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Contents lists available at ScienceDirect

Journal of Acute Disease

journal homepage: www.jadweb.org

Medical emergency research http://dx.doi.org/10.1016/j.joad.2015.04.005

Triiodothyronine levels in acute pulmonary embolism predict in-hospital mortality

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ARTICLE INFO

Article history:
Received 9 Apr 2015
Received in revised form 16 Apr 2015
Accepted 25 Apr 2015
Available online 9 Jul 2015

Keywords:
Pulmonary embolism
Venous thromboembolism
Thyroid
Thyroxine
Triiodothyronine

ABSTRACT

Objective: To assess the thyroid function in patients with acute pulmonary embolism, in order to evaluate the prognostic value of thyroid hormones.

Methods: We studied 31 consecutive patients with acute pulmonary embolism. Measured variables upon admission included the ratio of the partial pressure of oxygen in arterial blood to the inspired oxygen fraction (PaO_2/FiO_2), acute physiology and chronic health evaluation II score, risk stratification indices and plasma levels of triiodothyronine, free thyroxine, and thyroid stimulating hormone.

Results: Plasma levels of triiodothyronine were below normal level in 7 patients (22.6%). Plasma triiodothyronine correlated with PaO_2/FiO_2 ($P < 0.05$) and with acute physiology and chronic health evaluation II score ($P < 0.01$). In four patients (12.9%) who died, triiodothyronine levels were significantly lower ($P < 0.01$) than that in patients who survived. In contrast both groups had similar levels of free thyroxine, and thyroid stimulating hormone. Moreover, triiodothyronine levels negatively correlated with serum markers of right ventricular dysfunction. Accordingly, in multivariate logistic regression analysis, the only factors independently associated with an increased risk of death were triiodothyronine and PaO_2/FiO_2.

Conclusions: Our preliminary data suggest that low plasma triiodothyronine is an independent predictor of in-hospital death in patients with acute pulmonary embolism.

1. Introduction

A plethora of nonthyroidal illnesses are characterized by thyroid function abnormalities, which are more prominent during critical illness[1,2]. These abnormalities of the thyroid axis have been collectively named as euthyroid sick syndrome[2,3] or alternatively as nonthyroidal illness syndrome (NTIS)[4,5]. Mild cases of NTIS usually comprise decreased serum levels of free (FT3) and total triiodothyronine (T3) and high levels of reverse T3. However, as the severity and duration of the underlying illness increase, both serum T3 and thyroxin (T4) decrease, while thyroid-stimulating hormone (TSH) remains normal or slightly decreased[1,2]. Previous studies have reported low serum levels of thyroid hormones in multiple pathological conditions including respiratory failure[6], sepsis[7,8], acute respiratory distress syndrome[9], multiple trauma[10] and surgery[11].

Likewise, NTIS can be encountered in patients with cardiovascular diseases such as heart failure[12,13], acute myocardial infraction[14–16] and cardiopulmonary bypass[17]. More importantly, in the majority of these studies, thyroid dysfunction has been associated with the severity and the prognosis of the underlying disease. Nevertheless, the interpretation of the hormonal components constituting NTIS has been the cause of divergent opinions. Initially, the aforementioned thyroid abnormalities were considered as distinct from a clinically significant state of hypothyroidism or even as laboratory artifacts[18]. Meanwhile, other researchers claim that the key element of NTIS is a combination of central hypothyroidism with altered peripheral metabolism of T4 and T3 that results in the reported depletion of thyroid hormones from the circulation and tissues[19]. In this context, a thyroid hormone replacement therapy has been proposed for the reversal of NTIS[19], but the efficacy of this therapeutic modality has not been proven so far in terms of reduced mortality.

Pulmonary embolism (PE) may result in high morbidity and mortality, especially when associated with hemodynamic instability or signs of right ventricular (RV) dysfunction[20,21]. Current

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Peer review under responsibility of Hainan Medical College.

guidelines stratify patients with PE into 3 groups depending on the prognostication of early mortality risk[20,21]. Hemodynamically unstable patients are included in the high-risk group that is characterized by a short-term mortality greater than 15%. Intermediate risk PE depends on the identification of either RV dysfunction or blood markers of myocardial injury in patients with hemodynamic stability. Finally, the low risk group includes the rest of the patients with acute PE. Early mortality risk refers to in-hospital or 30-day mortality. Nevertheless, prognostication in PE remains an unsettled issue and there is an ongoing need for the identification of markers that can be incorporated into the clinical practice and improve the predictive ability of early risk stratification. Prognostic assessment is also useful for the selection of the optimal treatment for every risk class of patients. To date, no study has determined the thyroid function in patients with acute PE. Similarly, the prognostic ability of thyroid indices has not been evaluated in this clinical setting. We therefore undertook a prospective, observational study of a small cohort of patients with acute PE. The aim of this study was to assess the thyroid function and to test the ability of thyroid hormone levels to predict in-hospital mortality in this group of patients.

2. Materials and methods

2.1. Study population

The present observational study was approved by the Institutional Ethics Committee. An informed, written consent was obtained by every patient included in the study.

The study was conducted prospectively from August 2013 through August 2014 in a tertiary care hospital. We analyzed 39 consecutive patients admitted to the emergency room with PE, confirmed with computed tomographic pulmonary angiography. A total of 4 patients were excluded due to previously diagnosed intrinsic thyroid disorders, and 4 more patients were excluded because of concomitant hormonal replacement therapy or because they were receiving amiodarone or corticosteroids at time of the admission. The final study samples consisted of 31 patients.

Following the confirmation of PE diagnosis, all patients received supportive therapy at the time of admission and were treated according to guidelines. Briefly, oxygen was supplied to achieve an arterial oxygen saturation of $\geq$92%. Hemodynamically stable patients received standard anticoagulation therapy with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin. Thrombolytic therapy was conferred for patients with hemodynamic instability and no high-risk of bleeding. Collectively, 5 patients received thrombolysis (2-h infusion of 100 mg recombinant tissue plasminogen activator).

2.2. Study protocol

At baseline, a structured clinical history and physical examination were carried out in all patients. Demographic and clinical characteristics, including age, heart rate, respiratory rate, systolic blood pressure and diastolic blood pressure of all patients were obtained on admission to the Emergency Department. Arterial blood gas sampling was performed, and the ratio of arterial oxygen tension to inspired oxygen fraction (PaO_2/FiO_2) was calculated. A 20-mL blood sample was taken and an intravenous line was established shortly after admission to the Emergency Department. In patients with compatible clinical history and/or suggestive clinical findings, PE was confirmed based on CT pulmonary angiography. The co-existence of deep vein thromboembolism was assessed by lower extremity ultrasonography. Patients with acute PE were classified, according to the risk of PE-related early death, as high-, intermediate- and low-risk. Initial risk stratification was based on the presence of the following risk markers.

Hemodynamic instability was diagnosed in patients that fulfilled at least one of the following criteria[21]: 1) sustained hypotension (systolic blood pressure < 90 mmHg or a pressure decrease of 40 mmHg for more than 15 min at arriving in the Emergency Department or requiring vasoactive support) not attributable to an alternative diagnonis (arrhythmia, acute left ventricular dysfunction, acute coronary syndrome, hypovolemia, or sepsis); 2) pulselessness (cardiac arrest); 3) persistent symptomatic bradycardia (heart rate <40 beats per minute with signs or symptoms of shock). Patients with hemodynamic instability were considered affected by high-risk PE and therefore as candidates for thrombolytic therapy.

Elevated levels of cardiac troponin T (cTnT) (>100 pg/mL) were considered as indicative of myocardial necrosis. RV dysfunction was confirmed by the presence of at least one of the following: 1) RV systolic dysfunction on echocardiography (echo); 2) RV dilation on CT or echo (apical 4-chamber RV diameter divided by LV diameter >0.9); 3) elevation of N-terminal pro-BNP (NT-Pro-BNP) (>500 pg/mL); or 4) electrocardiographic changes (new complete or incomplete right bundle branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion). Hemodynamically stable patients with confirmed acute PE and findings compatible with RV dysfunction and/or myocardial necrosis were classified as intermediate-risk patients.

Finally, hemodynamically stable patients with acute PE and no RV dysfunction or myocardial necrosis were considered as low risk patients.

All patients with diagnosed acute PE were followed up during their hospitalization. The end point of the study was death in the pulmonary clinic due to PE.

2.3. Measurements

At baseline, acute physiology and chronic health evaluation II (APACHE II) score (range from 0 to 71) was calculated based on the appropriate initial clinical, demographic and serological characteristics of each patient. Echocardiography was performed by a skilled cardiologist using standard views with a GE VIVIDi ultrasound device (General Electric Company, Wauwatosa, WI, USA) using 2.4 MHz multiplane transducer.

Thyroid function was assessed at admission by measurement of plasma levels of T3, free T4 (fT4), and TSH. Thyroid function was reevaluated upon discharge from the respiratory clinic by measurement of the same parameters. T3, fT4 and TSH were measured by immunochemiluminometric assay on the Roche Modular E170 Analytics (Roche Diagnostics GmbH, Mannheim, Germany). The normal ranges of serum hormone concentrations in our laboratory are as follows: 80–200 ng/dL for T3, 0.93–1.7 ng/dL for fT4 and 0.27–4.2 μIU/mL for TSH.

Serum creatinine and albumin levels were determined on a Roche/Hitachi Modular System P (Roche Diagnostics GmbH, Mannheim, Germany) by enzymatic assay. Serum cTnT levels

were measured using the electrochemiluminescence immunoassay on a Roche modular system E170 (Roche Diagnostics GmbH, Mannheim, Germany). Serum NT-pro-BNP was determined using an electrochemiluminescence immunoassay method (NT-pro-BNP, Roche) with a Roche modular E170 immunoassay analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

For the measurement of the aforementioned parameters in all eligible subjects blood samples were obtained shortly after the admission of patients to the Emergency Department. Therefore, in all the cases, blood was obtained before the administration of anticoagulants or thrombolysis.

2.4. Statistical analysis

The comparison of means of continuous variables was performed by the unpaired-samples Mann–Whitney test and the paired-samples Wilcoxon test. Results are reported as medians and ranges, while categorical variables are expressed as percentages. The possibility of a linear association between variables was assessed by Spearman's correlation coefficient (ρ).

Univariate logistic regression analyses were performed to examine the association between mortality and each of the predictors separately in order 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. All variables with $P < 0.1$ were then tested in a multivariable logistic regression analysis model aiming to identify the independent predictors of in-hospital mortality.

A two-sided P value less than 0.05 was considered statistically significant. All analyses were performed using SPSS version 13.0 software (SPSS, Inc, Chicago, IL, USA).

3. Results

In 7 out of 31 patients (22.6%) plasma levels of T3 were below normal range, while fT4 plasma concentrations were below normal level in 1 patient only (3.2%). TSH plasma levels were below the normal range in 1 patient (3.2%). Patients' baseline clinical and laboratory data are reported in Table 1.

No significant difference was detected between fT4 or TSH levels at admission (median fT4 1.4 ng/dL; median TSH 1.9 μIU/mL) compared with the respective levels at the time of discharge (median fT4 1.34 ng/dL, median TSH 2.1 μIU/mL). On the contrary, T3 levels upon discharge were normalized being higher ($P < 0.05$, median T3 97.3 ng/dL; range: 73–143 ng/dL) than T3 levels at admission (median T3 86.7 ng/dL; range: 54.5–152.4 ng/dL). Initial plasma concentrations of T3 were significantly correlated ($\rho = 0.435$, $P < 0.05$) with the severity of gas exchange impairment in terms of PaO_2/FiO_2 ratio (Figure 1A). Moreover, a significant inverse correlation ($\rho = -0.502$, $P < 0.01$) was found between T3 levels and APACHE II score (Figure 1B).

Four (12.9%) of the 31 patients died during their stay in the pulmonary clinic. Three of these patients were initially classified as high-risk patients, while 1 patient belonged in the group of intermediate risk. No significant difference was observed between these patients and those who survived as to age, sex, fT4, TSH and albumin or creatinine. On the other hand, patients who died were characterized by significantly lower T3 levels (unpaired t-test; $P < 0.01$; median T3 60.3 ng/dL; range, 54.5–80.0 ng/dL, $n = 4$), in comparison with patients who survived (median T3 92.8 ng/dL; range, 67.1–152.4 ng/dL, $n = 27$) as shown in Figure 2.

Table 1
Characteristics of study population at admission.

Characteristics	Median (range) or number (%)
Age (years)	65.7 (20–95)
Sex (male)	13 (42)
APACHE II score	16 (4–27)
Blood gases	
PaO_2/FiO_2	328 (130–450)
PaO_2 (mmHg)	88.7 (41–137)
$PaCO_2$ (mmHg)	36.4 (22.3–62.9)
HCO_3 (mmol/L)	23.1 (13.4–28.2)
Thyroid hormones	
T3 (ng/dL)	93.61 (54.5–152.4)
fT4 (ng/dL)	1.33 (0.70–1.80)
TSH (μIU/mL)	2.13 (0.2–4.5)
Creatinine (mg/dL)	1.11 (0.42–2.76)
Albumin (mg/dL)	3.6 (2.5–4.6)
d-dimers (mg/L)	3.3 (0.37–10.39)
cTnT (pg/mL)	47 (3–225.8)
NT-pro-BNP (pg/mL)	842.81 (10.38–4229)
Echo or ECG indices of RV dysfunction	9 (29)
DVT	16 (51.6)

$PaCO_2$: partial pressure of carbon monoxide, arterial; DVT: deep venous thromboembolism; ECG: electrocardiogram.

APACHE II score was also significantly lower in patients who died (median APACHE II score, 28.25; range, 26–32, $n = 4$) than that in those who survived (median APACHE II score, 13.07; range, 2–29 pg/ml, $n = 27$). Pulmonary gas exchange impairment was significantly greater ($P < 0.01$, unpaired t-test) in patients who died (median PaO_2/FiO_2 ratio 175; range 127–212, $n = 4$) than in those who survived (median PaO_2/FiO_2 ratio 319.59; range 130–450, $n = 27$). Finally, cTnT levels were significantly higher ($P < 0.05$, unpaired t-test) in patients who died (median cTnT 103.38 pg/mL; range 53–193 pg/mL, $n = 4$) than in those who survived (median cTnT 38.72 pg/mL; range 3–225.8 pg/mL, $n = 27$).

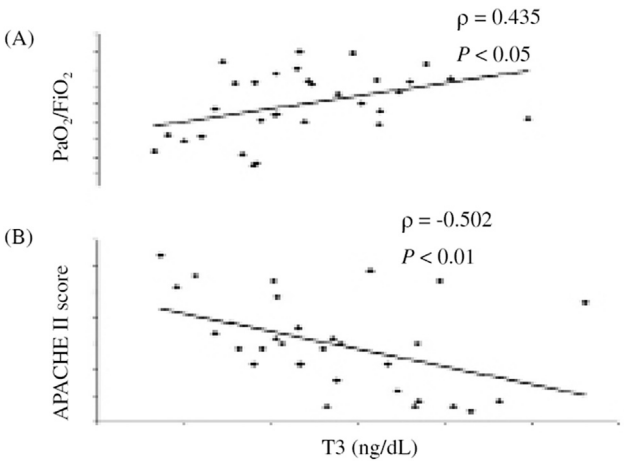

Figure 1. Relationship between plasma levels.
A: Relationship between plasma levels of T3 and the ratio of the partial pressure of oxygen in arterial blood to the fraction of oxygen in inspired gas (PaO_2/FiO_2); B: Relationship between plasma levels of T3 and APACHE II score. Data were obtained in 31 patients with acute pulmonary embolism upon admission to the pulmonary department.

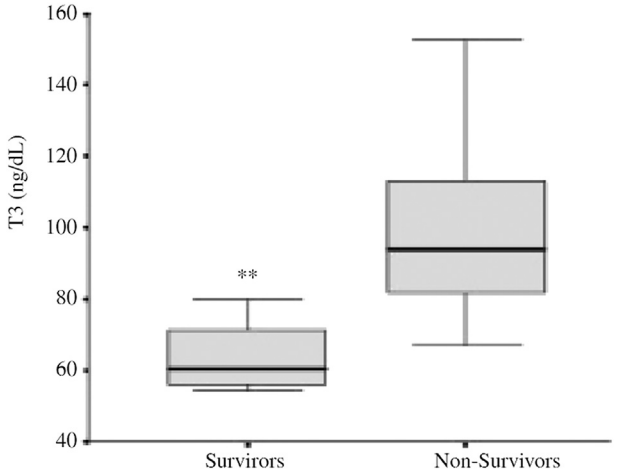

Figure 2. Difference of plasma T3 levels between survivors (n = 27) and non-survivors (n = 4) from acute PE.
T3 levels were compared by analysis of variances. **: $P < 0.01$ *vs.* non-survivors.

Statistical analysis revealed significantly lower T3 levels in patients with hemodynamic instability ($P < 0.05$; median T3 72.48 ng/dL; range 54.5–102.7 ng/dL, n = 5) or in patients with RV dysfunction or myocardial necrosis ($P < 0.01$; median T3 80.61 ng/dL; range 62.5–95.8 ng/dL, n = 8) compared with low risk patients (median T3 102.15 ng/dL; range 75.90–152.4 ng/dL, n = 18). In contrast, no significant difference in TSH and fT4 levels was detected between the three groups of patients. In accordance with these findings, a significant inverse correlation was found between T3 and cTnT (Spearman's ρ = –0.462, $P < 0.01$) or NT-pro-BNP levels (ρ = –0.464, $P < 0.01$). No significant correlation was observed between serum fT4 or TSH and cTnT or NT-pro-BNP levels. The correlation analysis of thyroid hormones levels and serum markers of myocardial injury and RV function is showed in Table 2.

APACHE II score was also significantly lower in high-risk patients ($P < 0.01$; mean APACHE II score 26.2 ± 2.51, n = 5) and intermediate risk patients ($P < 0.05$; mean APACHE II score, 19 ± 1.94, n = 8) compared with low risk patients (mean APACHE II score, 10.16 ± 1.58, n = 18). Furthermore, PaO_2/FiO_2 ratio was significantly lower in patients with hemodynamic instability ($P < 0.05$; mean PaO_2/FiO_2 208.2 ± 33.72, n = 5) compared with low risk patients (mean PaO_2/FiO_2 323.67 ± 21.58, n = 18). In this study sample, none of the thyroid parameters was correlated with length of in hospital stay. The length of in hospital stay was negatively correlated with PaO_2/FiO_2 ratio (ρ = –0.395, $P < 0.05$) and positively correlated with APACHE II score (ρ = 0.518, $P < 0.01$) and troponin levels (ρ = 0.577, $P < 0.001$).

In univariate logistic regression analysis, the only factor significantly associated with an increased risk of death was T3 (OR = 1.229; 95% *CI* 1.022–1.477, P = 0.028) (Table 3).

Table 2
Correlation analysis of thyroid hormones levels with serum markers of myocardial injury and cardiac function.

Variables	cTnT	NT-pro-BNP
T3	ρ = –0.574, $P < 0.01$	ρ = –0.460, $P < 0.01$
fT4	ρ = –0.21, P = 0.909	ρ = 0.075, P = 0.69
TSH	ρ = –0.45, P = 0.811	ρ = 0.051, P = 0.786

Table 3
Univariate logistic regression analysis for variables associated with mortality in patients with acute PE.

Variables	P	OR	95% *CI*
T3	0.028	1.229	1.022–1.477
PaO_2/FiO_2 ratio	0.083	1.013	0.998–1.028
APACHE II score	0.110	0.592	0.84–1.040
cTnT	0.075	0.987	0.973–1.001
Age	0.309	0.965	0.901–1.034
FT4	0.946	1.172	0.012–113.577
TSH	0.696	0.850	0.376–1.921
Albumin	0.141	4.691	0.598–36.806
NT-pro-BNP	0.891	1.000	0.999–1.001

Table 4
Multivariate logistic regression analysis of risk factors associated with mortality in patients with acute PE.

Variables	P	OR	95% *CI*
T3	0.034	1.226	1.016–1.479
PaO_2/FiO_2 ratio	0.047	1.007	0.987–1.028

Multivariate logistic regression analysis, including variables with $P < 0.1$, was performed to identify factors with independent predictive value for in hospital mortality, controlling for possible confounders. T3 was independently related to increased risk of death (OR = 1.229; 95% *CI* 1.022–1.477, P = 0.028). The results of multivariate analysis are shown in Table 4.

4. Discussion

This preliminary prospective study evaluated and tested the prognostic value of thyroid hormones measured at admission in a small cohort of patients with acute PE. A literature search revealed that the present study is the first to investigate the thyroid status in patients with acute PE. Of the 31 patients included in the analysis, reduced T3 levels were found in 22.6% of the patients, while fT4 and TSH plasma levels were reduced in only 1 patient. Plasma levels of T3 were related to severity, risk status and gas exchange defect, as reflected by APACHE II score, the levels of cTnT and NT-pro-BNP and PaO_2/FiO_2 ratio respectively. The remaining two of the evaluated indicators of thyroid function, TSH and fT4, did not show any association with the aforementioned parameters. In several previous studies, low plasma T3 or fT3 levels are associated with severity scores such as APACHE II score and/or a worse prognosis of the underlying disease in critical ill patients[6,8,10,12,18,22]. Furthermore, lower fT3 levels have been reported in patients with respiratory failure from different pulmonary disorders[6]. In the past, NTIS had long been considered as an adaptive physiologic response, but growing evidence suggests that this syndrome may contribute or directly promote clinical deterioration in the setting of a critical illness[5,19].

In our study, plasma T3 levels were significantly lower in non-survivors than those who survived to hospital discharge. Conversely, there was no difference in age, sex and metabolic parameters between the two groups of patients. In fact, T3 was the only thyroid indicator that proved to be an independent predictor of in-hospital mortality in logistic regression analysis. Similarly, a number of previous studies have demonstrated low plasma T3 levels as a predictor of worse clinical outcome in

various cardiovascular disorders[23,24] including heart failure[13,25], coronary artery disease[26] or patients with coronary artery bypass[17]. In addition, our results show that T3 levels were significantly lower in patients with risk factors of early mortality compared with low-risk patients. More interestingly, plasma T3 negatively correlated with cTnT or NT-pro-BNP levels which have been shown to be independent predictors of short-term mortality in patients with acute PE[20,21]. Therefore, we could hypothesize that the T3 level may serve as an indicator of hemodynamic compromise, poor RV function or myocardial injury in patients with PE.

There is still great uncertainty concerning the possible interactions between lower plasma fT3 or T3 levels and the major pathophysiological pathways implicated in critical cardiopulmonary distress. Low T3 serum concentrations have been associated with cardiac function and NT-pro-BNP levels in patients with heart failure[13,25,26] or acute coronary syndromes[12]. Recently, fT3 levels have been also correlated with echocardiographic and serum markers of myocardial dysfunction and injury including serum cardiac troponin I in patients with acute myocardial infraction[16,27]. Moreover, the elevation of serum T3 levels above normal by the intravenous administration of T3 in patients with coronary artery bypass was coupled with enhanced cardiac output and reduced need for vasoactive support[28]. Relevantly, endogenous T3 has been shown to possess positive inotropic and chronotropic properties[29]. Furthermore, it appears to promote a more efficient diastolic relaxation, thus improving the myocardial metabolism[30]. Finally, T3 exhibits a rapid upregulating effect on the rat alveolar epithelial Na-K-ATPase that enhances the removal of edema fluid from the alveolar space[31]. On the other hand, small clinical studies of thyroid hormone replacement therapy in critically ill patients with NTIS failed to demonstrate an improvement in survival[32,33].

In summary, our preliminary clinical study suggests that plasma T3 levels may be used as a predictor of outcome in patients with PE. Furthermore, T3 levels correlated with other markers indicating the risk of PE-related early death. In other words, T3 levels may be as an additional marker for the stratification of patients with PE depending on the risk of in-hospital or short-term death. The small size of our study sample hinders any attempt to further clarify if this low T3 state represents an adaptive response to stress that coincides with respiratory and/or circulatory compromise or if it actually contributes to the pathogenesis of this compromise. In any case, the potential prognostic ability of thyroid indicators such as T3 seems compatible with the role of thyroid hormones in maintaining homeostasis and promoting adaptation in the face of acute stress through modulation of various multifactorial mechanisms. The preliminary observations of our study require further validation in larger populations in order to clarify the underlying mechanisms implicating thyroid dysfunction during acute PE. Larger studies may also warrant the investigation of a possible benefit from reversal of NTIS by thyroid hormone replacement therapy in patients with acute PE. This therapeutic modality could be conferred for the subgroup of patients with increased risk of early death caused by acute PE.

The present study has its limitations. To begin with, for the assessment of thyroid function we used a selected panel of thyroid indicators (T3, fT4, TSH) which is commonly used by our laboratory in every day practice. Generally, plasma T3 and fT3 are both reduced in NTIS. However, T3 or T4 levels are partly dependent upon the concentration or the binding ability of binding proteins mainly thyroxine-binding globulin. Therefore T4 and to a lesser degree T3 levels may be affected by various pathological conditions (for example liver insufficiency) or by a number of therapeutic agents. On the other hand, the measurement of T3 in hospitalized patients is useful for the recognition of nonthyroidal illness due to the decreased 5′-monodeiodinase activity. It is possible that a more extensive testing for thyroid function (T3, fT3, reverse T3, T4, fT4, TSH) would provide a more integrative evaluation, but this was not within the available resources of our institution.

Second, although patients with overt thyroid disorders were excluded, the probability of previously undiagnosed thyroid disease in some patients before admission could not be completely ruled out in the present study. In addition, given that numerous drugs may affect the thyroid axis, it is difficult to adjust for every one of these drugs. However, patients receiving amiodarone, corticosteroids or any kind of replacement therapy were excluded from the study, while blood samples were obtained from patients at the time they were admitted to the emergency room and before the administration of any anticoagulant agent.

In conclusion, in this preliminary study, baseline plasma T3 was a predictor of mortality in patients with acute PE. T3 levels significantly correlated with the severity as reflected by the APACHE II score and with impairment of oxygenation as reflected by the PaO_2/FiO_2 ratio. Furthermore, T3 levels correlated with baseline NT-pro-BNP and cTnT levels that are used for the early stratification of patients as markers indicating the risk of early death from PE.

Conflict of interest statement

The authors report no conflict of interest.

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