Respiratory Muscle Strength in Hypothyroidism*

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To investigate respiratory muscle strength in patients with hypothyroidism, global respiratory muscle strength was assessed by measuring mouth pressure during Pmax and Pmax efforts. Maximum pressures, VC, FEV₁, FVC, T₁, T₂, and TSH were measured in 43 hypothyroid patients. Measurements were made before and three months after replacement therapy with thyroxine. The results showed that the mean value of Pmax and Pmax increased after treatment. Significant change was found in the mean value of VC, FEV₁, and FVC after treatment but not in the FEV₁/FVC ratio. A highly statistically significant linear relationship was found between Pmax and TSH and between Pmax and T₄.

We studied 43 hypothyroid patients, 15 with idiopathic (primary) and 28 with iatrogenic myxedema. All patients were ambulatory and were recruited from the Endocrinology Department in a consecutive order. Patients with iatrogenic myxedema had had a thyroidectomy for papillary thyroid carcinoma at least one year before this study. Four weeks before measurements, replacement (thyroxine) therapy had been stopped in order for the patients to be investigated for metastatic disease. Anthropometric data regarding the patients are shown in Table 1. The diagnosis of hypothyroidism was made by medical history and clinical examination and was confirmed by measuring T₄, T₃, and TSH. Measurements of T₄, T₃, and TSH were made by radioimmunoassay technique (Amerlex T3 and T4, Amersham, England, and TSH, Sori). The normal values for T₄ were 6.4 to 12.5 ng/dl; for T₃, they were 52 to 196 ng/dl; and for TSH they were 0.6 to 10 μU/ml.

Only patients with myxedema and heart failure or those on drugs affecting muscle function (eg, beta blockers) or metastatic disease were excluded from the study. All measurements were made long after episodes of febrile illness. Patients who smoked (n=14; 33 percent) did not change their smoking habits during the study and did not show any significant symptoms related to smoking (cough or sputum) when the measurements were made. Measurements were performed at the time of diagnosis of hypothyroidism, before any treatment, and three months after replacement therapy with T₄. Three months after therapy, only 21 patients became euthyroid as estimated by the values of TSH. The rest had a reduced value of TSH but the value did not reach the normal range. Vital capacity, FVC, and FEV₁ were measured by a dry spirometer (Vitalograph, Buckingham, England), and the FEV₁/FVC ratio was calculated. All volumes were corrected to BTPS and expressed as a percentage of predicted values, and the FEV₁/FVC ratio was expressed as a percentage of FVC.19

Global respiratory muscle strength was assessed by measuring Pmax and Pmax mouth pressures. The Pmax was measured near RV and Pmax near TLC. Patients were seated and wore a nose clip. Their mouths were connected to the instrument that measured maximum pressures by a hard, stiff rubber piece. The instrument was a metal cylinder 15 cm long with an internal diameter of 3 cm and a small leak (2 mm) at the distal end to minimize oral pressure artifacts.15 The distal end was connected to two pressure transducers (Maxant, Paris), one measuring negative pressures (from 0 to −200 mm Hg) and the other positive pressures (from 0 to +350 mm Hg).

Materials and Methods

Clinical Data

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Both manometers had two needles, one of which rested at the maximum pressure produced during each effort, enabling us to read the pressure with accuracy.

Efforts were considered satisfactory when maximum pressures were maintained for at least 1 s. These efforts were recorded when the variability was less than 5 percent and the highest value was used for calculations.

Statistical Analysis

Data are presented as mean value ± 1 SD. The Student t test was used to evaluate statistically significant differences between the mean values of the two groups. Differences in mean values of the complete data before and after treatment were evaluated by the paired t test. The least squares method was used to calculate linear relationships. A probability value less than 0.05 was considered to indicate statistical significance.

RESULTS

The mean value of Pimax (± 1 SD) for all 43 patients was 83 ± 25 cm H₂O before and 117 ± 98 cm H₂O after three months of replacement treatment with thyroxine. This change was statistically significant (p<0.0001). The mean value of Pmax (± 1 SD) was 79 ± 31 before and 115 ± 32 after treatment and this difference in the mean values was statistically significant (p<0.0001). The mean values of Pmax and Pmax ± 1 SD of the two groups and of the total number of patients are shown as histograms in Figure 1. Table 2 shows the mean values ± 1 SD of Pmax and Pmax as well as of VC, FEV₁, FVC, the FEV₁/FVC ratio, and thyroid hormone levels (T₃, T₄, and TSH) before and after treatment in the two groups of patients (idiopathic and iatrogenic) and in the total number of patients. It can be seen (Table 2, Fig 1) that the mean values of all measured parameters of the two subgroups of myxedema patients did not differ significantly before treatment except for the value of T₃ (p = 0.046).

The mean value of lung volumes (VC, FEV₁, and FVC) of all patients increased significantly after treatment (p<0.001) but the FEV₁/FVC ratio did not change (p = 0.06). The mean value of TSH of all

![Table 1 — Anthropometric Data and Mean Changes in Weight after Treatment (Mean ± 1 SD)]

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>Sex</th>
<th>No.</th>
<th>Male</th>
<th>Female</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (Kilograms)</th>
<th>(% Predicted)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iatrogenic</td>
<td></td>
<td>15</td>
<td>5</td>
<td>10</td>
<td>57.6 ± 9.4</td>
<td>162 ± 9</td>
<td>82.6 ± 12.3</td>
<td>129.3 ± 24.3</td>
<td>Before</td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
<td>28</td>
<td>6</td>
<td>22</td>
<td>53.0 ± 14.5*</td>
<td>160 ± 7*</td>
<td>75.4 ± 13.3</td>
<td>121.5 ± 20.7*</td>
<td>Before</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>43</td>
<td>11</td>
<td>32</td>
<td>54 ± 14</td>
<td>160.8 ± 7.8</td>
<td>78 ± 13.2</td>
<td>124.2 ± 22</td>
<td>Before</td>
</tr>
</tbody>
</table>

*No significant difference between iatrogenic and idiopathic.
†Statistically significant (p<0.0001) difference in the mean weight before and after treatment.

![Figure 1. The Pmax and Pmax (mean ± 1 SD) in iatrogenic and idiopathic myxedema and in all patients before and after treatment. The probability values are between the pretreatment and posttreatment measurements.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21649/ on 06/21/2017)
Table 2—Mean Values of Maximum Pressures, Lung Volumes, and Thyroid Hormones in the Two Groups of Thyroid Patients and in the Total Number before and after Treatment (Mean ± SD)

<table>
<thead>
<tr>
<th>Myxedema</th>
<th>Treatment</th>
<th>Pmax (cm H₂O)</th>
<th>Pemax (cm H₂O)</th>
<th>VC (% Pred)</th>
<th>FEV₁ (% Pred)</th>
<th>FVC (% Pred)</th>
<th>FEV₁/FVC Ratio (%)</th>
<th>T₄ (mg/dl)</th>
<th>T₃ (ng/dl)</th>
<th>TSH (µU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic (n = 15)</td>
<td>Before</td>
<td>76 ± 27</td>
<td>78.1 ± 17</td>
<td>83 ± 17</td>
<td>92 ± 21</td>
<td>82 ± 16.4</td>
<td>82 ± 8.5</td>
<td>4.7 ± 2.0</td>
<td>87.6 ± 30</td>
<td>65.5 ± 22.3</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>106 ± 31</td>
<td>111 ± 33</td>
<td>86 ± 17</td>
<td>99.5 ± 17</td>
<td>85.5 ± 16</td>
<td>85 ± 10</td>
<td>9.7 ± 4.8</td>
<td>120.8 ± 37.5</td>
<td>18.0 ± 17.8</td>
</tr>
<tr>
<td>Iatrogenic (n = 28)</td>
<td>Before</td>
<td>85 ± 24</td>
<td>79 ± 29</td>
<td>92 ± 14</td>
<td>105 ± 26</td>
<td>91 ± 17.4</td>
<td>85 ± 16</td>
<td>6.0 ± 5.0</td>
<td>68.0 ± 28</td>
<td>53.3 ± 22.0</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>120 ± 26</td>
<td>117 ± 31</td>
<td>98 ± 15</td>
<td>112 ± 26</td>
<td>98 ± 16.4</td>
<td>87 ± 16</td>
<td>12.0 ± 7.8</td>
<td>110.3 ± 40</td>
<td>13.4 ± 12.4</td>
</tr>
<tr>
<td>Total (n = 43)</td>
<td>Before</td>
<td>83 ± 25</td>
<td>79 ± 31</td>
<td>90 ± 15</td>
<td>100 ± 25</td>
<td>89 ± 18</td>
<td>84 ± 13</td>
<td>5.6 ± 4.2</td>
<td>75 ± 30</td>
<td>55.8 ± 22.0</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>117 ± 28</td>
<td>115 ± 32</td>
<td>95 ± 16</td>
<td>108 ± 25</td>
<td>94 ± 17</td>
<td>86 ± 14</td>
<td>11.2 ± 6.5</td>
<td>114 ± 39</td>
<td>15.0 ± 14.5</td>
</tr>
<tr>
<td>p value*</td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.06</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Between the mean values of idiopathic vs iatrogenic before treatment (t test).
†Between the mean values of the total (idiopathic + iatrogenic) before and after treatment (paired t test).

subjects was reduced, and the mean values of T₄ and T₃ were increased significantly after treatment (p<0.0001) (Table 2).

Figure 2A, is a plot of the values of Pmax against TSH obtained before and after treatment in all patients. A highly statistically significant negative linear relationship was found between Pmax and TSH (r = -0.461, p<0.0001), expressed by the regression equation:

(1) Pmax = 118.6 - 0.528 TSH.

Figure 2B, is a similar plot of Pemax against TSH. A highly statistically significant negative linear relationship was found (r = -0.513, p<0.0001) with the regression equation:

(2) Pemax = 121 - 0.68 TSH.

Figure 3A, is a plot of Pmax against T₃. A highly statistically significant linear relationship was found (r = 0.462, p<0.0001), expressed by the regression equation:

(3) Pmax = 65 + 0.37 T₃.

Figure 3B, is a plot of Pmax against T₄. A statistically significant linear relationship was found (r = 0.308, p<0.0006) and the regression equation follows:

(4) Pmax = 70.3 + 0.28 T₄.

No significant relationship was found between the maximum pressures (Pmax, Pemax) and T₄.

Figure 4 shows plots of VC against Pmax and...
A highly statistically significant linear relationship was found between VC and Pimax ($r = 0.493$, $p < 0.0001$) and between VC and PEmax ($r = 0.394$, $p < 0.0001$) with regression equations of:

(5) $VC = 67 + 0.25 \cdot Pimax$

and

(6) $VC = 75 + 0.17 \cdot PEmax$.

**DISCUSSION**

Respiratory muscle strength was assessed by measurements of maximum inspiratory and expiratory static mouth pressures in 15 patients with primary and 28 with iatrogenic myxedema. The results of this study showed that global respiratory muscle strength was reduced in ambulatory hypothyroid patients. Both
Pmax and Pemax increased significantly statistically after three months of replacement therapy with thyroxine. These results are in agreement with previous reports that showed respiratory muscle weakness in isolated cases of hypothyroidism.\textsuperscript{5,6,12}

Freedman\textsuperscript{a} showed reduced respiratory maximum pressures in three hypothyroid patients and Martinez et al\textsuperscript{b} showed reduced Pdi in another three. Laroche et al\textsuperscript{c} reported a severe decrease in Pdi and abnormal phrenic nerve conduction in a 58-year-old woman with significant breathlessness and hypothyroidism.

In contrast to these reports, we have studied 43 consecutive hypothyroid patients. All patients were ambulatory and no selection was made based on respiratory (shortness of breath) or muscle (fatigue) symptoms and signs.

Our results showed that respiratory muscle weakness was present in both groups of myxedema patients (idiopathic and iatrogenic). The patients with iatrogenic myxedema were treated for thyroid carcinoma they were kept slightly hyperthyroid in an effort to suppress their tumor disease and this might alter respiratory muscle function. Although their maximum pressures did not differ from those of patients with idiopathic myxedema four weeks after the discontinuation of replacement therapy, eg, at the beginning of this study. Taking into account the fact that iatrogenic myxedema was induced for only four weeks and that idiopathic myxedema could be of long duration before diagnosis, we conclude that respiratory muscle weakness is related not to the duration of illness but to the degree of thyroid dysfunction. Consonant with this conclusion is our finding of statistically significant linear relationships between maximum static pressures and thyroid function when data points from iatrogenic and idiopathic patients before and after treatment were plotted (Figs 1 and 2).

All individual values of Pmax and Pemax increased after three months of treatment, as well as the mean values of the pressures, even though only 21 patients became euthyroid after treatment. It is possible that this increase in the maximum static pressures might have been the result of a learning effect of the procedure or an improvement in the patients' motivation. However, this would be most unlikely, since we took care to instruct the patients until a reproducible result was obtained on both occasions before and three months after treatment. We cannot entirely exclude patient motivation but the proportional improvement in the pressures seen in all patients regardless of whether they had become euthyroid after three months of treatment makes this most unlikely.

Skeletal muscle myopathy in hypothyroidism has been reported\textsuperscript{d} as early as 1890 and more recently by Khalleli et al\textsuperscript{e} in 15 patients in a prospective study. Respiratory muscle function, however, had not been systematically studied until now. Unique to the present study is the linear relationship that was found between respiratory muscle strength and thyroid function as assessed by TSH and T3. Although not an accurate measurement of the biochemical changes that occur with hypothyroidism, TSH is the best index of the degree of the disease. Furthermore, the effect of the thyroid hormones in many tissues is related to the degree of saturation of special receptors (nuclear receptors) by T3. These receptors have about tenfold higher affinity for T3 than T4, explaining in part why T3 is the active hormone in the regulation of protein synthesis. The results of our study are in agreement with the previously noted results, since we found a significant relationship between the respiratory pressure and TSH and T3, but not with T4. Similar results have been reported in patients with hyperthyroidism.\textsuperscript{f}

Hamley et al\textsuperscript{g} reported bilateral phrenic nerve paralysis in two patients with hypothyroidism. In the report by Laroche et al,\textsuperscript{h} diaphragmatic weakness was attributed to both myopathy and neuropathy since phrenic nerve conduction time and twitch Pdi were reduced. Since we did not measure respiratory nerve function, we could only speculate that respiratory muscle weakness was due either to myopathy or neuropathy or both. However, Laroche et al\textsuperscript{h} believe that the increase in respiratory muscle strength after treatment was mainly due to an improvement in the myopathy.

In addition, our results showed that the mean values of VC, FVC, and FEV, were within the normal range (>80 percent of predicted) before treatment, but increased significantly (p<0.001) after treatment. No significant change was noticed in the FEV/FVC ratio. These results are in agreement with those reported by Wilson and Bedell,\textsuperscript{i} who showed that VC was normal in nonobese, uncomplicated hypothyroid patients.

Our patients had a mean weight of 124 percent of the desirable weight and showed a small (mean, 2 kg) reduction in weight after three months of treatment (121 percent of desirable). Therefore the improvement in the maximum pressures as well as in the lung volumes could not be attributed to this weight loss but was most probably due to the increase in respiratory muscle strength.

It is well known that changes in lung volumes (TLC, RV) can influence the generation of maximum respiratory pressures due to the length-tension properties of the respiratory muscles.\textsuperscript{j,18} Even though there was a significant change in VC, the results of the present study showed that both pretreatment and posttreatment values of VC were within the normal range. Thus, we conclude that the changes in VC were the result of improved respiratory muscle function and not
The opposite.

The result of this study showed that hypothyroidism affects both inspiratory and expiratory muscles and that weakness and recovery are distributed between the two groups of muscles. This is in agreement with results in previous studies of hypothyroidism and in undernourished patients reported by Arora and Rochester.10

The results of our study demonstrated respiratory muscle weakness in humans at least four weeks after the development of iatrogenic myxedema and are in agreement with those reported by Johnson et al10 showing alteration in the proportion of type 1 fibers of the diaphragm and intercostal muscles in hypothyroid rats four weeks after total thyroidectomy. Similarly, Ianuzzo et al11 reported modification of the overall enzymatic capacity of the rat diaphragm six weeks after thyroidectomy. Our results showed a reversible respiratory muscle weakness in hypothyroidism which might be consistent with transient myopathy, which would be in accord with the histologic findings in experimental animals and humans.14 However, to identify the precise mechanism of myopathy in hypothyroid patients further studies are needed, including respiratory muscle biopsies and histopathologic and enzymatic analyses.

The present study confirms that mild respiratory muscle weakness is a common finding in ambulatory patients with either primary or iatrogenic short-duration hypothyroidism. This weakness was proportional to the degree of thyroid dysfunction and was reversible by replacement therapy with thyroxine. These results are of clinical importance because they illustrate that the respiratory muscles are commonly affected in hypothyroidism. Furthermore, since respiratory muscle strength was shown to be related to thyroid function, this could lead to respiratory pump failure in severe hypothyroid cases.

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