metabolism and inhibits iodothyronine 5'-deiodinase (11), an enzyme located primarily in microsomes of liver and kidney (23). Impaired enzyme function is the suggested mechanism underlying similar thyroid hormone abnormalities found in patients with hepatic cirrhosis (24).

Our finding that SGOT and bilirubin concentrations were higher in the patients with a low free T_3 index/reverse T_3 ratio supports the hypothesis that impairment of hepatic function secondary to passive congestion in these patients may reduce the iodothyronine 5'-deiodinase activity and consequently lead to low free T_3 index and high reverse T_3 . However, because T_3 production is known to be reduced in the fasting state (25,26), poor nutritional status may also contribute to altered thyroid metabolism in chronic heart failure. This is supported by our finding that serum albumin and total lymphocyte count, indicators of nutritional status, were lower in patients with a low free T_3 index/reverse T_3 ratio than in those with normal T_3 metabolism. However, total body fat was not reduced, suggesting that the patients were not severely malnourished.

Prognostic importance of abnormal thyroid hormone levels. In previous reports (27,28), elevated right atrial pressure and low serum sodium have been identified as indicators of poor prognosis in patients with congestive heart failure. In this study, however, a low free T_3 index/reverse T_3 ratio was shown to be a more significant prognostic factor than any hemodynamic or electrolyte variable and in fact was the only independent predictor of short-term mortality. In patients with cirrhosis, free T_3 index/reverse T_3 ratio predicted death only if it was 10-fold lower than normal (29), whereas in our patients with heart failure, any reduction in this ratio below the normal range was associated with a poor prognosis.

Significance of alterations in thyroid hormone metabolism in heart failure. It is possible that the thyroid function abnormalities in these patients with heart failure predict poor outcome strictly as an indicator of severe disease, in which

the low conversion to T_3 may be an adaptive mechanism to reduce catabolism. Conversely, the low T_3 levels could contribute to the severity of illness. Hypothyroidism is known to impair the intrinsic contractile state of the myocardium (30), which could accelerate the deterioration of ventricular function. Hypothyroidism can also cause atrioventricular block (31) or prolong the ventricular refractory period and the dispersion of refractoriness (32), possibly predisposing patients to lethal arrhythmias. In addition, hypothyroidism inhibits the release of atrial natriuretic factor, a cardiac hormone that helps counteract the fluid retention in heart failure (33). Because thyroid hormone modulation of myocardial cell function is believed to occur through specific T_3 nuclear receptors (34), it is possible that even in patients who appear "euthyroid" by T_4 and thyroid-stimulating hormone criteria, low T_3 could exacerbate heart failure by these mechanisms and contribute to the poor prognosis.

Conclusions. This study demonstrates that thyroid hormone metabolism is frequently altered in patients with advanced heart failure in a different manner than has been previously described for other severe nonthyroidal illnesses; free T_4 index levels are preserved, but the free T_3 index is often low and reverse T_3 high. Although an abnormal free T_3 index/reverse T_3 ratio is associated with lower ejection fraction, higher filling pressures, lower serum sodium and worse nutritional status, this ratio is the strongest predictor yet identified for short-term outcome in patients with severe heart failure.

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