

Original Article

Is non-thyroidal illness syndrome a predictor for prolonged weaning in intubated chronic obstructive pulmonary disease patients?

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Abstract: Introduction: Non-thyroidal illness syndrome (NTIS) is considered to be associated with adverse outcomes in intensive care unit (ICU) patients. In this study, we evaluated the association between NTIS and prolonged weaning in chronic obstructive pulmonary disease (COPD) patients admitted to the ICU. Materials and methods: In total, 125 patients with COPD admitted to our ICU who underwent invasive mechanical ventilation (MV) were enrolled. We collected each patient's baseline characteristics including Acute Physiology and Chronic Health Evaluation (APACHE) II score, body mass index (BMI), and thyroid hormones 24 h after ICU admission. The presence of pulmonary infection was also recorded. The primary outcome was prolonged weaning, defined as patients who failed at least three weaning attempts or required > 7 days of weaning after the first spontaneous breathing trial. Results: Of the 127 patients studied, 64 had normal thyroid function tests and 61 had NTIS. Patients with NTIS had significantly higher APACHE II scores, prolonged weaning, and pulmonary infection. Patients with NTIS had a higher risk for prolonged weaning (odds ratio, OR = 3.21; 95% CI = 1.31-7.83). The presence of pulmonary infection was also an independent risk factor for prolonged weaning. Conclusions: NTIS may be an independent predictor for prolonged weaning in intubated COPD patients.

Keywords: NTIS, prolonged weaning, ICU, COPD

Introduction

Non-thyroidal illness syndrome (NTIS) is a variable condition of abnormal thyroid hormone concentrations that can rise in the serum following any acute or chronic illness that is not due to an intrinsic abnormality in thyroid function [1]. The prevalence of NTIS is about 11-18% in records of non-selected hospitalized patients and rises to 60-70% in patients admitted to the ICU [2, 3]. The pathogenesis of the syndrome is still not well understood; an imbalance between the activities of types I and II deiodinase, decreased sensitivity of the hypothalamus and pituitary gland to thyroid hormones, and reduced T4 protein binding and cellular uptake have been proposed [4]. It has been much debated whether NTIS represents a physiological adaptive response to systemic illness or conversely a maladaptive state at the tissue level [4]. NTIS and adverse outcomes have

been associated in patients with sepsis, acute respiratory distress syndrome, respiratory failure, and mechanical ventilation (MV) in ICU patients [5-9]. The magnitude of changes in serum T3 and T4 do not depend on the type of illness, but rather on its severity [10].

Chronic obstructive pulmonary disease (COPD) is characterized by significant chronic inflammation not only in the pulmonary compartment, but also in the systemic circulation. This disorder is associated with clinically significant systemic changes in biochemistry and organ function [11, 12]. There are also significant changes in thyroid hormones, which are related to the severity of disease and hypoxemia. In addition, the severity of disease, through hypoxemia, is important in determining the peripheral metabolism of thyroid hormones. COPD patients frequently have difficulties weaning from invasive MV. Moreover, prolonged invasive ventilation causes various complications in these patients.

The weaning process is a key element of MV, taking up to 50% of its total duration [13]. Based on the overall duration of weaning and the number of spontaneous breathing trials required to liberate a patient from a ventilator, weaning from MV has been categorized as simple, difficult, or prolonged by an international task force of the American Thoracic Society, European Respiratory Society, European Society of Intensive Care Medicine, Society of Critical Care Medicine, and Société de Réanimation de Langue Française (**Table 1**) [14]. The spontaneous breathing trial has been identified as the major diagnostic test to determine whether patients can be extubated successfully. Prolonged weaning is associated with increased mortality and morbidity in the ICU [15].

Predictors can be important for intensive care physicians to know when to expect prolonged weaning. A few studies have shown that NTIS is associated with prolonged MV and worse outcomes in patients admitted to the ICU [5, 7, 16] but not according to these weaning categories. In this study, we evaluated the relationship between NTIS and various factors and to clarify whether it can be a predictor of prolonged weaning in COPD patients.

Materials and methods

This study was planned as a prospective cohort. Patients with COPD admitted to our ICU who had undergone invasive mechanical ventilation were enrolled. These patients were known to have a history of COPD that was diagnosed by their primary physician according to previous pulmonary function tests and GOLD criteria [17]. They were also under medication for COPD. We excluded patients who received non-invasive ventilation without subsequent intubation, patients who died or were transferred to another ICU before they were ready to wean, and patients who experienced unplanned extubation before or during the weaning process. The additional exclusion criteria were the following: intrinsic thyroid or pituitary-hypothalamic disease; use of iodine contrast agents in the previous 8 weeks; renal or hepatic failure, transfusion of plasma protein within 48 h prior to thyroid hormone assessment; MV for < 24 h; and use of special drugs known to affect serum thyroid hormone concentrations, such as , ami-

odarone, moderate to high dose of vasopressors (dopamine or dobutamine $\geq 5 \mu\text{g}/\text{kg}/\text{min}$; epinephrine or norepinephrine $\geq 0.5 \mu\text{g}/\text{kg}/\text{min}$). We collected each patients demographic and baseline characteristics including age, gender, BMI, APACHE II score, thyroid hormone that was calculated 24 h after admission. Accompanying infection in ICU also recorded. The study was approved by the Ethics Committee of our hospital.

Diagnosis of NTIS was established when free triiodothyronine (fT3) levels were below the lower limit, and/or free thyroxin (fT4) levels were within the normal or low limits and TSH levels were within the normal or low limits mentioned.

Thyroid laboratory tests

Serum thyroid hormone concentrations were analyzed by chemo-luminescence, immune-assay method in an ADVIA Centaur hormone analyzer. Blood was drawn from nonheparinized arterial lines.

Anthropometric measurement

For anthropometric measurement, BMI [weight (kg)/height (m)²] was calculated. Subjects were categorized according to World Health Organization classification (BMI: < 18 kg/m² thin, 18-25 kg/m² of acceptable weight, 25-30 kg/m² of excessive weight and > 30 kg/m² obese) [18]. The diagnosis of infection was established by means of clinical and microbiological criteria described elsewhere [19-22]. Prolonged weaning was defined as patients who fail at least three weaning attempts or require > 7 days of weaning after the first spontaneous breathing trial [14].

Weaning procedures

Weaning was conducted according to the current statement of the ERS, ATS, ESICM, SCCM and SRLF [14]. Weaning was considered as early as possible and a two-step strategy was applied. First, readiness for weaning was assessed daily according to the criteria in the panel pronouncement [14]; patients who fulfilled these criteria underwent a spontaneous breathing trial as a diagnostic test to determine the likelihood of successful extubation. The initial spontaneous breathing trial lasted 30 min

NTIS a predictor for prolonged weaning

Table 1. Classification of patients according to the weaning process

Group/category	Definition
Simple weaning	Patients who proceed from the initiation of weaning to successful extubation on the first attempt without difficulty
Difficult weaning	Patients who fail initial weaning and require up to three spontaneous breathing trials or as long as 7 days from the first spontaneous breathing trial to achieve successful weaning
Prolonged weaning	Patients who fail at least three weaning attempts or require > 7 days of weaning after the first spontaneous breathing trial

NTIS a predictor for prolonged weaning

Table 2. Baseline and demographic characteristics of study subjects

Variables	NTIS (n=64)	No NTIS (n=61)	P
Age (yr. median, range)	66 (61-75)	65 (58-72)	0.17
Male (n, %)	51 (79)	50 (81)	0.74
APACHE II score (median, range)	29 (23-35)	24 (19-28)	<0.001
BMI (median, range)	26 (27-34)	28 (26-31)	0.51
Accompanying infections (n, %)	48 (75)	18 (30)	<0.001
Prolonged Weaning (n, %)	46 (71)	19 (31)	<0.001
Thyroid function			
fT3 (pg/mL)	1.60 (0.90-1.88)	2.48 (2.31-2.70)	<0.001
fT4 (pg/mL)	0.97 (0.73-1.13)	1.21 (1.06-1.67)	<0.001
TSH (mIU/mL)	0.75 (0.38-1.47)	0.45 (0.14-2.20)	<0.001

NTIS: Non-thyroidal illness syndrome. APACHE II, Acute Physiology and Chronic Health Evaluation II, fT3, free triiodothyronine, fT4, free thyroxine, TSH, thyroid-stimulating hormone.

and consisted of breathing with a T-tube. When a patient successfully passed the spontaneous breathing trial according to these specified criteria's, extubation was suggested. The final decision to extubate was made by the physician in charge. When a patient failed the initial spontaneous breathing trial according to the these criteria [14], mechanical ventilation was re-instituted. Then the clinician reviewed the possible reversible etiologies for the failure. The spontaneous breathing trial was repeated on the next day, if the patient was again ready-to-wean. If the patients failed SBT for three consecutive days, they were connected to the ventilator in PSV mode and pressure support was reduced gradually until 10 cm H₂O of pressure support is tolerated [23].

A patient was rated as successfully weaned when he or she was extubated and was breathing spontaneously without any invasive or non-invasive ventilatory support for ≥ 48 h. Patients who had undergone tracheotomy before they were ready to be weaned were considered successfully weaned when they were breathing spontaneously either through the tracheal cannula or directly via tracheotomy for 48 h without any support [14]. If a patient was re-intubated after successful primary weaning and subsequently recommenced secondary weaning, only the primary weaning episode was used to define the patient's weaning category.

Statistical analysis

Data analysis was performed by using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL,

United States). Continuous data were shown as median (25th-75th percentiles) and compared with Mann-Whitney U test or Kruskal Wallis test in case of more than 2 groups are present. When the *p* value from the Kruskal Wallis test statistics are statistically significant Conover's non-parametric multiple comparison test was used to know which group differ from which others. Categorical data were shown as numbers with percent-

ages and analyzed Fisher's exact test, where applicable. A *p* value less than 0.05 was considered statistically significant. But, all possible multiple comparisons, the Bonferroni Correction was applied for controlling Type I error.

Results

One hundred and twenty seven patients (81% male and 19% female, mean age 65 \pm 11 years) were included. Of the 127 patients, 64 had NTIS, while 61 had not. Two patients who did not have a clinical diagnosis were found to have hypothyroidism based on laboratory studies and excluded from the study.

The baseline clinical and laboratory characteristics of the patients are listed in **Table 2**. Groups were similar in terms of age, sex and BMI. In the univariate analysis the level of fT3, fT4 and TSH were lower (*P*<0.001) while the APACHE II score, presence of pulmonary infection and prolonged weaning were significantly higher (*P*<0.001) in patients with NTIS when compared to the normal hormone group.

The analysis of the study population showed no difference between prolonged weaning and the others regarding age, sex, BMI and level of fT4 and TSH. Patients in prolonged weaning group showed higher APACHE II score, presence of pulmonary infection, NTIS and ICU deaths (*P*<0.001). Prolonged weaning group also had lower baseline levels of fT3 (*P*<0.001). (**Table 3**) Patients with newly diagnosed hypothyroidism were treated with thyroid supplement therapy and both of them were successfully liberated from mechanical ventilation.

NTIS a predictor for prolonged weaning

Table 3. Comparison of prolonged weaning group with simple or difficult weaning groups

Variables	Weaning category		P
	Prolonged (n=65)	Simple or difficult (n=60)	
Age yr.	65 (60-75)	65 (57-72)	0.25
Male %	51 (83)	50 (81)	0.5
APACHE II score (points)	30 (24-35)	23 (20-28)	<0.001
BMI	28 (26-33)	29 (28-33)	0.1
NTIS	46 (70)	18 (30)	<0.001
Accompanying infections (%)	46 (70)	20 (33)	<0.001
ICU deaths	45 (69)	6 (10)	<0.001
Thyroid function			
fT3 (pg/mL)	1.70 (1.01-2.07)	2.19 (1.60-2.54)	0.001
fT4 (pg/mL)	1.01 (0.70-1.32)	1.17 (0.99-1.55)	0.06
TSH (mIU/mL)	0.68 (0.24-1.62)	0.51 (0.29-1.70)	0.94

APACHE II, Acute Physiology and Chronic Health Evaluation II, BMI, body mass index, NTIS, Nonthyroidal Illness Syndrome, fT3, free triiodothyronine, fT4, free thyroxine, TSH, thyroid-stimulating hormone.

Table 4. Independent predictors of prolonged weaning by multivariate logistic regression model

Predictor	OR	95 % CI	P
FT3	0.76	0.44-1.33	0.34
FT4	1.02	0.61-1.71	0.93
Presence of pulmonary infection	2.67	1.13-6.29	0.025
NTIS	3.21	1.31-7.83	0.01

FT3, free triiodothyronine, FT4, free thyroxine, NTIS, Non-thyroidal illness syndrome.

We performed a forward stepwise multivariate logistic regression analysis to evaluate the independent predictors of prolonged weaning. The results are shown in **Table 4**. The multivariate model showed that FT3 (OR: 0.76, 95% CI 0.44-1.33), FT4 (OR: 1.02, 95% CI 0.61-1.71), NTIS (OR: 3.21, 95% CI 1.31-7.83) and accompanying infection (OR: 2.67, 95% CI 1.13-6.23) were associated with prolonged weaning.

Discussion

The main finding of this study is that NTIS may be an independent predictor of prolonged weaning in intubated COPD patients. Higher APACHE II scores and the presence of pulmonary infection may also be associated with prolonged weaning in these patients.

Previous studies have shown that NTIS is a predictor of outcome in patients admitted to the ICU [7, 16, 24, 25]. Patients with NTIS have

been found to receive MV more often than those with normal hormone levels [7]. The pathophysiological mechanism underlying this association has yet to be fully explained. Several compounds, such as cytokines (e.g., IL6, TNF, INF- α), some drugs (e.g. glucocorticoids, furosemide, amiodarone), and free fatty acids may contribute to thyroid hormone levels. TT3 and TT4 levels can be affected by the concentration or binding ability of thyroxin-binding globulin (TBG), which may be affected by some health conditions such as liver disease, and many commonly used drugs including glucocorticoids, non-steroidal anti-inflammatory drugs, furosemide, and heparin. Conversely, FT3 and FT4 levels are relatively less affected by these factors. We used FT3 and FT4 levels because they may be better than TT3 and TT4

levels for predicting ICU outcomes in COPD patients.

In addition, especially inflammation and cytokines in COPD patients can affect FT3 levels. FT3 levels have also been shown to be correlated with the frequent presence of and an adverse prognosis for patients with coronary artery disease, even after adjusting for traditional risk factors [26]. NTIS, especially low FT3 levels, may represent an integrative measure of multiple harmful pathological processes occurring simultaneously in patients with COPD, such as inflammation status, hypoxia, and cardiac dysfunction, which are associated with adverse outcomes. Thus, latent or unrecognized pathological processes may become manifest with the initiation of weaning attempts. NTIS can be used as an independent predictor of these processes that cause prolonged weaning. Bello et al. reported that NTIS was a risk factor for pro-

longed MV [6]. Our findings are consistent with this. However, there are some differences between that study and ours, such as variation in the definition of prolonged weaning and the study population. We defined prolonged weaning as patients who failed at least three weaning attempts or required > 7 days of weaning after the first spontaneous breathing trial according to the ERS classification [14]. Only patients with COPD were enrolled in our study.

Hypothyroidism is a reversible cause of ventilator-dependent respiratory failure. Correction of hypothyroidism was reported to be helpful for the weaning of patients [27, 28]. Our results for two patients with newly diagnosed hypothyroidism were similar. They were successfully liberated from MV following appropriate therapy with thyroid supplements. Obesity may contribute to prolonged MV in patients with hypothyroidism [27]. Reduced lung volumes and diaphragmatic dysfunction in patients with hypothyroidism have been assumed to be due to obesity [29]. However, there are some controversial studies on the role of obesity in prolonged MV [30, 31]. For example, Kumar et al. showed that rates of prolonged MV were similar between obese and non-obese patients [30]. Similarly, in our study, we found no significant difference between BMI and prolonged weaning.

Indicators such as TT3, TT4, TSH, FT3, and FT4 have previously been detected in connection with ICU outcomes [7, 24, 32, 33]. Ray et al. showed that there was no association between FT3 and adverse outcomes in ICU patients [33]. In contrast, Wang et al. reported that FT3 was the *only* predictor of ICU mortality [16]. Our study is consistent with this finding. We found that FT3 was significantly lower in patients with prolonged weaning than in others. In addition, mortality in the ICU was higher in patients with prolonged weaning.

We found that NTIS was an independent predictor of prolonged weaning in patients with COPD admitted to our ICU. Likewise, taking into consideration baseline thyroid function tests can add to the predictive capacity of the APACHE II score [24]. Prolonged weaning is associated with increased mortality and morbidity in the ICU [15]. It is also associated with increased days spent in the ICU, increased rates of pneumonia, and increased cost of treatment.

Previous studies have reported that an early tracheostomy resulted in increased successful weaning and ICU discharge rate, and a reduced incidence of pneumonia [34-37]. This should be kept in mind for patients where prolonged weaning is anticipated. Early and intensified physiotherapy and rehabilitation may be useful for this group of patients in the ICU [38]. For these reasons it is important for intensive care physicians to expect prolonged weaning and develop more appropriate management plans for these patients. It is easier to expect prolonged weaning in patients with myopathic, neurological, or neurosurgical causes of admission than patients with COPD. Our findings may help physicians decide on an early tracheostomy and intensified physiotherapy and rehabilitation for patients with COPD.

In this study, pulmonary infections were detected more frequently in patients with NTIS. Several inflammatory cytokines can suppress, via direct or indirect pathways, thyroid function at different levels [39]. And also, immune system cells can affect thyroid hormone activity [40]. According to these findings, treating especially pulmonary infections carefully in patients with NTIS may play an important role in the management of prolonged weaning.

This study has several limitations. First, the sample size was small. Second, it is clear that many drugs (e.g., propranolol, barbiturates, benzodiazepines, furosemide, and dopamine) may interfere with thyroid functions. In clinical practice, it is difficult to adjust for these confounders in clinical practice, especially in the ICU, because so many drugs are involved. However, blood samples were obtained from patients at the time they were admitted to the ICU. Most of the patients had not been given any new drugs before obtaining blood samples. Moreover, FT3 levels seem not to be affected greatly by these factors.

In conclusion, NTIS may be an independent predictor of prolonged weaning, as assessed by APACHE II score and the presence of pulmonary infection, in intubated COPD patients. It should be kept in mind in this patient group if the weaning duration exceeds 1 week. Furthermore, further studies are needed to determine whether substitution treatment with thyroid hormones can be helpful in weaning.

Disclosure of conflict of interest

None.

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NTIS a predictor for prolonged weaning

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