Hypothyroidism and Failure To Wean in Patients Receiving Prolonged Mechanical Ventilation at a Regional Weaning Center*

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Objective: Hypothyroidism is cited as an uncommon cause of ventilator-dependent respiratory failure. The objective of this study was to determine the incidence of hypothyroidism in patients with respiratory failure, receiving prolonged mechanical ventilation (PMV) with failure to wean, referred to a regional weaning center (RWC) for weaning.

Setting: RWC.

Design: Retrospective.

Methods: Medical records were reviewed of 173 patients admitted to this RWC between January 1999 and March 2002. One hundred forty patients were noted to have had screening serum thyroid stimulating hormone (TSH) levels obtained at admission. Records of these patients were further evaluated. The following data were abstracted: age, sex, body mass index, serum TSH levels, number of patients with previously diagnosed hypothyroidism, and number of patients with hypothyroidism diagnosed clinically and by laboratory tests following admission to the RWC. Primary outcome was liberation from PMV, which was defined as being off ventilatory support for > 1 week. Univariate analysis was performed to determine relation between serum TSH levels and outcome; p < 0.05 was deemed statistically significant.

Results: Of 140 patients studied, 67 were male (48%) and 73 were female (52%), with a mean age of 66+15 years (± SD). Only one patient had a history of previously diagnosed hypothyroidism. A clinical diagnosis of hypothyroidism was made in 4 of 140 patients (3%) following admission. Serum TSH levels ranged from 0.19 to 121 mU/L in the studied subjects. Seventeen of 140 patients (12%) had elevated serum TSH levels. Serum tri-iodothyronine and/or thyroxine levels confirmed diagnosis of hypothyroidism in four of these patients (3%). Patients with newly diagnosed hypothyroidism were treated with thyroid supplements, and three patients were liberated from PMV while one patient died from other medical causes. Of the 140 patients, 92 patients (67%) were liberated from PMV while 48 patients (33%) could not be weaned. Mean serum TSH levels were 4.2+13 mU/L in the liberated patients and 4+4.7 mU/L in the patients who could not be weaned (p = 0.25).

Conclusion: Hypothyroidism is an uncommon cause of failure to wean in patients receiving PMV (with an incidence of 3%). However, it is a potentially treatable cause and should be considered in all patients who fail to wean. Serum TSH level does not appear to affect successful weaning from PMV.

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Key words: failure to wean; hypothyroidism; respiratory failure

Abbreviations: BMI = body mass index; PMV = prolonged mechanical ventilation; RWC = regional weaning center; TSH = thyroid-stimulating hormone; T3 = tri-iodothyronine; T4 = thyroxine

Hypothyroidism is a known but uncommon cause of ventilator-dependent respiratory failure. However, literature in this regard is limited. Respiratory failure related to hypothyroidism with ventilatory dependency and failure to wean has been attributed to respiratory muscle weakness, including diaphragmatic dysfunction, and impaired ventilatory drive. Hypothyroidism can have numerous effects on...

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the respiratory system, including upper airway obstruction, respiratory muscle weakness, central and obstructive sleep apnea, alveolar hypoventilation, and pleural effusion.

Critical illnesses, including respiratory failure, often result in neuroendocrine activation with altered serum thyroid stimulating hormone (TSH), tri-iodothyronine (T3), and thyroxine (T4) levels. Abnormal thyroid function test results are reported to occur in 10 to 50% of such patients, but in the absence of true thyroid disease constitute the sick euthyroid syndrome. Whether imbalances in serum TSH as part of critical illness-induced cytokine-mediated neuroendocrine activation affect weaning in ventilator-dependent respiratory failure is not known.

We have detected previously undiagnosed hypothyroidism in patients admitted with failure to wean to our institution, a regional weaning center (RWC). This prompted the question: how common is hypothyroidism in this group of patients receiving prolonged mechanical ventilation (PMV) who fail to wean? Does the serum TSH level affect weaning? The objective of our study was to determine the following: (1) the incidence of hypothyroidism in patients receiving PMV with failure to wean; and (2) the effect of serum TSH levels on liberation from mechanical ventilation.

Materials and Methods

Medical records of 173 patients with respiratory failure receiving PMV with failure to wean, admitted to our RWC between January 1999 to March 2002, were reviewed. PMV was defined as dependence on mechanical ventilation for >3 weeks. Serum TSH levels were obtained in 140 of these patients on admission. Obtaining serum TSH levels at the time of admission is now a routine practice at this center, but was not so in the earlier part of the study period.

The patients’ age, sex, cause of ventilator-dependent respiratory failure, body mass index (BMI), serum TSH levels at admission, previous diagnosis of hypothyroidism or hyperthyroidism, and the use of thyroid supplements or antithyroid medications were noted. The number of patients with a clinical diagnosis of hypothyroidism following admission, as well as clinical features that prompted the diagnosis of hypothyroidism, were determined from physicians’ notes. The number of patients liberated from mechanical ventilation and the number of patients who could not be weaned were noted. Liberation from PMV was defined as being off ventilatory support for >1 week.

The number of patients with a diagnosis of hypothyroidism based on laboratory results (serum TSH, T3, and/or T4 levels) was determined and correlated clinically. The clinical course and weaning outcome of these patients with newly diagnosed hypothyroidism were also noted.

Mean serum TSH levels of the groups of successfully liberated patients and patients who could not be weaned were abstracted. Univariate analysis was performed to determine the relation between serum TSH levels and liberation from mechanical ventilation. A t test was used to test statistical significance; p < 0.05 was considered statistically significant.

Results

Of 140 patients studied, 67 patients (48%) were male and 73 patients (52%) were female, with a mean age of 66 ± 15 years (± SD). The underlying cause of respiratory failure resulting in admission to the RWC was cardiovascular surgery in 28%, non-cardiovascular surgery in 15%, pneumonia in 15%, COPD in 28%, and neuromuscular disease in 14%. Mean BMI was 27.5 ± 8. One patient had a previous history of hypothyroidism and was receiving thyroid supplements.

A clinical diagnosis of hypothyroidism was made in three patients. Clinical features that resulted in diagnosis were abnormal mentation and flat affect in two of these patients, one of whom also had diffuse oropharyngeal swelling noted on laryngoscopy. This diffuse oropharyngeal swelling was presumed to be due to submucosal mucopolysaccharide deposits. The clinical features prompting a diagnosis of hypothyroidism were not mentioned in the medical records of the third patient. No mention was made of goiter size on physical examination in any of the patients.

Seventeen patients (12%) were found to have elevated serum TSH levels. Of the 17 patients with elevated serum TSH levels, 1 patient had previously diagnosed hypothyroidism. Serum T3 and/or T4 values were not obtained in all patients with mildly elevated TSH. Nine patients with serum TSH levels >8 mU/L had serum T4 and/or T3 levels checked. T3 and T4 levels confirmed the diagnosis of hypothyroidism in four patients (3%). The TSH values of these 17 patients with elevated TSH as well as the available T3 and/or T4 values are shown in Table 1. Additional tests such as free T4 or T3 resin uptake were not performed in any of the patients.

Elevated serum TSH levels in patients with normal serum T3 and/or T4 levels probably represented recovery from their critical illness. Thyroid studies confirmed hypothyroidism in two of the three patients who had diagnoses on clinical grounds. One of the patients with mental status changes, who had a clinical diagnosis of hypothyroidism, did not have abnormal thyroid study results. Two patients who did not have a clinical diagnosis were found to have hypothyroidism based on laboratory studies. The mean BMI of the four patients with hypothyroidism was 24 ± 5, which was not significantly different from that of the remaining patients without hypothyroidism (27 ± 8, p > 0.05).

All patients with newly diagnosed hypothyroidism were treated with thyroid supplement therapy. Three of these patients were successfully liberated from mechanical ventilation after a mean period of
20 days following institution of thyroid replacement therapy. The fourth patient died from other medical causes. The one patient with previously diagnosed hypothyroidism was successfully liberated from mechanical ventilatory support, but was transferred to an acute care facility for management of uncontrolled hematuria that developed during her stay in the RWC.

The serum TSH levels in the study population ranged from 0.19 to 121 mU/L. Individual serum TSH values of studied subjects (excluding the outlier with serum TSH of 121 mU/L) are graphically represented in Figure 1. The serum TSH values of the hypothyroid patients ranged from 11.7 to 121 mU/L (individual values are shown in Table 1). The mean serum TSH value in the remaining patients without hypothyroidism was 2.7 ± 2 mU/L. Weaning and survival outcome of the 17 patients with elevated serum TSH levels are also shown in Table 1.

The mean serum TSH level was 4.2 ± 13.5 mU/L in the patients liberated from mechanical ventilation (2.9 ± 3.5 mU/L, excluding the outlier). The mean serum TSH level was 4 ± 4.7 mU/L (range, 0.19 to 22.5 mU/L) in the patients who could not be weaned. This was not statistically significant by univariate analysis (t test, p > 0.05).

**Discussion**

Hypothyroidism, although recognized to cause respiratory failure, is not considered an important cause of ventilator dependency with failure to wean. However, literature in this regard is limited. Our retrospective study found that the incidence of hypothyroidism is low in patients receiving PMV who fail to wean. The incidence noted in our study was 3%. However, this may not be a true representation, considering the highly selected patient group studied.

Pandya et al reported four cases of hypothyroidism diagnosed in a 1-year period in a similar population of patients with ventilator-dependent respiratory failure at a long-term weaning facility. None of

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=data/journals/chest/22017/)

**Figure 1.** Scatter diagram showing serum (S) TSH values of studied subjects. The outlier with a serum TSH value of 121 mU/L is not included in this graph. No statistically significant difference is noted in serum TSH levels between these two groups (p = 0.25).
these patients had clinical evidence of hypothyroidism, which was discovered during evaluation of neurologic and cardiologic problems. Serum TSH level tests were not routinely done in all patients in this long-term weaning facility. No prior studies have determined the incidence of hypothyroidism based on screening serum TSH levels in patients with ventilator-dependent respiratory failure.

Hypothyroidism can be difficult to diagnose in critically ill patients, especially in the elderly, who constitute a majority of these patients. Typical signs and symptoms of hypothyroidism are often absent. A study by Bahemuka and Hodkinson reported that only 10% patients with laboratory confirmation of hypothyroidism received a diagnosis on clinical examination. Another study by Lloyd and Goldberg revealed that 28% of hypothyroid patients had no clinical evidence of hypothyroidism. In the series reported by Pandya et al, the evaluation of an abnormal mental status led to the diagnosis in three of four patients.

Lung volumes are generally normal or mildly reduced with an impairment of diffusion capacity in hypothyroid patients. A study by Wilson and Bedell found that 61.5% patients with myxedema had no clinical evidence of lung disease. These patients had normal lung volumes but reduced diffusion capacity, with a mean value of 68% of predicted. The diffusion capacity in these patients normalized following thyroid replacement therapy. Patients with myxedema and obesity had moderately reduced lung volumes, diffusion capacity (60% of predicted), and maximal breathing capacity. Therapy resulted in a mean loss of a 69 lb of body weight and normalization of these parameters.

The cause of these aforementioned abnormalities is unclear. The reduction in lung volumes in patients with hypothyroidism has been presumed to be due to obesity, whereas the impairment in diffusion capacity is postulated to be due to reduction in pulmonary capillary bed and increase in permeability of pulmonary capillaries, as well as an increase in alveolar and capillary wall thickness caused by a deficiency of thyroid hormones. Change in maximal breathing capacity may be secondary to changes in respiratory muscle function either due to a defect in their contractility or in neural conduction.

Several mechanisms have been postulated as to the cause of respiratory failure in hypothyroidism (Table 2). Hypothyroidism has been shown to affect central ventilatory control and can impair the ventilatory response to hypoxia and hypercapnia. In the classic study by Zwillich et al, hypoxic ventilatory drive was found to be moderately reduced in hypothyroidism and markedly reduced in myxedema. It improved in both groups with thyroid hormone replacement. The hypercapnic ventilatory drive was found to be mildly depressed in hypothyroidism and more depressed in myxedema, but did not increase significantly in either group following thyroid replacement therapy. A more recent study by Ladenson et al reported restoration of normal ventilatory responsiveness (to both hypoxia and hypercapnia) in patients following a week of thyroid hormone therapy.

The presence of myopathy in hypothyroidism is well known. Skeletal myopathy with mild skeletal muscle weakness has been reported to occur in 30 to 40% of hypothyroid patients. Thyroid myopathy is believed to involve the respiratory muscles. Diaphragmatic dysfunction has been postulated in isolated cases of myxedema, and has been reported in obese and nonobese hypothyroid patients. This can be mild, with limitation of exercise tolerance, or severe with dyspnea at rest and chronic respiratory acidosis. Martinez et al showed the presence of diaphragmatic dysfunction in three patients with hypothyroidism who had reduced maximal transdiaphragmatic pressure and increased diaphragmatic time index with a fatiguing breathing pattern. With thyroid replacement therapy, these values normalized, as did lung volumes and exercise tolerance. Diaphragmatic dysfunction may be caused by demyelination of the phrenic nerve, leading to a delayed nerve conduction velocity.

Isolated case reports of acute upper airway obstruction causing respiratory failure exist in the literature. The occurrence of mucopolysaccharide infiltration in patients with preexisting oropharyngeal anatomic defects may predispose to the development of acute upper airway obstruction. In our series, the hypothyroid patient with significant narrowing of her oropharynx due to diffuse oropharyngeal swelling had not presented with acute respiratory failure or stridor, but failed an extubation trial on three occasions prior to having undergone tracheostomy placement.

Hypothyroidism has also been recognized to cause obstructive sleep apnea. Obstructive sleep apnea is hypothesized to be due to narrowing of the upper airway secondary to deposition of mucopo-
lysozymes into the tissues of the oropharynx, as well as abnormalities in ventilatory control during sleep. The genioglossus has been shown to function as an inspiratory muscle, opposing pharyngeal closure caused by negative inspiratory force. Therefore, enlargement and functional abnormalities of this muscle can interfere with maintenance of a patent pharyngeal airway. Abnormalities in ventilatory control, which can reduce respiratory drive to the upper airway muscles, may result in loss of activation of genioglossus muscle, with airway narrowing or closure.22

Effusions into body cavities are known to occur in myxedema. Extravasation of hygroscopic mucopolysaccharides into body cavities, increase in capillary permeability, and inappropriate anti-diuretic hormone secretion have been hypothesized as possible causative factors. Pleural effusions can cause restriction of pulmonary function and contribute to respiratory failure. Pleural effusions in hypothyroidism can be unilateral or bilateral and often accompanies pericardial effusion and ascites. These effusions are usually exudative but may be transudative.

Cytokines in critically ill patients can result in neuroendocrine activation with consequent decrease in the secretion of thyrotropin-releasing hormone, TSH, and T3. This can lead to increased catabolism, altered body composition, immune dysfunction, and increased morbidity. Altered thyroid hormone levels may cause catabolism with loss of muscle mass, which may potentially affect weaning from ventilatory support. A study by Ray et al.25 of 180 ICU patients found that thyroid function test results obtained within 3 hours of admission to the ICU were not predictive of outcome. Whether altered serum thyroid hormone levels in this group of patients perpetrate respiratory failure with ventilator dependency has not been addressed. We found no significant differences in the serum TSH levels of patients who were successfully liberated compared to patients who could not be weaned.

During the chronic phase of critical illness, serum TSH levels are reduced and correlate with low serum T3 level. Normalization or a frank elevation of serum TSH may herald recovery from the critical illness. In this group of patients studied, the abnormal serum TSH values possibly indicated recovery from the acute phase of their illness.

One limitation of this study is that the use of serum TSH as a screening method may have missed patients with subclinical hypothyroidism. Current literature indicates that serum TSH and free T4 levels have similar sensitivities for detecting hypothyroidism. A study by Viera29 found that if serum TSH is normal, the likelihood of free T4 being abnormal is small. However, patients in these studies were not critically ill.

We were unable to find any studies in literature comparing the sensitivity of serum TSH and free T4 in detecting hypothyroidism in critically ill patients. Serum TSH levels can be affected by several factors in the acute critically ill patient, such as the use of dopamine and steroids. Although the acute phase of their critical illness had resolved in the patients in this study, it is possible that other confounding factors may have affected the serum TSH values. The use of serum TSH may not be the optimal method to screen for hypothyroidism in patients with ventilator-dependent respiratory failure. Free T4 levels may need to be obtained in addition to serum TSH as part of the screening for hypothyroidism in the critically ill patient, acute and chronic. Further prospective studies are needed to address this issue.

Another limiting factor of this study is the absence of serum T3 and T4 levels in all patients with mildly elevated serum TSH, which could again have missed patients with mild/subclinical hypothyroidism. Our study is also limited by its retrospective nature and limited number of patients. However, we did determine that hypothyroidism is a rare but important cause of respiratory failure. Although not common, it is certainly a prevalent entity that needs to be investigated in patients with respiratory failure.

Hypothyroidism is one of the few reversible causes of ventilator-dependent respiratory failure. Patients with this condition can be liberated from PMV following appropriate therapy. This was seen in our series as well as the series reported by Pandya et al. Three of our patients with a diagnosis of hypothyroidism were liberated from mechanical ventilation following initiation of therapy with thyroid supplements. Considering the physical and psychological implications of a ventilator-dependent life, as well as the economic burden of ventilator-dependent patients with respiratory failure on the health infrastructure, every effort should be made to detect this disorder.

**Conclusion**

Hypothyroidism is difficult to diagnose clinically, especially in the elderly. Although it is a fairly uncommon cause of ventilator-dependent respiratory failure, with an incidence of 3%, it is a potentially treatable condition. All patients with difficulty weaning from ventilatory support should be routinely evaluated and screened for hypothyroidism. More studies are needed to determine whether serum TSH or free T4 is the better screening tool for...
detecting hypothyroidism in the chronic critically ill patient with respiratory failure. Prospective studies are also needed to further evaluate the true incidence and significance of hypothyroidism in patients with respiratory failure and failure to wean.

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