

# End-tidal CO<sub>2</sub> levels lower in subclinical and overt hypothyroidism than healthy controls; no relationship to thyroid function tests

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**Background:** Hypoventilation is a frequently suspected complication of hypothyroidism.

**Objective:** In this study we examined the hypothesis that changes in alveolar ventilation, as measured by end-tidal carbon dioxide (Et-CO<sub>2</sub>), differ between patients with mild (subclinical) and overt (clinical) thyroid hormone deficiency, and both differ from healthy control subjects.

**Methods:** A total of 95 subjects, including 33 with subclinical hypothyroidism (an elevated thyroid-stimulating hormone (TSH) level and a normal thyroxine (fT<sub>4</sub>) level), 31 with overt hypothyroidism (elevated TSH and decreased fT<sub>4</sub>), and 31 healthy controls. All subjects were female and were evaluated clinically by an endocrinologist for evidence of thyroid disease and categorized on the basis of thyroid hormone levels. Et-CO<sub>2</sub> was measured using a capnograph. Et-CO<sub>2</sub> levels were measured three times and the mean value was considered as the mean level for the individual.

**Results:** Mean Et-CO<sub>2</sub> values of the subclinical hypothyroidism group were significantly lower than those of the healthy controls (31.79 ± 2.75 vs 33.81 ± 2.38; *P* = 0.01). Moreover, mean Et-CO<sub>2</sub> values for the overt hypothyroidism group were significantly lower than those for healthy controls (32.13 ± 3.07 vs 33.81 ± 2.38; *P* = 0.04). There was a significant correlation between Et-CO<sub>2</sub> values and TSH levels (*r* = -0.24; *P* = 0.01). However, Et-CO<sub>2</sub> values were not correlated with fT<sub>4</sub> levels (*r* = 0.13; *P* = 0.20).

**Conclusions:** Alveolar ventilation, as inferred from lower Et-CO<sub>2</sub> levels, is higher in subjects with subclinical hypothyroidism and overt hypothyroidism (lower Et-CO<sub>2</sub>) than in healthy controls. Furthermore, Et-CO<sub>2</sub> levels have no relationship to the levels of TSH or fT<sub>4</sub>. The lower Et-CO<sub>2</sub> in these patients with hypothyroidism, particularly at the subclinical stage, suggests presence of hyperventilation, which may be related to direct effect of TRH on respiratory center or to local changes within the lung.

**Keywords:** end-tidal CO<sub>2</sub>, hypothyroidism, lung, respiratory, ventilation

## Introduction

Hypothyroidism is a relatively common problem worldwide often with insidious onset and is relatively asymptomatic. It is divided in two stages: mild stage (subclinical), or symptomatic (overt). A community survey carried out in the United States identified hypothyroidism in 4.6% of the US population: 0.3% had overt hypothyroidism and 4.3% had what was described as subclinical or mild hypothyroidism.<sup>1</sup> Subclinical hypothyroidism can progress to overt hypothyroidism, particularly in thyroid peroxidase (TPO)-positive patients in whom the annual risk of developing overt hypothyroidism can approach 4%.<sup>2</sup> There can be clinical manifestations in mild hypothyroid patients requiring hormone replacement therapy.<sup>3</sup> Hypothyroidism can affect all organ systems, and its manifestations are largely a function of the degree of hormone deficiency.<sup>3</sup>

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There has been interest in the cardiorespiratory consequences of hypothyroidism as coronary heart disease, congestive heart failure, hypertension, pericardial effusion, and rhythm disturbances have been documented as complications of the hypothyroid state.<sup>4-9</sup> Furthermore, there is growing evidence regarding an association between subclinical hypothyroidism and atherosclerosis, coronary heart diseases, and hypertension.<sup>4,7,8,10</sup> Subclinical and overt hypothyroidism can lead to a variety of respiratory changes. First, observational studies and case reports have associated hypothyroidism with obstructive sleep apnea (OSA).<sup>11,12</sup> These studies report conflicting data: a high association between OSA and hypothyroidism has been reported in some studies, while no association has been documented in others. Second, abnormalities in pulmonary function tests including a decrease in the diffusing capacity for carbon monoxide and an increased incidence of pleural effusions in patients with overt hypothyroidism have been reported.<sup>13-15</sup> Alveolar hypoventilation is a particularly important issue among respiratory complications of hypothyroidism. Myxedema and hypothyroid states can cause depression of the hypoxic ventilatory drive which is responsive to hormone replacement therapy.<sup>16</sup> In the extreme case of myxedema, respiratory depression can lead to alveolar hypoventilation and progressive hypoxemia, and ultimately to marked hypercapnia and coma.<sup>17</sup> In addition, mild respiratory muscle weakness proportional to the degree of thyroid dysfunction is a common finding in primary and iatrogenic hypothyroid states of short duration. This weakness, which affects both inspiratory and expiratory muscles, is reversible with treatment.<sup>18</sup>

The current study utilized a simple and noninvasive method to evaluate alveolar ventilation in ambulatory hypothyroid patients (both clinical and subclinical), focusing particularly on ventilation in patients suffering from subclinical hypothyroidism. The study examined the hypothesis that changes in ventilation differ significantly between patients with mild (subclinical) and overt (clinical) thyroid hormone deficiency, and that these two groups differ from healthy controls.

## Materials and methods

Sixty-four ambulatory adult females aged 18–65 years referred to a university-affiliated endocrinology clinic with clinical suspicion of thyroid disease were selected and enrolled in this study. The study was approved by the local ethics committee and written informed consent was obtained from each subject. For selection, subjects underwent a comprehensive history and physical examination,

and medical, drug, and habitual history were taken into consideration. In particular, history of oral contraceptives, salicylates, methylxanthines, and  $\beta$ -adrenergic administration; presence of any cardiorespiratory, renal, or endocrinologic diseases potentially affecting respiration; and habits such as smoking of any kind and duration, drug use, or opiate consumption were considered as exclusion criteria. All subjects were clinically evaluated by an endocrinologist for evidence of thyroid disease and categorized on the basis of thyroid hormone levels. Physical examination revealed goiter in some patients; however these were not large enough to affect the respiratory system. Body mass index (BMI) was calculated for all subjects. Thyroid-stimulating hormone (thyrotropin, TSH) and free thyroxine ( $fT_4$ ) were measured in all subjects using a radioimmunoassay. Subclinical hypothyroidism was defined as normal serum  $fT_4$  with slightly elevated serum TSH levels. Overt hypothyroidism was diagnosed in those with decreased  $fT_4$  and elevated TSH levels. The normal ranges for TSH and  $fT_4$  were considered to be 0.3–4.2  $\mu$ U/mL and 0.8–1.7 ng/dL, respectively.

End-tidal carbon dioxide ( $Et-CO_2$ ) was measured in all subjects using a capnograph (Microstream<sup>®</sup>; Oridion, Needham, MA), which is a portable monitor that measures and displays  $Et-CO_2$  values and respiratory rates. It has a nasal prong and an oral cannula extending downward. In this study, after inserting the nasal prong into the nostrils, a normal capnographic waveform was recorded after 2–5 minutes. To achieve a power of 80% with a type I error rate of 0.05, the sample size was calculated as 31 patients for each group. The mean value of three independent measurements was considered to be the  $Et-CO_2$  value of the individual. Data were presented as mean  $\pm$  standard deviation or median (interquartile range). Statistical analysis was performed with SPSS software (version 16.0 for Windows; SPSS Inc., Chicago, IL), analysis of variance (ANOVA), and Student's *t*-test. A Spearman correlation test was used to identify correlations between values in the experimental groups. A *P* value less than 0.05 was considered statistically significant.

## Results

Ninety-five individuals were included in the study: 33 with subclinical hypothyroidism, 31 with overt hypothyroidism, and 31 healthy controls. The mean ages and BMI measurements for each of the groups were comparable and are summarized in Table 1. Mean values for TSH,  $fT_4$ , and  $Et-CO_2$  for each of the three groups are presented in Table 2. Mean  $Et-CO_2$  values for the subclinical hypothyroidism group was significantly lower than those for healthy controls ( $31.79 \pm 2.75$  vs  $33.81 \pm 2.38$ ;

**Table 1** Age and BMI of the patients in three studied groups ( $P > 0.05$ )

	Control (n = 31)	Subclinical hypothyroidism (n = 33)	Overt hypothyroidism (n = 31)
Age (year)	30.3 ± 4.9	35.3 ± 11.7	33.3 ± 12.41
BMI (kg/m <sup>2</sup> )	25.22 ± 4.46	25.40 ± 5.39	26.14 ± 5.73

**Abbreviation:** BMI, body mass index.

$P = 0.012$ ). Moreover, mean Et-CO<sub>2</sub> values for the overt hypothyroidism group were significantly lower than those for healthy controls ( $32.13 \pm 3.07$  vs  $33.81 \pm 2.38$ ;  $P = 0.048$ ). Nonetheless, mean Et-CO<sub>2</sub> values for overt and subclinical hypothyroidism groups were comparable ( $P > 0.05$ ).

Analysis of data for relationship between Et-CO<sub>2</sub> values and TSH levels revealed a significant correlation ( $r = -0.24$ ;  $P = 0.01$ ). However, Et-CO<sub>2</sub> values were not correlated with fT<sub>4</sub> levels ( $r = 0.13$ ;  $P = 0.20$ ). There was a statistically significant positive correlation between Et-CO<sub>2</sub> values and BMI measurements ( $r = 0.288$ ;  $P = 0.005$ ). However, there was no significant correlation between Et-CO<sub>2</sub> values and respiratory rate or age of the subjects ( $P > 0.05$ ).

## Discussion

Most studies on the relationship between hypothyroidism and alveolar ventilation emphasize the depression of respiratory system in hypothyroidism. Zwillich et al demonstrated that myxedema and the hypothyroidism state after thyroid ablation depressed the hypoxic ventilatory drive, and that this depression was responsive to thyroid hormone replacement therapy.<sup>16</sup> In addition, depression of the hypercapnic ventilatory drive was reported in myxedema but this relationship was not significant in individuals suffering from milder hypothyroidism, and there was no improvement after hormone replacement therapy.

**Table 2** Et-CO<sub>2</sub> values, respiratory rates, and thyroid function values in the three groups

	Control (n = 31)	Subclinical hypothyroidism (n = 33)	Overt hypothyroidism (n = 31)
Et-CO <sub>2</sub>	33.81 ± 2.38	31.79 ± 2.75 <sup>a</sup>	32.13 ± 3.07 <sup>b</sup>
TSH (μU/mL)	1.1 (0.9–2.4)	8.2 (6.85–11.3)	44 (30–92)
fT <sub>4</sub> (ng/dL)	1.17 ± 0.22	1.05 ± 0.20	0.42 ± 0.19
Respiratory rate <sup>c</sup>	17.81 ± 2.72	17.85 ± 2.65	18.29 ± 2.51

**Notes:** <sup>a</sup> $P = 0.012$  between subclinical hypothyroidism and controls; <sup>b</sup> $P = 0.048$  between overt hypothyroidism and controls; <sup>c</sup>No significant difference between three groups ( $P > 0.05$ ).

**Abbreviations:** Et-CO<sub>2</sub>, end-tidal carbon dioxide; fT<sub>4</sub>, free thyroxine; TSH, thyroid stimulating hormone.

In the present study, a simple and noninvasive method was used to evaluate the alveolar ventilation in patients with thyroid hormone deficiency. Alveolar ventilation, the main determinant of arterial and Et-CO<sub>2</sub> levels, is defined as the portion of minute ventilation that reaches the alveoli and participates in gas exchange. In our study, minute ventilation inferred from Et-CO<sub>2</sub> was significantly higher in subjects suffering from subclinical hypothyroidism than those with overt hypothyroidism or healthy controls. This would suggest that patients with thyroid hormone deficiency, particularly mild (subclinical) or moderate, hyperventilate relatively more often compared to normal individuals.

A year-long study by Pandya et al documented four cases of severe hypothyroidism with long-term dependency on ventilators; thyroid hormone replacement therapy was successful in weaning three of the subjects off the ventilation.<sup>19</sup> Similarly, several retrospective studies have confirmed ventilatory dependency in hypothyroidism patients.<sup>20</sup> There have been reports related to CO<sub>2</sub> retention in myxedema coma.<sup>13</sup>

It has been reported that hypothyroidism can cause weakness of inspiratory and expiratory muscles, and that respiratory pump failure could be secondary to muscle weakness in severe hypothyroidism.<sup>18</sup> Furthermore, a study by Baldwin et al demonstrated that thyroid deficiency in rats limited the endurance capacity of skeletal muscles.<sup>21</sup>

Diaphragmatic dysfunction ranging from mild weakness to severe forms of diaphragmatic paralysis and phrenic nerve neuropathy are proposed as mechanisms of respiratory failure in patients with thyroid hormone deficiency.<sup>22,23</sup> In the present study, the patients with mild/moderate hypothyroidism presented with higher minute ventilation, rather than lower, compared to the healthy controls. This paradoxical result may be related to direct stimulatory effect of TRH on ventilation while no muscular weakness has settled in yet. Another explanation for this apparently discrepant finding would be the effect of secondary changes in the lung with lung juxtacapillary receptor stimulation that in turn increases ventilation with lowering arterial and Et-CO<sub>2</sub> values. Therefore, it seems that even though severe hypothyroidism is an etiological factor in alveolar hypoventilation, it is unclear what relationship, if any, exists between subclinical and mild symptomatic hypothyroidism and the pulmonary ventilation system.

The respiratory system is controlled by the autonomic nervous system but hormones also play a role. In a comprehensive article regarding breathing and hormones, Saaresranta demonstrated that a number of hormones, including thyrotropin-releasing hormone (TRH), are involved

in controlling the breathing.<sup>24</sup> There is a growing body of evidence that there is an association between TRH and the respiratory system. Injecting TRH into an important component of the rostral ventrolateral medulla, the retrotrapezoid nucleus, of anesthetized rats had powerful stimulatory effects on the product of integrated phrenic amplitude and frequency, and this response was dose-dependent.<sup>25</sup> There was an increase in ventilation, O<sub>2</sub> consumption, and body temperature after TRH injection into the retrotrapezoid nucleus in conscious rats, and it was concluded that TRH could have an important role as a state-dependent modulator of breathing control.<sup>26</sup> It has also been demonstrated that intracerebroventricular application of TRH induces a dose-dependent and sustained increase in the ventilation rate, relative tidal volume, and relative respiratory minute volume.<sup>27</sup> A study carried out on anesthetized, vagotomized, paralyzed, and artificially ventilated rabbits concluded that microinjection of TRH into different regions of the medullary respiratory center exerted a depressant effect on respiration at medullary levels by acting on rostral expiratory neurons, but emphasized that TRH could have stimulatory effects if injected into other regions of the respiratory center.<sup>28</sup> Despite numerous studies, the exact physiological effect of TRH on the respiratory system and its participation in the adjustment of breathing during disease has not been elucidated.

In the present study, mean Et-CO<sub>2</sub> values were lower in subclinical hypothyroid patients than in the control group. In addition, there was no correlation between mean TSH and fT<sub>4</sub> levels, and Et-CO<sub>2</sub> values. The ultimate test to assess adequate ventilation is the invasive determination of partial pressure of CO<sub>2</sub> in arterial blood, but capnography, utilized in this study, provides information concerning ventilation, perfusion, and metabolism.<sup>29</sup> However, some studies have demonstrated a correlation between Et-CO<sub>2</sub> and arterial CO<sub>2</sub> levels.<sup>30,31</sup>

Several pathophysiological mechanisms, ranging from neuromuscular and pulmonary factors such as diaphragmatic and respiratory muscle weakness, to central factors such as decreased ventilatory drive, can be considered as causes of respiratory failure and resulting hypercapnia. In severe hypothyroidism, myxedematous involvement of respiratory muscles and depression of both the hypoxic and hypercapnic ventilatory drive can cause alveolar hypoventilation and CO<sub>2</sub> retention, which in turn can contribute to the development of myxedema.<sup>3</sup> However, in mild symptomatic or subclinical hypothyroidism, interactions between hormonal changes such as increased TRH and/or TSH and neuromuscular and pulmonary changes affecting respiratory function could be

important. Such interactions could account for the variations in minute ventilation in this study.

There were important limitations to the current research. Measurements of TSH and fT<sub>4</sub> are sufficient for diagnosis and the categorization of hypothyroid patients, but measuring serum levels of fT<sub>4</sub> would have been of use in defining relationships between variables. Another limiting factor in this study was the small sample size.

## Conclusions

Unlike patients suffering from severe hypothyroidism and myxedema, asymptomatic or mild symptomatic hypothyroid patients are often regarded as 'stable' in terms of clinical status. Interactions between several factors affect the respiratory system including neurohumoral, neuromuscular, and pulmonary factors. Hypothyroidism, particularly at the subclinical stage, results in hyperventilation as demonstrated by a low Et-CO<sub>2</sub>. It is possible that such patients demonstrate increased alveolar ventilation in relation to CO<sub>2</sub> production.

## Disclosure

No conflicts of interest were declared in relation to this paper.

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