Exertional Dyspnea and Ventilation in Hyperthyroidism

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Dyspnea is recognized to be an important feature in patients with hyperthyroidism at rest and during exercise. However, its etiology is not well-understood. Since dyspnea is thought to be related to the perception of excessive ventilatory effort, we explored the possibility that dyspnea in these patients might be related to an inappropriate ventilatory response to the increased metabolic rate. We studied 11 hyperthyroid patients and 11 age- and sex-matched controls, performing spirometry, lung volumes, mouth pressure measurements, and incremental exercise test. Central drive was estimated by measuring $P_{a_1}$ and sensation of dyspnea by the Borg scale. We found that hyperthyroid patients (1) have higher ventilation than normal subjects during exercise even when corrected for $V_{CO_2}$ levels; (2) this increased ventilation is secondary to increased central drive which is correlated to the $T_r$ level ($r = 0.85$, $p < 0.01$); (3) hyperthyroid patients are more dyspneic than controls; and (4) the increased drive can be normalized by $\beta$-blockade. We conclude that the main ventilatory abnormality in hyperthyroid patients is an inappropriate increase in respiratory drive, possibly secondary to increased adrenergic stimulation.

(Chest 1992; 101:1268-73)

MEF = maximal expiratory pressure; MIP = maximal inspiratory pressure; $P_{a_1}$ = inspiratory occlusion pressure; RMI = respiratory muscle index

Dyspnea is recognized to be an important feature in patients with hyperthyroidism at rest and during exercise even in the absence of overt cardiopulmonary disease. However, its cause is not well-understood. Increased dyspnea is considered to result from increased ventilation secondary to the increased O$_2$ consumption ($V_{O_2}$) and CO$_2$ production ($V_{CO_2}$) these patients have as a consequence of their increased metabolic rate. Abnormal results of pulmonary function tests and respiratory muscle weakness have been reported in hyperthyroid patients and these abnormalities have also been considered to play an important role in the increased dyspnea found in this disease.

McElvaney et al. have recently reported that patients with hyperthyroidism had weaker respiratory muscles than controls and that this weakness improved after treatment. However, the respiratory muscle weakness was not associated with increased breathlessness.

Since dyspnea is considered to be related to the perception of excessive ventilatory effort, we explored the possibility that dyspnea in these patients might be related to an inappropriate response to the excessive stimulus provided by their increased metabolic rate.

In the present investigation, we studied hyperthyroid patients during exercise to characterize their ventilatory stimulus and breathing responses with the hypothesis that dyspnea could be secondary to an excessive central respiratory drive.

Material and Methods

Subjects

Eleven (nine female, two male) newly diagnosed sedentary hyperthyroid subjects and 11 (nine female, two male) naive and sedentary control subjects matched for sex and age participated in the study. The study was approved by the institutional ethics committee and informed consent was given by all subjects.

The study protocol involved the performance of baseline pulmonary function tests as well as maximal symptom-limited incremental exercise on a cycle ergometer. After receiving 80 mg/day of propranolol for ten days, eight of the 11 hyperthyroid subjects were restudied with the same protocol. Four of the 11 control subjects were restudied at a time interval of two to three weeks after the original study.

Spirometry was performed with the subject in a seated position with a calibrated electronic spirometer (System 1070 Medical Graphics Corporation, St. Paul, Minn.). Lung volumes were determined by body box plethysmography (PK Morgan Limited, England). Maximum static mouth pressures (best of three efforts) were determined in a standard fashion with maximal inspiratory pressure (MIP) being performed from RV, and maximal expiratory pressure (MEP) from TLC. Respiratory muscle index (RMI) was calculated as (MIP + MEP)/2. Maximum voluntary ventilation was measured as previously described.

Exercise was performed on an electrically braked cycle ergometer (Mijnhardt) with stepwise increasing workloads of 15 W every 2 min. Subjects were seated, wore a nose clip, and breathed through a mouthpiece into a modified low-resistance two-way valve (model 6115, Hans Rudolph Inc, Kansas City, Mo). Expiratory gases were analyzed breath by breath with a computerized exercise system (System 2001, Medical Graphics Corporation, St Paul, Minn.). The breath-by-breath signal was integrated by the system computer to yield 15-s moving averages of minute ventilation ($V_{E}$), tidal volume ($V_t$), respiratory rate (RR), $V_{O_2}$, $V_{CO_2}$, and end-tidal $PCO_2$ ($PrCO_2$). Air flow and gas measurements were corrected for ambient temperature, barometric pressure, and water vapor, and expressed in
BTPS units. Exercise equipment was calibrated prior to each study with gases of known concentrations and a 3-L calibration syringe. A differential pressure transducer (Validyne Engineering Corporation, Waltham, Mass) calibrated with a water manometer was connected to the valve for measurements of inspiratory occlusion pressure (P1.). Pressure at the airway opening was recorded continuously with a chart-recorder (Hewlett-Packard). Inspiratory airway occlusion was achieved by random inflation during expiration of a silent rubber balloon in the inspiratory port of the valve and subsequent deflation after 150 to 200 ms of inspiration (model 6115, Hans Rudolph Inc, Kansas City, Mo). The P1. value was determined as the inspiratory occlusion pressure achieved 100 ms after the pressure tracing crossed the zero pressure line.

Determinations of levels of dyspnea were obtained by having the subjects rate their "degree of shortness of breath" according to the modified Borg scale (0 = none to 10 = maximal dyspnea).* Dyspnea values, followed by P1. measurements, were obtained in the last 30 s of each 2-min interval.

Mean values of pulmonary function and measured exercise parameters were compared between hyperthyroid and control subjects using Students t test for groups with independent means and analysis of variance with multiple comparisons. All data are reported as mean ± standard error (SE) of the mean. Ninety-five percent confidence limits for normal control subjects were established as previously described. Regression lines for exercise relationships were determined by least squares method.

**RESULTS**

Hyperthyroid and control subjects were of similar age, sex, and body mass index. Flow rates, although within normal limits, were significantly lower in hyperthyroid subjects than in controls (FEV1: 99.7 ± 2.9 percent predicted vs 109.3 ± 3.0 percent predicted, p = 0.03; FVC: 89.6 ± 2.2 vs 101.5 ± 3.3, p = 0.01). Lung volumes (RV, FRC, TLC) were similar between groups (Table 1). There was considerable intersubject variation in mouth pressures but as a group, the hyperthyroid subjects had significantly lower MEPS (64.3 ± 5.0 percent predicted vs 92.6 ± 7.7 percent predicted; p = 0.001) whereas MIPS, though lower in hyperthyroid subjects, were not statistically significant from controls.

**Table 1 — Baseline Characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hyperthyroid</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>34.6 ± 2.6</td>
<td>31.2 ± 1.8</td>
</tr>
<tr>
<td>Sex</td>
<td>9F, 2M</td>
<td>9F, 2M</td>
</tr>
<tr>
<td>Body mass index*</td>
<td>21.5 ± 0.9</td>
<td>21.1 ± 0.8</td>
</tr>
<tr>
<td>T, mmol/L</td>
<td>4.8 ± 0.32</td>
<td>4.8 ± 0.32</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>89.6 ± 2.2†</td>
<td>101.5 ± 3.3</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>99.7 ± 2.9†</td>
<td>109.9 ± 3.0</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>116.8 ± 6.4</td>
<td>106.4 ± 6.9</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>100.5 ± 2.9</td>
<td>104.3 ± 2.5</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>103.2 ± 3.0</td>
<td>100.7 ± 2.5</td>
</tr>
<tr>
<td>Dco, % predicted</td>
<td>107.5 ± 4.3</td>
<td>101.2 ± 3.6</td>
</tr>
<tr>
<td>MVV, % predicted</td>
<td>99.2 ± 4.5‡</td>
<td>119.1 ± 3.5</td>
</tr>
<tr>
<td>MIP, % predicted</td>
<td>71.2 ± 8.4</td>
<td>78.3 ± 5.0</td>
</tr>
<tr>
<td>MEP, % predicted</td>
<td>64.9 ± 5.0‡</td>
<td>92.6 ± 7.7</td>
</tr>
<tr>
<td>RMI, MIP + MEP/2</td>
<td>68.1 ± 14.5†</td>
<td>85.6 ± 18.8</td>
</tr>
</tbody>
</table>

*p<0.05.  †p<0.01.

**Table 2 — Exercise Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hyperthyroid</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work, W</td>
<td>78 ± 8.5*</td>
<td>120 ± 10.5</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>116 ±5.7*</td>
<td>86 ± 3.6</td>
</tr>
<tr>
<td>Maximal</td>
<td>179 ± 6.3</td>
<td>178 ± 1.9</td>
</tr>
<tr>
<td>V02, m/min/kg</td>
<td>4.4 ± 0.4</td>
<td>3.7 ± 0.3</td>
</tr>
<tr>
<td>Resting</td>
<td>21.2 ± 1.5†</td>
<td>26.5 ± 1.4</td>
</tr>
<tr>
<td>Peak exercise</td>
<td>4.2 ± 0.4</td>
<td>3.5 ± 0.4</td>
</tr>
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*p<0.01.  †p<0.05.

Table 2 lists the exercise parameters at rest and peak exercise. Hyperthyroid subjects reached a lower level of exercise compared with the controls (78 ± 8.5 W vs 120 ± 10.5 W, p = 0.005). Resting heart rates were significantly higher in the hyperthyroid subjects than in controls (116 ± 5.7 vs 86 ± 3.6; p = 0.003), but there was no significant difference in the heart rate at maximal exercise either as an absolute value or as percent predicted. Resting VO2 was not significantly different in both groups, though the maximal VO2 achieved was significantly lower in the hyperthyroid subjects compared with the controls (21.2 ± 1.5 vs 26.5 ± 1.4 mLV/min/kg; p<0.02). Similar results were observed for VCO2.

The relationship of ventilation to work rate is shown graphically in Figure 1. The area between the dashed lines represents the 95 percent confidence limit for this relationship in control subjects whose mean slope was 0.209. The slope of this relationship in the hyperthyroid subjects varied from 0.28 to 0.63 with a mean slope of 0.40, which was significantly higher than controls (p<0.01). At rest, only six of the 11...
hypothyroid patients had levels of ventilation greater than controls but by 40 W; all of the hyperthyroid subjects were above the 95 percent confidence limits.

In Figure 2, watts have been replaced by VCO₂ in order to "normalize" for the increased CO₂ production in the hyperthyroid patients. The ventilatory response to progressive exercise expressed for VCO₂ was linear in all subjects (r values = 0.93 to 0.99). The ventilatory responses in the hyperthyroid subjects were above the control 95 percent confidence limits throughout exercise in all but one subject and the mean slope in hyperthyroidism was significantly different than in controls (p<0.01). Those subjects (subjects 1, 9, 10, and 11) with low mouth pressures (RMI below 2 standard error of predicted) did not behave differently than the rest. The higher levels of VE in the hyperthyroid subjects were associated with significantly lower end-tidal values for Pco₂ at rest and throughout exercise (p<0.005 for analysis of variance between hyperthyroid and control subjects). This increased ventilation in the hyperthyroid subjects was accomplished by higher respiratory rates and similar tidal volumes during all levels of exercise.

The behavior of P₀.₆ during exercise is shown in Figure 3. The slopes for the regression lines for the relation VCO₂/P₀.₆ for the control subjects ranged from 0.19 to 0.35 cm H₂O/ml/min/kg with a mean slope of 0.25 and for the hyperthyroid subjects ranged from 0.23 to 0.54 cm H₂O/ml/min/kg with a mean slope of 0.34 that was significantly higher than in controls (p<0.01). There was a strong linear correlation between P₀.₆ and VCO₂ for patients and controls with r values ranging from 0.84 to 0.98. At rest, eight of the 11 hyperthyroid subjects had P₀.₆ values that were within the 95 percent confidence limits for the control subjects but with mild levels of exercise, ten of the 11 hyperthyroid subjects had values that were above the 95 percent confidence limits for the controls. Those subjects with low mouth pressures (dashed lines) did not differ in their respiratory drive from the rest of the patients (Fig 3).

The relationship between respiratory drive (expressed as the slope of P₀.₆-VCO₂) and the degree of hyperthyroidism (T₉5IA) could be fitted best by a first order exponential (y = 0.51 + 0.19x + 0.03x²; r value = 0.85; p<0.001) (Fig 4).

In Figure 5, the mean dyspnea ratings in patients and controls at different levels of work and ventilation are shown. Differences in dyspnea perception are apparent by 30 W and remain significantly higher at 45 and 60 W. As work progresses, the number of patients able to continue exercise decreases and the overall differences between patients and controls by analysis of variance become nonsignificant. However, the level of dyspnea during exercise was identical in patients and controls when expressed as a function of ventilation.

The response of the central respiratory drive (expressed as slope of P₀.₆/VCO₂) to β-blockade is shown in Figure 6. As a group, the decrease in respiratory drive after β-blockade approached but did not reach a significant level (p=0.07). However, there was a substantial decrease in P₀.₆/VCO₂ after a ten-day ad-
ministration of β-blockade in the three subjects with the highest degree of respiratory drive. There were no significant differences in any of the exercise parameters of the four control subjects who underwent repeated exercise studies.

**DISCUSSION**

This study shows that the ventilatory response to incremental exercise in patients with hyperthyroidism is increased when compared with normal subjects and is out of proportion to their increased CO₂ production. This increase in ventilation is related to an increase in central respiratory drive, which is proportional to the degree of hyperthyroidism.

The pattern of pulmonary function abnormalities in our patients was similar to what has been previously reported in hyperthyroidism showing lower FEV₁ and VC than controls. However, the levels of abnormalities were minimal and the mean values were still within the predicted normal range. It would be unlikely that this degree of abnormality could have influenced the ventilatory response to exercise in our patients. Maximum expiratory mouth pressures (64.9 ± 5.0 percent predicted) were certainly abnormal and probably related to the proximal muscle involvement these patients are known to develop. Maximum inspiratory pressures were also lower than in controls but did not reach significant levels since some patients showed a more selective expiratory weakness. The disparity of the measurements might best be explained by the known differences in muscle fibers between the diaphragm and other skeletal muscles and therefore, disease states might have different effects on these muscles. We have shown this to be the case in neuromuscular diseases.

As shown below, however, muscle weakness did not seem to play a major role in the ventilatory response to exercise in these patients. McElvaney et al showed similar results in their group of hyperthyroid patients.

The ventilatory response to exertion in hyperthyroid patients showed a large range of values, as shown in Figure 1, but it was always excessive for the amount of work performed and always higher than in the controls. It has been postulated that the excessive ventilation during exercise in patients with hyperthyroidism is an appropriate response to the excessive CO₂ production resulting from their hypermetabolic state. That this is not the case is clearly shown in Figure 2 in which ventilation is shown to be excessive and higher than in controls when related to the CO₂ production during exercise. If the ventilatory response was a function of the excessive CO₂ production, the level of ventilation should be similar to controls for the same degree of CO₂ production. Thus, patients with hyperthyroidism ventilate beyond the expected for the VCO₂ level. End-tidal Pco₂ values were lower in all hyperthyroid patients during exercise suggesting that indeed they were hyperventilating in relation to their CO₂ production. Most of our patients had normal ventilatory function as suggested by pulmonary function tests, and hence, end-tidal Pco₂ is probably a good reflection of the arterial Pco₂ since an excellent correlation between arterial and end-tidal Pco₂ has been shown during exercise in subjects with normal lungs.

Since increased ventilatory drive to other stimuli such as hypoxemia and hypercapnia has been shown in hyperthyroidism, we hypothesize that increased ventilatory drive might also account for the excessive ventilation shown by these patients during exercise. We quantitated respiratory drive by using the Ptf/1, a measurement that has been shown to be a good index of central respiratory output. The use of Ptf/1 during
exercise is probably a valid index since it is not substantially altered by changes in FRC and, in fact, FRC does not change significantly during exercise in normal subjects. The \( P_{a1} \) response to increasing \( V_{O2} \) in normal controls was linear with minimal intersubject variability. Patients with hyperthyroidism also had linear slopes and by midexercise, ten of the 11 patients had \( P_{a1} \) higher than the controls indicating that the increased ventilation during exercise in these patients is secondary to an excessive response to a given stimulus, in this case, \( V_{CO2} \). Thus, increased ventilation during exercise in patients with hyperthyroidism seems to be secondary to a variable but often markedly inappropriate increase in central respiratory drive in response to the increased \( V_{CO2} \) (Fig 3).

For the same level of work, patients with hyperthyroidism were more dyspneic than controls (Fig 5); however, when dyspnea grading was correlated with the level of ventilation, no difference was observed between the two groups (Fig 5), suggesting that the inappropriate increase in the respiratory drive to the hypermetabolic state produces inappropriate increases in ventilation perceived by these patients as dyspnea. This is similar to the finding of McElvaney et al who showed that Borg scale ratings of dyspnea were higher than controls at certain levels of exercise, though overall the difference between the two groups was not statistically significant. In both our study and that of McElvaney et al., the sicker hyperthyroid subjects exercised for shorter periods, so with ongoing exercise, fewer and healthier patients remained, making the comparisons between the two groups more difficult with differences becoming nonsignificant toward the end of exercise.

The respiratory muscle weakness that these patients often have has been suggested as the explanation for this increase in minute ventilation and dyspnea. This could occur by leading to a breathing pattern characterized by rapid shallow breaths which would then cause an increase in dead space ventilation and necessitate an increase in total ventilation for the adequate elimination of \( CO2 \). Although four of our patients exhibited lower mouth pressures than the control subjects, they were not different from the rest of the patients in their ventilatory, respiratory drive, dyspnea, or pattern of breathing responses to exercise. Similar conclusions have been reported recently by McElvaney et al.

Increased hypoxic and hypercarbic ventilatory responses in hyperthyroid subjects have been reported before by Zwillich et al. and Stockley and Bishop. These investigators also showed that this increased ventilatory response to hypercarbia and hypoxemia normalized after the patients were rendered euthyroid. Neither of these investigations explored the potential cause of this increase in ventilatory response. We found that the inappropriate increase in central drive response to the increased \( V_{CO2} \) (slope of \( P_{a1}/V_{CO2} \)) was significantly correlated in our patients with their \( T_{3} \) level (Fig 4), which measures what is considered to be the most active thyroid hormone. This could again suggest the possible important role of the excess thyroid hormone in the cause of the increased central respiratory drive and the consequent hyperventilation during exercise in these patients.

The mechanism of the excess thyroid hormone mediating an increase in central drive is certainly not clear. Zwillich et al have suggested that an increase in adrenosympathetic activity in hyperthyroidism might be responsible for the increase in the ventilatory responses to \( CO2 \) seen in these patients. This was suggested because the increase in hypercarbic and hypoxic ventilatory response is similar in hyperthyroidism, hyperthermia, and other illnesses characterized by an increase in metabolic rate. Conversely, when the metabolic rate is decreased as in myxedema, the ventilatory response to hyperthermia and hypoxemia has been shown to be decreased. The fact that the excess ventilatory response to inhaled \( CO2 \) and to hypoxemia seen in hyperthyroidism decreases after the patients are rendered euthyroid would certainly suggest that it is the excess thyroid hormone that is playing an important role in the control of ventilation and the excess ventilatory drive seen in these patients. Our results with the \( \beta \)-blockade suggest that these effects might be, at least in part, mediated by sympathomimetic hormones. Exercise tests were repeated two weeks after diagnosis while patients were receiving \( \beta \)-blockade. No specific antithyroid treatment was given and circulating hormones were still high. \( \beta \)-Blockade markedly decreased central respiratory drive in the patients more severely affected before treatment, and this suggests that the action of the thyroid hormone in the respiratory centers may be mediated, at least in part, by adrenergic receptor stimuli that can be blocked by \( \beta \)-antagonists. This effect is quite plausible since there is a high adrenergic state in hyperthyroidism. However, it is possible that adrenergic blockers altered respiratory drive by other mechanisms. It is known that \( \beta \)-blockade can alter the concentration of thyroid hormones probably by decreasing the conversion of \( T3 \) to \( T4 \), but the actual decrease in serum thyroxine after \( \beta \)-blockade has been found to be small or nonexistent. Harrower et al administered 160 mg of propranolol daily for two weeks to 12 hyperthyroid patients and found that \( T3 \) decreased by about 5 percent but still remained significantly above normal. We do not know if small changes in \( T3 \) concentration after propranolol administration would account for the decrease in central respiratory drive observed in some of our...
hyperthyroid subjects. Likely, β-blockade would act at least in two ways, i.e., by blocking adrenergic action and by decreasing circulating T₃.

In conclusion, we have found that hyperthyroid patients exhibit an abnormal sense of exertional dyspnea that is related to a minute ventilation that is out of proportion to both workload and CO₂ production. An increase in central drive plays an important role in this hyperventilation, is related to the circulating hormone level, and may be altered by β-receptor antagonists. This suggests that the hormonal effects in the respiratory centers might be at least in part secondary to increased adrenergic stimulation.

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