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Nonthyroidal Illness Syndrome and Prolonged Mechanical Ventilation in Patients Admitted to the ICU*

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Background: **The effect of the nonthyroidal illness syndrome (NTIS) on the duration of mechanical ventilation (MV) has not been extensively investigated. This study aims to determine whether the NTIS is associated with the duration of MV in patients admitted to the ICU.**
Methods: **We evaluated all patients admitted over a 6-year period to our ICU who underwent invasive MV and had measurement of serum free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) performed in the first 4 days after ICU admission and, subsequently, at least every 8 days during the time they received MV. The primary outcome measure was prolonged MV (PMV), which was defined as dependence on MV for > 13 days.**
Results: **Two hundred sixty-four patients were included. Fifty-six patients (normal-hormone group) had normal thyroid function test results, whereas 208 patients (low-fT3 group) had, at least in one hormone dosage, low levels of fT3 with normal (n = 145)/low (n = 63) levels of fT4 and normal (n = 189)/low (n = 19) levels of TSH. Patients in the low-fT3 group showed significantly higher mortality and simplified acute physiology score II, and significantly longer duration of MV and ICU length of stay compared with the normal-hormone group. Two of the variables studied were associated with PMV, as follows: the NTIS (odds ratio [OR], 2.25; 95% confidence interval [CI], 1.18 to 4.29; p = 0.01); and the presence of pneumonia (OR, 1.17; 95% CI, 1.06 to 3.01; p = 0.03).**
Conclusion: **The NTIS represents a risk factor for PMV in mechanically ventilated, critically ill patients.** ***(CHEST 2009; 135:1448–1454)***

Abbreviations: APACHE = acute physiology and chronic health evaluation; ARF = acute respiratory failure; fT3 = free triiodothyronine; fT4 = free thyroxine; LOS = length of stay; MV = mechanical ventilation; NTIS = nonthyroidal illness syndrome; PMV = prolonged mechanical ventilation; SAPS = simplified acute physiology score; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine

The nonthyroidal illness syndrome (NTIS) is a variable situation of abnormal thyroid function test results found in patients with acute or chronic systemic illnesses.[1–6] The laboratory parameters of NTIS include low serum levels of triiodothyronine (T3) and high levels of reverse T3, with normal or low levels of thyroxine (T4) and normal or low levels of thyroid-stimulating hormone (TSH).[5,7,8] This condition affects 60 to 70% of critically ill patients.[1,9–11] In this context, NTIS has been proven to be a predictor of outcome.[12–15]

The widespread changes in serum thyroid hormone levels in the critically ill patient seem to occur as a result of the following: (1) alterations in the peripheral metabolism of the thyroid hormones; (2) alterations in TSH regulation; and (3) alterations in the binding of thyroid hormone to thyronine-binding protein. A myriad of medications as well as a number of factors and clinical conditions commonly present in the very ill patient may induce a NTIS.

Although primary hypothyroidism alters respiration by causing abnormalities in the respiratory system,[16] while responding to the thyroid hormone therapy,[17–19] the role of the NTIS on the duration of mechanical ventilation (MV) remains to be elucidated. The aim of this study was to evaluate the effect of the NTIS on the duration of MV in mechanically ventilated patients admitted to the ICU.

Materials and Methods

Our institutional review board approved the protocol. Considering that the retrospective nature of the investigation focused on aspects of our usual clinical practice, the informed consent was waived.

Setting and Study Design

We evaluated all patients admitted between January 1, 2001, and December 31, 2006, to our 18-bed general ICU who had undergone invasive MV and had measurements made of serum-free T3 (fT3), free T4 (fT4), and TSH levels in the first 4 days after admission and, subsequently, at least every 8 days during the period they received MV. The following two groups of patients were considered for analysis: (1) the normal-hormone group, in which serum levels of fT3, fT4, and TSH were normal throughout all the period of MV; and (2) the low-fT3 group, whose patients had, at least in one measurement during MV, low serum levels of fT3, normal or low serum levels of fT4, and normal or low serum levels of TSH. The latter group was divided into the following two subgroups: (1) patients with normal serum levels of fT4; and (2) patients with low serum levels of fT4 at least in one measurement during MV.

Criteria for Evaluating Thyroid Function

FT3, fT4, and TSH were ordered in the case of a clinical suspicion for thyroid dysfunction, according to the protocol routinely followed in our institution. Hypothyroidism was suggested by the following clinical manifestations in the absence of other evident explanation: goiter (enlarged thyroid gland on sonography); mental obtundation; dry skin; hypothermia; bradycardia and hypotension; large tongue; sluggish tendon reflexes; constipation; pericardial or peritoneal effusion; weight gain; thinning hair or hair loss; and laboratory abnormalities such as anemia and increased serum levels of cholesterol, triglycerides, creatinine phosphokinase, lactate dehydrogenase, or glutamic-oxaloacetic transaminase.

The signs and symptoms that suggested hyperthyroidism and that were not otherwise explained were the following: goiter; tachyarrhythmias; tremors or nervousness; weight loss; hair loss; increased sweating; increased bowel movements; lumpy and reddish thickening of the skin in front of the shins; and clinically evident ophthalmopathy including eyelid retraction, proptosis, conjunctival exposure, scleral injection, ocular chemosis, periorbital edema, retrobulbar pressure or pain, and extraocular muscle dysfunction. Some of the patients included in this study had more than one thyroid hormone assessment because of a persisting clinical suspicion of thyroid dysfunction that remained after the first determination.

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Thyroid Laboratory Tests

The normal ranges of serum hormone concentrations for our laboratory are as follows: fT4, 8.5 to 15.5 pg/mL; fT3, 2.3 to 4.2 pg/mL; and TSH, 0.35 to 2.8 mIU/mL. Serum thyroid hormones concentrations were determined by standard radioimmunoassays. For measuring thyroid hormone levels, blood was drawn from nonheparinized arterial lines.

Prolonged MV and Pneumonia

Prolonged MV (PMV) was defined as dependence on MV for > 13 days, according to the median value of duration of MV in the whole study population. The diagnosis of pneumonia was established by means of clinical and microbiological criteria.[20–23] A modified Clinical Pulmonary Infection Score[20,21] of > 6 was used to diagnose pneumonia.

Patients

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 (respectively, creatininemia ≥ 3.5 mg/dL and bilirubinemia ≥ 6.0 mg/dL); 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, for example, IV glucocorticoids, amiodarone, moderate to high dose of vasopressors (dopamine or dobutamine ≥ 5 μg/kg/min; epinephrine or norepinephrine ≥ 0.5 μg/kg/min). Patients' underlying diseases were classified as follows: (1) COPD; (2) CNS disease (neurologic), including ischemic stroke, hypertensive intracerebral hemorrhage, subarachnoid hemorrhage, head trauma, meningoencephalitis, metabolic encephalopathy, and postneurosurgical states as a result of brain tumor; and (3) acute respiratory failure (ARF) of various etiologies including abdominal surgery, pneumonia, ARDS, sepsis, multiple trauma, heart failure, and acute GI bleeding.

Measurements

In addition to a thyroid profile, the following data were obtained and analyzed: age, sex, reason for ICU admission, duration of MV, length of stay (LOS) and mortality in the ICU, serum albumin concentration measured within 24 h of ICU admission, and the simplified acute physiology score (SAPS) II[24] calculated 24 h after ICU admission. In the case of extubation failure (reintubation within 24 h after extubation) or failure of a 24-h trial of MV discontinuation in patients with tracheostomy, the duration of MV was considered as though MV had never been discontinued.

Statistical Analysis

Data were analyzed using a statistical software package (SAS for Windows, version 8; SAS Institute; Cary, NC). Comparison between groups was performed by the unpaired Student t test, Mann-Whitney test, two-tailed χ^2 test, or Fisher exact test, as appropriate. A logistic regression model was used to identify factors independently associated with PMV. A univariate analysis was initially performed, obtaining for each variable the crude odds ratio; all variables showing $p < 0.2$ in the univariate analysis were entered into the multivariate model. The correlation and linear regression analyses were used to evaluate whether serum hormone levels could affect the duration of MV. Serum thyroid hormone levels considered for the analysis were those of the first measurement. A p value < 0.05 was considered to be statistically significant.

Results

Figure 1 shows the stratification of patients according to their serum thyroid hormone tests results. Over a period of 72 months, 5,285 patients were admitted to our ICU. In 866 of these patients, serum TSH, T3, and T4 levels were measured at least once during their ICU stay. Of these patients whose hormone levels were measured, 731 patients were approached for participation in the study; 135 patients were found not to be eligible because they had not received MV for > 24 h and/or they had not undergone thyroid function testing within the first 4 days of their ICU admission and had subsequently been checked every 8 days during their period of MV. Patients meeting at least one of the exclusion criteria were then excluded, as follows: 62 patients were found to be hypothyroid and 4 were found to be hyperthyroid during their ICU stay; 30 patients were receiving treatment with levothyroxine and 6 with methimazole at ICU admission; 2 patients had an unclear history of thyroid disease; 239 patients were given drugs that may have altered the thyroid hormone profile; 6 patients showed pituitary dysfunction following head injury; 15 patients had received iodine contrast agents in the previous 8 weeks; 59 had renal failure; 14 had hepatic failure; 20 underwent transfusion of plasma within 48 h prior to their serum hormone measurements; and 10 had a goiter. The sample thus included 264 patients.

Data about patients who were not eligible to enter the study were not collected. Of the 264 patients admitted to the study, 56 were assigned to the normal-hormone group, and 208 to the low-fT3 group. Sixty-three patients of the 208 in the low-fT3 group (30.3%) also had low serum levels of fT4 (60 patients at the first hormone assessment and 3 patients at the second assessment). Twelve patients with low fT3 levels and normal fT4 levels, and 7 patients with low levels of either fT3 or fT4 showed low levels of TSH at least in one measurement (Fig 1). Because of their limited number, patients with low TSH levels were not analyzed as a separate subgroup. The analysis performed after excluding these patients showed similar results. Serum thyroid hormone concentrations did not change significantly over time during MV, as assessed by comparing hormone values at the first measurement with those obtained lately.

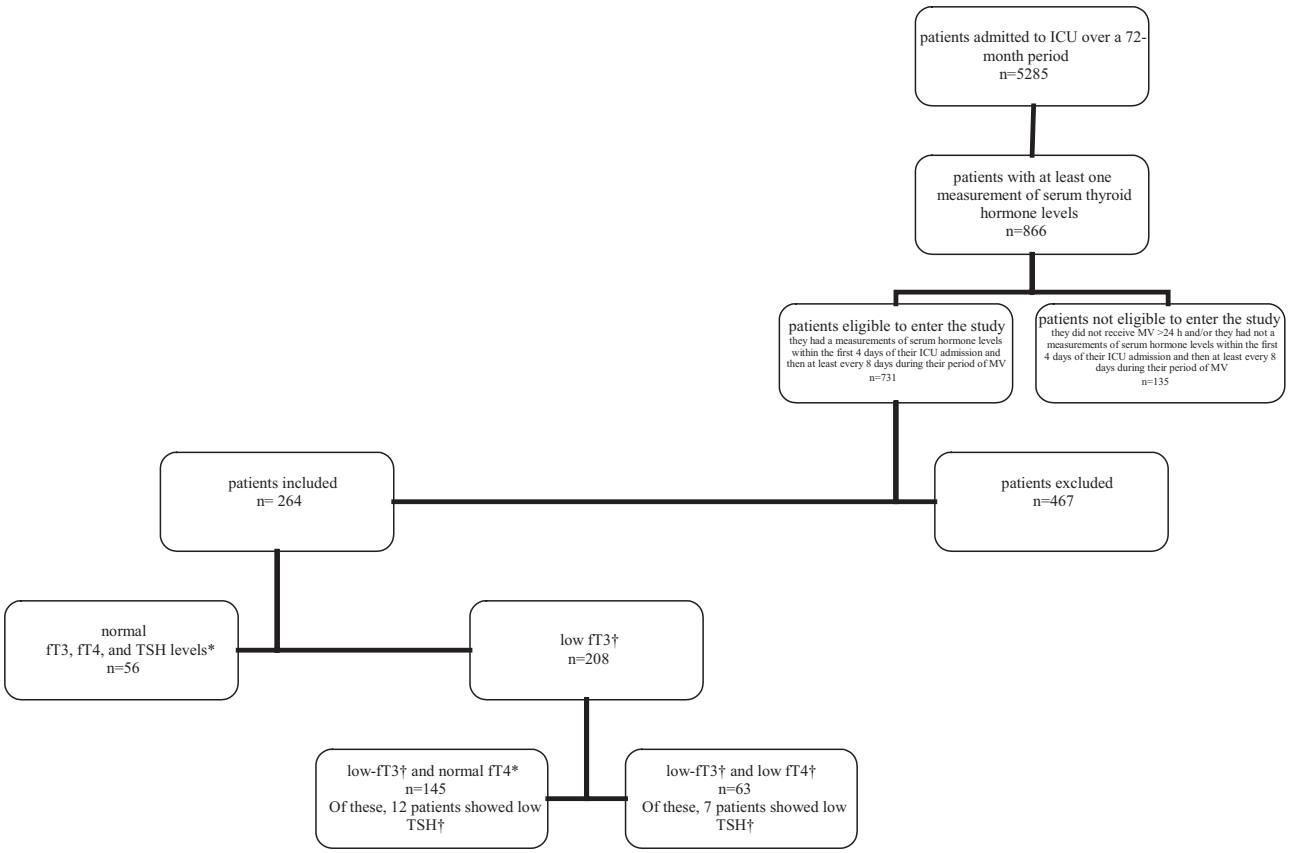

Figure 1. Selection and stratification of patients according to their serum thyroid hormone concentrations. * = throughout the entire period of MV; † = at least in one measurement during MV.

Table 1—*Characteristics of Study Population and Main Outcomes

Variables	Normal-Hormone Group (n = 56)	Low-fT3 Group (n = 208)	p Value
Age, yr	70 (58–76)	71 (60–77)	0.959
Male sex	30 (54)	105 (50)	0.681
Underlying disease			
COPD	11 (20)	50 (24)	0.489
Neurologic	13 (23)	57 (27)	0.528
ARF of various etiologies	32 (57)	101 (49)	0.254
Pneumonia			
Overall	32 (57)	134 (64)	0.317
VAP	21 (38)	102 (49)	0.124
CAP	11 (20)	32 (15)	0.444
SAPS II	38 (31–45)	43 (35–53)	< 0.001
Duration of MV, d	10 (4–14)	13 (7–21)	< 0.001
ICU LOS, d	19 (11–27)	22 (15–33)	0.008
ICU deaths	3 (5.4)	78 (37.5)	< 0.001
Thyroid hormones†			
fT3, pg/mL	2.5 (2.4–2.7)	1.6 (1.1–1.9)	< 0.001
fT4, pg/mL	11.9 (10.9–13.7)	10.0 (8.1–12.3)	< 0.001
TSH, mIU/mL	1.70 (0.93–2.17)	1.06 (0.69–1.70)	< 0.001

*Data are expressed as median (25th to 75th percentile) or No. (%), unless otherwise indicated. CAP = community-acquired pneumonia; VAP = ventilator-associated pneumonia.
†Serum levels at the first dosage.

Table 2—*Characteristics and Main Outcomes of Survivors and Nonsurvivors in the Entire Study Population

Variables	Survived (n = 183)	Died (n = 81)	p Value
Age, yr	69 (58–76)	73 (63–79)	0.074
Male sex	95 (52)	40 (49)	0.705
Underlying disease			
COPD	41 (22)	17 (21)	0.798
Neurologic	51 (28)	19 (23)	0.454
ARF of various etiologies	91 (50)	45 (56)	0.382
Pneumonia			
Overall	113 (62)	53 (65)	0.568
VAP	81 (44)	42 (52)	0.254
CAP	32 (17)	11 (14)	0.428
SAPS II	39 (31–48)	48 (41–57)	< 0.001
Duration of MV, d	11 (6–16)	16 (10–26)	< 0.001
ICU LOS, d	21 (15–31)	24 (14–37)	0.328
Thyroid hormones†			
fT3, pg/mL	2.0 (1.7–2.4)	1.2 (0.9–1.6)	< 0.001
fT4, pg/mL	11.1 (9.4–13.0)	9.4 (7.2–11.3)	< 0.001
TSH, mIU/mL	1.20 (0.78–1.89)	1.10 (0.63–1.71)	0.264

*Data are expressed as median (25th to 75th percentile) or No. (%), unless otherwise indicated. See Table 1 for abbreviations not used in the text.
†Serum levels at the first dosage.

Table 1 reports patients characteristics and main outcomes. Groups were similar in terms of age, sex, diagnosis on admission to the ICU, and the presence of pneumonia.

Patients in the low-fT3 group showed a higher SAPS II and mortality, and a longer LOS in the ICU in comparison to the normal-hormone group (all $p < 0.01$). The median duration of MV was 10 days in the normal-hormone group and 13 days in the low-fT3 group ($p < 0.001$) [Table 1]. Similar results were observed by comparing the normal-hormone group to the two subgroups of the low-fT3 group that were obtained according to the serum levels (normal or low) of fT4 (see online supplemental data).

Stratifying by serum levels of the different thyroid hormones, the duration of MV was found to increase with the decrease in serum levels of fT3 according to the following equation: $y = 25.95 + (-5.97) \times x$, where y is the duration of MV (days) and x is the serum concentration of fT3 (in picograms per milliliter). However, this negative correlation was weak ($r = -0.32$; 95% confidence interval, −0.42 to −0.21; $p < 0.001$), whereas no correlation was observed between either fT4 or TSH levels and the duration of MV.

The analysis of the overall study population showed no significant difference between survivors and nonsurvivors regarding age, sex, underlying disease, and presence of pneumonia. Conversely, nonsurvivors showed a higher SAPS II ($p < 0.001$) and a longer duration of MV ($p < 0.001$) and ICU LOS ($p = 0.328$) when compared to survivors. Nonsurvivors also had lower baseline levels of fT3 ($p < 0.001$), fT4 ($p < 0.001$), and TSH ($p = 0.264$) [Table 2].

According to multiple logistic regression analysis, only the NTIS and the presence of pneumonia showed a univariate association ($p < 0.2$) with PMV, thus entering into the multivariate model. The final model showed that both the NTIS and the presence of pneumonia were associated with PMV (Table 3). This study was not sufficiently powered to support a subanalysis of only those patients with serum thyroid hormone levels measured within the first 24 h of their ICU admission.

Discussion

The main result of this study was that NTIS is associated with a PMV. It still remains controversial whether the NTIS represents a protective or a maladaptive response to illness[6,8,11,25,26] and whether the tissues of patients with NTIS are chemically hypothyroid or euthyroid.[2,6,11,25,26] As some authors have noted,[2,26] a more specific cellular marker for hypothyroidism than those actually available would be needed. Even though this condition has been considered for many years as a transient adaptive process, increasing evidence indicates that an in-

Table 3—*Univariate and Multivariate Analysis of Risk Factors for Prolonged MV (> 13 Days) in the Entire Study Population*

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p Value*	OR	95% CI	p Value*
Age, yr	1	0.98–1.01	0.91			
Male sex	1.33	0.81–2.17	0.24			
Underlying disease						
COPD	0.85	0.48–1.53	0.59			
Neurologic	0.94	0.54–1.63	0.83			
ARF of various etiologies	1.17	0.72–1.9	0.52			
SAPS II	1	0.98–1.02	0.64			
NTIS	2.31	1.22–4.39	0.008	2.25	1.18–4.29	0.01
Pneumonia	1.83	1.09–3.07	0.02	1.17	1.06–3.01	0.03
Serum albumin, g/dL	1.1	0.72–1.69	0.65			

*χ^2 test (analysis of maximum likelihood estimates). The outcome under study was generalized by using a dichotomous variable that could take value 1 in the case of MV duration of > 13 days and 0 in case of MV duration of ≤ 13 days. All variables showing $p < 0.2$ in the univariate analysis were entered into the model. The cutoff value of the duration of MV was assessed based on the median value of the distribution.

duced hypothyroid-like state may be associated with the NTIS.[6,11] Arem et al[27] compared thyroid hormone levels in the autopsy samples from 12 patients who died of NTIS with those of 10 previously healthy subjects who died suddenly from trauma. The major finding was that mean T3 concentrations in many tissues of NTIS patients were significantly lower than those of controls, although mean values in heart and skeletal muscle did not differ significantly between the two groups. In a more recent study on 79 critically ill patients who died in the ICU, Peeters at al[28] found that serum iodothyronine levels were positively correlated with both liver and muscle iodothyronine levels, suggesting that the decrease in serum T3 and T4 levels during critical illness also results in decreased levels of tissue T3 and T4.

In the critically ill patients admitted to the ICU with a suspicion of thyroid dysfunction, a complete serum thyroid hormone determinations may be useful to promptly distinguish the low-T3 state from either hypothyroidism or hyperthyroidism. Although respiratory function has been widely studied in patients with primary hypothyroidism, few data exist on the dependence on MV in patients affected by NTIS compared with those with normal thyroid function test results.

Hypothyroidism is a known cause of ventilator-dependent respiratory failure.[29,30] The mechanisms postulated to be the cause of respiratory failure in hypothyroidism include impairment of the normal ventilatory responses to hypercapnia and hypoxia,[17,18,31–33] diaphragmatic and skeletal muscle dysfunction,[18,19,32,34–37] pleural effusions,[38] and obstructive sleep apnea.[39] Also a propensity for respiratory alkalosis that may persist even with appropriately decreased minute ventilation in mechanically ventilated patients has been described.[40] In hypothyroidism, muscle biopsy specimens have shown type II fiber atrophy[34,41] and up to 50% loss of total mass.[34] These findings seem to be a result of increased membrane permeability and decreased adenosine triphosphate formation, manifesting as a rise in creatine kinase levels.[42]

Pandya et al[29] reported four cases of hypothyroidism diagnosed in a 1-year period in a group of patients with ventilator-dependent respiratory failure at a long-term weaning facility. Correction of hypothyroidism was helpful in weaning three of these patients from MV. Similar results were observed by Datta and Scalise[30] in an analogous patient population. Unlike these studies, we examined only patients with NTIS and those with normal thyroid hormone tests, indeed excluding patients affected by hypothyroidism.

Some of our results are consistent with those presented in other studies. The NTIS is a predictor of outcome in patients admitted to the ICU.[12–15] Chinga-Alayo et al[14] showed that mortality prediction, as assessed according to the acute physiology and chronic health evaluation (APACHE) II, is improved by combining this score with thyroid hormone measurements. In our study, baseline serum levels of either fT3 or fT4 were significantly lower in nonsurvivors compared with survivors. Moreover, ICU mortality was significantly higher in patients with low serum levels of fT3 compared with patients with normal hormone tests.

In a retrospective study conducted in 2007 by Plikat et al,[15] patients with NTIS were found to receive MV more often in comparison with those with normal hormone levels (44.3% for euthyroidism, 50% for low fT3, and 83.3% for low fT3/fT4). However, no report exists on the correlation be-

tween the NTIS and duration of MV in patients with respiratory failure. In mechanically ventilated patients who were admitted to our ICU, NTIS was found to be a risk factor for PMV, as estimated by the logistic regression model.

This study has several limitations, especially because of its retrospective nature. First, we do not know whether the results obtained from this study would be replicable by evaluating all the patients admitted to the ICU, regardless of the clinical suspicion of thyroid dysfunction. However, testing thyroid function in all ICU admissions is clearly unpractical. Second, the use of serum fT3, fT4, and TSH levels as a screening method may be insufficient to define the nature of the various abnormalities in thyroid function tests accurately. In the critical care setting, hyperthyroid patients may have paradoxically low levels of thyroid hormones until their recovery from the critical illness,[43] and patients with primary hypothyroidism may fail to manifest increased TSH.[44] Moreover, the presence of a nonelevated serum TSH level may be associated with a NTIS per se but also with pituitary or hypothalamic disease. However, given the low incidence of either secondary or tertiary hypothyroidism, we believe the screening method used in this study did not cause significant flaws. Third, serum TSH levels usually remain within normal low range in the NTIS, but they may modestly increase during recovery; also serum fT4 concentrations may be slightly high in the early phase of the NTIS.[1,9] We cannot exclude that some patients affected by NTIS were not included in the study because only those patients with normal/low levels of TSH and normal/low levels of fT4 were assigned to the low-fT3 group.

In conclusion, NTIS represents a risk factor for PMV in mechanically ventilated, critically ill patients admitted to the ICU. It is unclear, however, whether the NTIS is only a biochemical prognostic marker or it actually contributes to the development and progression of respiratory failure. An answer to this issue could be obtained by evaluating possible benefits in the respiratory function of these critically ill patients after a substitution treatment with thyroid hormones or hypothalamic peptides, in the setting of randomized studies.

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Nonthyroidal Illness Syndrome and Prolonged Mechanical Ventilation in Patients Admitted to the ICU

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