CLINICAL STUDY

Low triiodothyronine (T3) state: a predictor of outcome in respiratory failure? Results of a clinical pilot study

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Abstract

Background and aim: Various low triiodothyronine (T3) states have been described in severe nonthyroidal diseases and associated with a poor prognosis in cardiovascular disease patients. We assessed thyroid function in patients with severe respiratory failure from pulmonary disorders, and needing invasive or noninvasive mechanical ventilation, in order to evaluate the prognostic value of nonthyroidal illness syndrome.

Methods: We studied 32 consecutive patients with acute or acute-on-chronic respiratory failure. Measured variables upon admission included APACHE II score, the ratio of the partial pressure of oxygen in arterial blood to the fraction of oxygen in inspired gas ($\text{PaO}_2/\text{FiO}_2$), and plasma levels of free T3 (fT3) and free thyroxine (fT4), and TSH levels. Thyroid function was further evaluated at discharge.

Results: Plasma levels of fT3 were below normal in 17 patients (53%). Plasma fT3 was correlated with $\text{PaO}_2/\text{FiO}_2$ ($P < 0.001$), and with APACHE II score ($P = 0.003$). In four patients (12.5%) who died, fT3 levels were significantly lower ($P = 0.002$) than in patients who survived. In univariate logistic regression analysis, fT3 was the only factor significantly associated with an increased risk of death (odds ratio, 64.23; 95% confidence interval, 1.78–2316.86, $P = 0.023$). Normalization of thyroid function was observed at discharge with a significant correlation between the percent increase in both fT3 and $\text{PaO}_2/\text{FiO}_2$ ($P = 0.015$). P values were calculated using Spearman's Correlation Coefficient.

Conclusion: Our preliminary data suggest that the low T3 state is a predictor of outcome in pulmonary patients with respiratory failure.

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Introduction

Abnormal plasma levels of thyroid hormones have been reported in patients with a variety of nonthyroidal illnesses (1). Several conditions are described, the most important of which is the low T3 syndrome (2), which is characterized by reduced plasma levels of triiodothyronine (T3) due to impaired activity of specific 5' monodeiodinases converting thyroxine (T4) to T3 in peripheral tissues (3). Circulating levels of T4 range from reduced to slightly elevated, with either normal or slightly suppressed thyroid-stimulating hormone (TSH) levels (3).

The low T3 state has been described in starvation (4), sepsis (5), surgery (6), myocardial infarction and heart failure (7, 8), cardiopulmonary bypass (9), bone marrow transplantation (10) and any other severe illness (11).

To date, there are few data on thyroid function in patients with respiratory diseases due to pulmonary disorders (12–15), and there are no data available on thyroid function in respiratory failure patients needing invasive or noninvasive mechanical ventilation.

The aim of this study was to evaluate thyroid function in a group of patients with respiratory failure due to pulmonary disorders who were admitted to the respiratory intensive care unit of our institution. This study was approved by the ethics committee of our institution.

Subjects and methods

Study population

We evaluated 44 consecutive patients admitted to our respiratory intensive care unit because of acute or acute-on-chronic respiratory failure requiring mechanical ventilation. For the acquisition of data on pulmonary patients, 11 subjects were excluded because of intrinsic thyroid disorders (two patients) or comorbid conditions known to alter thyroid function (10 patients). Comorbid conditions included advanced congestive heart failure (two patients), recent myocardial infarction (two patients), acute pancreatitis (one patient), neurologic disorders (two patients) and renal failure (two patients). One further patient was excluded because of recent use of

amiodarone, which may interfere with thyroid hormone metabolism. At the time of admission, the patients had received no therapy with drugs known to alter the thyroid function, such as corticosteroid, dopamine, aspirin, etc. The final study sample consisted of 32 patients, whose characteristics are reported in Table 1.

All patients were on oxygen therapy at the time of admission and were treated with mechanical ventilation. Oxygen was supplied by nasal prongs or through the ventilator circuit to achieve an arterial oxygen saturation of $\geq 92\%$.

Intermittent negative pressure ventilation was used in 9 patients (28%) via iron lung (Mod. C 900; Coppa Biella, Biella, Italy). Twenty-three patients (72%) underwent positive pressure ventilation via a pressure-cycled ventilator in assist/control mode or pressure support mode. Positive end-expiratory pressure was applied when required, at a level of 4–5 cmH₂O. Mechanical ventilation was performed by nasal or facial masks in 17 patients, and by endotracheal tube in 6.

Study protocol

Clinical history and physical examination were performed in all patients at the time of admission. APACHE II score was also obtained (16). Arterial blood gases were measured, and the ratio of the partial pressure of oxygen in arterial blood to the fraction of oxygen in inspired gas ($\text{PaO}_2/\text{FiO}_2$) was calculated.

Thyroid function was evaluated by measuring plasma levels of free T3 (fT3), free T4 (fT4), and TSH with a direct chemiluminescence assay (ADVIA, Bayer Health Care LLC Tarrytown, NY, USA) within 24 h of

admission. According to the manufacturer's instructions, the normal range was 2.3–4.2 pg/ml for fT3, 0.8–1.76 ng/dl for fT4 and 0.35–5.5 $\mu\text{IU/ml}$ for TSH (the analytic and functional sensitivity of the TSH was 0.004 $\mu\text{IU/ml}$). Thyroid function was further evaluated upon discharge from the respiratory intensive care unit.

Routine blood tests were also obtained in order to exclude cachexia and/or any significant metabolic disorder which could alter thyroid hormone metabolism.

Statistical analysis

Data were reported as median and range. Continuous variables were compared by the nonparametric paired-samples Wilcoxon test or unpaired-samples Mann–Whitney test. Association between variables was assessed by Spearman's correlation coefficient. Univariate logistic regression was used to identify factors significantly associated with an increased risk of death; for each variable, the odds ratio (OR), and 95% confidence interval (CI), are given. For continuous variables, OR represents the factor by which the odds change when the variable increases by one unit; for dichotomous variables, it represents the factor by which the odds change for patients with a particular characteristic, as compared with those without the characteristic. Two-sided *P* values of <0.05 were considered statistically significant (17). The statistical program used was SPSS for Windows, Version 9.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' baseline clinical and laboratory data are reported in Table 1. All patients showed clinical severe impairment, as reflected by the APACHE II score, and derangement of pulmonary gas exchange. No patient had blood test results suggestive of cachexia or of any other relevant metabolic disorder which could interfere with thyroid hormone metabolism.

Plasma levels of fT3 were below the lower limit of the normal range in 17 patients (53%), and borderline low in 11 (34%). Free T4 plasma concentrations were below the lower limit of the normal range in 3 patients only (9%). TSH plasma levels were below the lower limit of the normal range in 10 patients (31%), and were borderline low in 11 (34%).

Plasma concentrations of fT3 were significantly correlated with the severity of pulmonary gas exchange impairment, as reflected by the $\text{PaO}_2/\text{FiO}_2$ ratio (Fig. 1A). A significant inverse correlation was found between fT3 levels and APACHE II score (Fig. 1B).

No statistically significant difference was observed between fT3 levels and age, sex and common metabolic parameters.

Four (12.5%) of the 32 patients died during their stay in the respiratory intensive care unit. No significant

Table 1 Characteristics of study population.

	Median (range), or number (%)	
Age (years)	75.5	(43–90)
Sex (male)	18	(56)
<i>Cause of respiratory failure</i>		
Chronic obstructive pulmonary disease	23	(72)
Pneumonia	6	(19)
Pulmonary fibrosis	3	(9)
APACHE II score	19	(11–29)
<i>Blood gases</i>		
PaO_2 (mmHG)	48	(23–115)
PaCO_2 (mmHG)	78	(31–113)
$\text{PaO}_2/\text{FiO}_2$	168	(63–271)
<i>Thyroid hormones</i>		
fT3 (pg/ml)	2.33	(1.00–3.50)
fT4 (ng/dl)	1.29	(0.56–2.00)
TSH ($\mu\text{IU/ml}$)	0.63	(0.03–2.90)
<i>Metabolic parameters</i>		
Cholesterolemia (mg/dl)	145	(70–291)
Triglyceridemia (mg/dl)	66.5	(49–248)
Protidemia (gr/dl)	7.25	(5.3–8.6)
Glycemia (mg/dl)	143	(73–198)
Creatininemia (mg/dl)	0.84	(0.61–2.49)

PaO_2 : partial pressure of oxygen, arterial.

PaCO_2 : partial pressure of carbon monoxide, arterial.

FiO_2 : fraction of oxygen in inspired gas.

Figure 1 (A) Relationship between plasma levels of fT3 and the ratio of the partial pressure of oxygen in arterial blood to the fraction of oxygen in inspired gas ($\text{PaO}_2/\text{FiO}_2$). (B) Relationship between plasma levels of fT3 and APACHE II score. Data were obtained in 32 patients with severe respiratory failure upon admission to the respiratory intensive care unit.

difference was observed between these patients and those who survived as to age, clinical status reflected by APACHE II score, pulmonary gas exchange and metabolic parameters. Conversely, plasma fT3 levels were significantly lower ($P = 0.002$) in patients who died (median fT3 1.41 pg/ml; range, 1.00–1.82 pg/ml) than in those who survived (median fT3, 2.40 pg/ml; range, 1.34–3.50 pg/ml). In a univariate logistic regression analysis, fT3 was the only factor significantly associated with an increased risk of death (OR, 64.23; 95% CI, 1.78–2316.86; $P = 0.023$) (Table 2).

Thyroid parameters tended to return to normal levels at the time of discharge from the respiratory intensive care unit. The median fT3 upon admission was 2.33 pg/ml (range, 1.00–3.50 pg/ml), and it was 2.72 pg/ml (range, 2.30–5.31 pg/ml) at discharge ($P = 0.002$). In this study sample, there was a significant correlation between the percent increase in fT3 levels and the percent increase in $\text{PaO}_2/\text{FiO}_2$ ratio ($\rho = 0.578$; $P = 0.015$).

The median TSH at discharge (1.070 $\mu\text{IU/ml}$) was higher than the median TSH observed at admission (0.634 IU/ml), but the increase was not statistically significant ($P = 0.3259$) in the nonparametric paired-samples Wilcoxon test. The median of fT4 (1.29 ng/dl) at admission was similar to the median

Table 2 Univariate logistic regression analysis.

	OR	95% CI	P
fT3	64.23	1.78–2316.86	0.023
fT4	22.99	0.71–745.33	0.077
TSH	0.66	0.17–2.54	0.542
Age	1.06	0.95–1.18	0.303
Sex (male)	1.33	0.16–10.87	0.788
APACHE II score	0.87	0.67–1.15	0.334
PaCO_2	1.01	0.96–1.07	0.642
PaO_2	1.01	0.96–1.07	0.707
$\text{PaO}_2/\text{FiO}_2$	1.03	0.99–1.05	0.060
Cholesterolemia	0.99	0.96–1.01	0.320
Triglyceridemia	1.01	0.98–1.03	0.746
Proteinemia	3.49	0.62–19.61	0.155
Glicemia	1.00	0.97–1.03	0.969
Creatininemia	0.83	0.17–4.08	0.814

of fT4 at discharge (1.28 ng/dl), and was not statistically significant.

Discussion

Various low T3 states have long been reported in a variety of severe acute and chronic diseases. For many years, this phenomenon has been considered as a transient adaptive process, but there is increasing evidence that an induced hypothyroid-like state may in itself worsen the patient's clinical status (3).

In our study, reduced fT3 levels were found in most patients with respiratory failure due to respiratory disorders. Plasma levels of fT4 were not reduced, and TSH levels varied at baseline from normal to reduced when compared with the normal range, as observed in patients with severe nonthyroidal diseases (3). Plasma levels of fT3 were related to clinical status and pulmonary gas exchange impairment, as reflected by APACHE II score and $\text{PaO}_2/\text{FiO}_2$ ratio respectively. Furthermore, the normalization of fT3 levels was associated with an improvement in gas exchange.

It has been suggested that fT3 levels may be a reliable predictor of clinical outcome (18). In patients undergoing cardiac surgery, fT3 levels did correlate with the time spent in intensive care unit, taken as an index of the overall clinical outcome (19). A recent report (20) found a strong correlation between low T3 state and the long-term prognosis in patients with various cardiovascular disorders.

In our study, patients who died had significantly lower fT3 levels than those who survived. Conversely, there was no significant difference between the two groups of patients in terms of age, sex, metabolic parameters, APACHE II score and severity of gas exchange impairment.

Reduced fT3 levels were also found as the only significant predictor of death in univariate logistic regression analysis, because, in spite of only four

deaths and large CI, the OR is higher by one unit and therefore statistically significant.

In conclusion, the preliminary data of our study suggest that fT3 plasma concentration may be used as a marker of disease severity in patients with respiratory failure due to pulmonary disorders. Given the small size of our study sample, it is still unclear whether the low T3 state represents only a biochemical prognostic marker or whether it actually contributes to the development and progression of respiratory failure. Nevertheless, the role of fT3 concentration (that is, <2.3 pg/ml) as a potential prognostic marker in respiratory patients is not surprising in view of its importance in maintaining the homeostasis of almost all organ systems, and its role in modulating systemic adaptations to acute injury. In this regard, fT3 could be more useful than systemic (APACHE II score) and organ-specific ($\text{PaO}_2/\text{FiO}_2$ ratio) functional parameters as an additional predictor of outcome.

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