Noninvasive measurement of the tension-time index in children with neuromuscular disease

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Mulreany, Laura T., Daniel J. Weiner, Joseph M. McDonough, Howard B. Panitch, and Julian L. Allen. Noninvasive measurement of the tension-time index in children with neuromuscular disease. J Appl Physiol 95: 931–937, 2003; 10.1152/japplphysiol.01087.2002.—Respiratory muscle weakness is common in children with neuromuscular disease (NMD). We hypothesized that weakness puts them at risk for respiratory muscle fatigue, a harbinger of chronic respiratory failure. We therefore measured a noninvasive index of respiratory muscle fatigue, the tension-time index of the respiratory muscles (TTmus), in 11 children with NMD and 13 control subjects. Spirometric flow rates and maximal inspiratory pressure, indicating decreased respiratory muscle strength reserve. We found a significant correlation between TTmus and the residual volume-to-total lung capacity ratio (r = 0.504, P = 0.03) and a negative correlation between TTmus and forced expiratory volume in 1 s (r = −0.704, P < 0.001). In conclusion, children with NMD are prone to respiratory muscle fatigue. TTmus may be useful in assessing tolerance during weaning from mechanical ventilation, identifying impending respiratory failure, and aiding in the decision to institute therapies.

respiratory muscles; muscular dystrophy

CHRONIC RESPIRATORY FAILURE may be due to lung (parenchymal) failure or failure of the respiratory pump. The respiratory pump includes the centers for control of breathing as well as the chest wall and the muscles of respiration. Lung failure typical of pneumonia or the adult respiratory distress syndrome usually results in mixed gas-exchange abnormalities, whereas pump failure, depending on severity, is predominantly characterized by hypoventilation and hypercarbia (13). Pump failure may be caused by central (respiratory drive) depression, muscle fatigue, or an imbalance between the respiratory pump and the load placed on it. Patients with neuromuscular disease (NMD) are at increased risk for pump failure and premature death due to decreased respiratory muscle strength (20); it is not clear whether they may also be at increased risk for respiratory muscle fatigue. Determining when a patient is imminently at risk for respiratory failure may aid in the decision to institute therapy for patients with NMD.

The tension-time index (TTI), a dimensionless index relating the force developed by the respiratory muscles to the time that they are being used, has been proposed as a measure of respiratory muscle fatigue (2). TTI is calculated as the product of two ratios: I) the ratio of mean inspiratory transdiaphragmatic pressure (Pdi) to maximal transdiaphragmatic pressure (Pdimax) and 2) the ratio of inspiratory time (T1) to respiratory cycle time (Ttr). Thus TTI = (Pdi/Pdimax) × (T1/Ttr). This can be thought of as a fraction of maximal effort that the diaphragm performs during its contraction time.

A noninvasive analog of the TTI, termed the tension-time index of the respiratory muscles (TTmus), has been described. The TTmus is based on pressure measurements at the mouth and, in adults, correlates well with the traditional TTI (18). It is defined by the following equation: TTmus = (PI/MIP) × (TI/TT), where PI is mean inspiratory pressure and MIP is maximal inspiratory pressure measured from functional residual capacity (FRC). Higher values of TTmus can result from increased respiratory load, decreased strength in the respiratory pump, or an imbalance between the two. Increased TTmus is indicative of respiratory muscle fatigue and, in turn, decreased endurance (2). Inspiratory resistive loading increases TTmus as a result of increased PI (16). Expiratory resistive loading decreases TTmus because of prolongation of expiratory time and decreased T1/Ttr (21). Patients with increased intrinsic resistive loads [chronic obstructive pulmonary disease or cystic fibrosis (CF)] have increased TTmus (6, 9), presumably because of an increased numerator in the PI/MIP term. Measurement of TTmus would be useful in a variety of settings, including guiding decisions to institute ventilatory support (i.e., predicting respiratory failure) and assessing a child’s tolerance of liberation (“weaning”) from mechanical ventilation during recovery.

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Several different mechanical defects contribute to impaired pulmonary function and respiratory failure in patients with NMD. Decreased flow rates [e.g., forced expiratory volume in 1 s (FEV₁)] and lung volumes [e.g., vital capacity and total lung capacity (TLC)] are due to respiratory muscle weakness and/or decreased respiratory system compliance. Expiratory muscle weakness inhibits chest wall distortion to residual volume (RV), increasing RV as a fraction of TLC (RV/TLC). Patients with NMD would be expected to be at increased risk for respiratory muscle fatigue due to the combination of mechanical abnormalities and pump weakness, decreasing the denominator of the P/MIP term of the TTₘus. We therefore hypothesized that children with NMD would be predisposed to development of respiratory muscle fatigue, as assessed by TTₘus.

MATERIALS AND METHODS

Subjects. Eleven patients with NMD (8–25 yr of age) were recruited from the Division of Pulmonary Medicine at The Children’s Hospital of Philadelphia. Representative diseases included Duchenne muscular dystrophy (DMD), prune belly syndrome, spinal muscular atrophy type II, and nonspecific muscular dystrophy. These patients were studied while undergoing routine pulmonary function testing and were clinically stable at the time of evaluation. They were compared with 13 healthy controls (8–26 yr of age) recruited from siblings of patients or children of faculty. Subjects were eligible if they were able to perform spirometric and plethysmographic or helium-dilution measurements. Informed consent was obtained from parents, and assent was obtained from children before the study. The protocol was approved by the Institutional Review Board of The Children’s Hospital of Philadelphia.

Measurements. Spirometry [forced vital capacity (FVC), FEV₁, and midmaximal expiratory flow (FEF₂₅–₇₅%) ] and lung volume measurements (TLC and RV) were performed according to standard techniques and procedures (1) (2130 Spirometer, Vmax Series Software, Sensormedics, Yorba Linda, CA). Lung volumes were measured by plethysmographic or helium-dilution techniques (Vmax22 series, Sensormedics) (1). Maximal respiratory pressures were measured using the Portaresp (model MRBP028, S & M Instrument, Doylestown, PA; operating range ±350 cmH₂O). MIP was measured at functional residual capacity (FRC) using the technique of Black and Hyatt (3). Subjects generated maximal respiratory efforts while breathing through the mouthpiece while the nose was occluded. At the distal end of the tube, a small leak (0.5–1 mm) prevented buccal pressure buildup and glottic closure during measurements. The occlusion was maintained for 2–3 s. At least five maneuvers were performed at each starting lung volume until three reproducible values were obtained, and the highest value was reported. Inadequate maneuvers due to mouth leak, assessed by observation, were excluded. Pulmonary function testing results were normalized to height and age using standard reference values (11, 12).

TTₘus. TTₘus was derived from measurements of the occlusion pressure measured at the mouth 100 ms after the onset of inspiration (P₁₀₀), MIP measured from FRC, Ti, and Tr. Mouth occlusion pressure was measured with a pressure transducer (model MP-45, Validyne, Northridge, CA; operating range ±22.5 cmH₂O). Pressure, flow, and volume signals were collected using a computerized system developed by the investigators and a digital signal-processing program (TestPoint, Capital Equipment, Billerica, MA), which sampled mouth pressure and flow at 200 Hz from an analog-to-digital converter (model KPCMCIA-12IAO, Keithley, Cleveland, OH). Volume was calculated by integrating the flow signal from the pneumotachometer (model PNT 3700A, Hans Rudolph, Kansas City, MO), and all three signals were displayed graphically.

The subjects were asked to breathe quietly, with the nose occluded, through a mouthpiece connected to the pneumotach with a two-way valve (Hans Rudolph). During the exhalation phase of breathing, a balloon (model 9300 occlusion valve, Hans Rudolph) was rapidly inflated in the inspiratory limb of the breathing circuit to occlude the subsequent inspiratory flow. It was released ~150–250 ms after the onset of the subsequent inspiration. The balloon was inflated with helium from a small gas cylinder, and the valve was controlled manually with a small switch. The subject was asked to continue to breathe normally despite the occlusions. After this maneuver was repeated ~10–15 times over a period of 3 min, testing was completed. The subject wore headphones and listened to music to dampen any noise from the switching device controlling the balloon, lest the subject anticipate the occlusions and change his or her respiratory pattern. The analysis portion of our computer program displayed flow, volume, and pressure waveforms and values. A cursor on the screen was used to identify the onset of inspiration (where pressure crossed 0 cmH₂O), and P₁₀₀ (20 samples) was determined (Figs. 1 and 2). Ti and Tr were measured for the breath immediately preceding the occlusion maneuver.

Calculation of TTₘus. P₁ was estimated as 5 × P₁₀₀ × Ti (6) (see APPENDIX). TTₘus was calculated as P/MIP × Ti/Tr. Calculations used the mean values for P₁₀₀ and respiratory timing variables. The highest and lowest values for TTₘus (in a given testing session) were excluded from analysis in calculating mean TTₘus.

Anthropometry. Height (measured with a stadiometer, in cm) and weight (digital standing scale, in kg) were recorded. Arm span was used as a surrogate for height in wheelchair-dependent subjects. Body mass index (BMI) was calculated as 10,000 × (wt/ht²). Ideal BMI (for age) was derived from Center for Disease Control growth charts.

Statistics. Statistical comparisons were performed using SigmaStat 2.03 (SPSS Software). Comparison of continuous variables for NMD patients and controls was performed using Student’s t-test or Mann-Whitney’s rank sum test, where appropriate. Differences were considered significant for P < 0.05. Relations between variables were quantified using Spearman’s correlation coefficient.

RESULTS

Mean anthropometric and pulmonary function data of the NMD and control groups are presented in Table 1. The clinical characteristics of the NMD patients are described in Table 2. Scoliosis curvature (Cobb angle) was measured from an anterior-posterior chest radiograph within 1 yr of study. There were no significant differences between the groups in age, weight, height, or percent ideal BMI, although the NMD patients tended to be lighter and have a lower BMI. The NMD group had significantly lower values for FVC, FEV₁ (% predicted), and FEF₂₅–₇₅% and significantly higher FEV₁/FVC and RV/TLC than controls. The NMD group tended to have lower TLC, although this difference did not reach statistical significance.
Mean values for breathing pattern, inspiratory muscle function, and respiratory mechanics are reported in Table 3. Duty cycle (T/I/Tr) and calculated PI were not statistically different between the NMD and control groups. P100 was significantly higher in the NMD group than in controls (P < 0.01). The NMD group had significantly lower MIP than controls (P < 0.001). The calculated values for PI/MIP and mean TTmus were significantly higher in the NMD group than in controls (P < 0.001 for both comparisons).

Figure 3 shows the relation between T/I/Tr and PI/MIP for the study subjects. Each isopleth represents a single value of TTmus, with higher isopleths representing increased likelihood of fatigue or fatigue potential. In our population, we found a significant correlation between TTmus and RV/TLC (r = 0.504, P = 0.03) and a negative correlation between TTmus and FEV1 (r = -0.704, P < 0.001; Fig. 4). However, when only subjects with NMD were analyzed, these correlations no longer were statistically significant (P = 0.360 and 0.08, respectively). TTmus was not significantly correlated with percent ideal BMI (r = 0.347, P = 0.09) or age (r = 0.02, P = 0.908).

DISCUSSION

The principal finding of our study is that the noninvasive TTI of the respiratory muscles is increased in children with NMD compared with healthy controls. A noninvasive test that is easy to perform clinically, this measure may be helpful in predicting worsening respiratory muscle fatigue and impending respiratory failure in patients with NMD. For a patient population at risk for respiratory failure, the ability to predict such deterioration may lead to earlier introduction of therapies to prevent or slow the progression to respiratory failure.
TTI of the diaphragm is a measure of impending respiratory muscle fatigue that negatively correlates with the time required to develop respiratory muscle fatigue (Tlim) (2). In the previously published values of controls subjects, TTI >0.2 was predictive of the development of respiratory muscle fatigue. Although Tlim is a measure of respiratory muscle endurance and TTI is a measure of muscle fatigue, they are complementary values in patients with respiratory muscle abnormalities. TTI has been studied in adults with chronic obstructive pulmonary disease, as well as in patients with quadriplegia and chronic congestive heart failure (14, 17). There have been no studies assessing TTI in children with NMD.

Methodological considerations. TTI is not ideally suited for use in children because of the invasive nature of the test, which involves placement of esophageal and gastric pressure transducers. Gaultier et al. (6) described the use of P100 to estimate P1 in the context of estimating inspiratory force reserve in children with obstructive lung disease. Ramonatxo et al. (18) utilized this technique to develop the noninvasive Tmus (18), which was strongly correlated with TTI (TTmus = 2.0 TTI + 0.024, r = 0.97, P < 0.001). This technique utilizes the MIP measured at the mouth, and a P1 extrapolated from P100, also measured at the mouth (6). It has subsequently been applied to the study of tension-time characteristics of the respiratory muscles in adults (4, 10, 21, 22) and children (9). On the basis of the TTI studies (2), it would be expected that patients with TTmus >0.4 would develop respiratory muscle fatigue.

Although MIP is highest when the maneuver is performed from RV (5, 8), the P1 values are measured during tidal breathing, near FRC, and it is therefore at this lung volume that the maximal pressures are measured for TTmus calculation.

It is traditionally assumed that P100 reflects respiratory drive. In patients with NMD, use of P100 has been preferred over other measures of drive such as ventilatory response to carbon dioxide, because it is less dependent on respiratory system mechanics. This preference arises from the fact that the pressures generated during the P100 maneuver are usually far lower than the maximal pressures that can be produced by a patient with even severe NMD. For this reason, extrapolation of the P100 to estimate P1 is likely valid in patients with NMD, inasmuch as the extrapolated pressure (P1) was still well below the MIP of our patients (Table 3). The higher P100 values in the NMD patients than in the controls likely reflect increased drive in response to altered respiratory system mechanics.

Our review of prior studies using TTmus measurements revealed that the measurement of P100 is not straightforward, inasmuch as the start of inspiration and pressure 100 ms later may not always be easily determined from chart recordings of pressure traces. Using a digitally sampled signal (Fig. 1), we developed a precise method for measurement of P100, and we defined the start of inspiration as the initial negative pressure deflection, which may be visually determined by the pressure wave trace and numerically determined when the recorded pressure equals zero. By providing a more exact measurement of P100, this method may be more helpful in comparing small changes in P100 that can occur with worsening disease or changes in therapy. Our signal-analysis program

### Table 1. Anthropometric, nutritional status, and pulmonary function data

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 13)</th>
<th>NMD Patients (n = 11)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>9/4</td>
<td>7/4</td>
<td>0.39</td>
</tr>
<tr>
<td>Age, yr</td>
<td>14.5 ± 5.2</td>
<td>16.6 ± 5.9</td>
<td>0.23</td>
</tr>
<tr>
<td>Height, cm</td>
<td>159.3 ± 17.0</td>
<td>150.1 ± 19.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>53.8 ± 26.2</td>
<td>41.62 ± 15.0</td>
<td>0.08</td>
</tr>
<tr>
<td>%iBMI</td>
<td>106.9 ± 24.8</td>
<td>97.1 ± 46.1</td>
<td>0.014</td>
</tr>
<tr>
<td>FVC, %pred</td>
<td>90.3 ± 10.3</td>
<td>48.4 ± 35.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1, %pred</td>
<td>88.9 ± 8.7</td>
<td>39.7 ± 29.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1 – 75%, %pred</td>
<td>86.5 ± 11.3</td>
<td>45.1 ± 34.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TLC, %pred</td>
<td>95.6 ± 8.9</td>
<td>71.6 ± 32.3</td>
<td>0.42</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>24.3 ± 6.0</td>
<td>52.0 ± 15.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means ± SD. iBMI, ideal body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FEF25–75%, midmaximal expiratory flow; TLC, total lung capacity; RV, residual volume; %pred, percent predicted.
the control subjects, values of TT mus were similar to increased TTmus and decreased lung function (e.g., lung disease. In these studies, an association between FEV1 has been shown. Children with mild CF lung disease had elevated TTmus (0.087 ± 0.014, P < 0.01) compared to healthy controls (0.056 ± 0.014, P < 0.01) (9). This was not surpris-
ing, because the population studied here is affected by disorders influencing intrinsic muscle strength in ways that may be dissociated from body mass (e.g., in patients with muscular dystrophy). In addition, when analyzing only patients with NMD, we did not find a significant correlation between TTmus and RV/TLC or FEV1. This lack of correlation is not particularly surprising, because measurement of TTmus specifically addresses the ability of the respiratory pump to overcome the imposed load. Standard measures of pulmonary function, such as spirometric flow rates or lung volumes, may not be sensitive to this balance.

The use of TTmus in evaluating patients with NMD may be especially informative for several reasons. Most patients with NMD have weakness that is not limited to the diaphragm. Because TTmus reflects the contrib-

Table 2. Clinical characteristics of patients with NMD

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Nocturnal Assisted Ventilation</th>
<th>BMI</th>
<th>Cobb Angle</th>
<th>FEV1, %pred</th>
<th>MIP, cmH2O</th>
<th>TTmus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21.8</td>
<td>M</td>
<td>DMD</td>
<td>+</td>
<td>17.5</td>
<td>36</td>
<td>24</td>
<td>27</td>
<td>0.283</td>
</tr>
<tr>
<td>2</td>
<td>22.0</td>
<td>F</td>
<td>Myopathy</td>
<td>-</td>
<td>19.7</td>
<td>15</td>
<td>32</td>
<td>37</td>
<td>0.106</td>
</tr>
<tr>
<td>3</td>
<td>8.8</td>
<td>M</td>
<td>Prune belly</td>
<td>-</td>
<td>27.0</td>
<td>&lt;15</td>
<td>78</td>
<td>66</td>
<td>0.102</td>
</tr>
<tr>
<td>4</td>
<td>25.7</td>
<td>F</td>
<td>SMA</td>
<td>-</td>
<td>12.4</td>
<td>48</td>
<td>17</td>
<td>48</td>
<td>0.102</td>
</tr>
<tr>
<td>5</td>
<td>14.8</td>
<td>M</td>
<td>MD</td>
<td>-</td>
<td>17.9</td>
<td>&lt;15</td>
<td>92</td>
<td>95</td>
<td>0.076</td>
</tr>
<tr>
<td>6</td>
<td>13.6</td>
<td>F</td>
<td>SMA</td>
<td>-</td>
<td>18.2</td>
<td>57</td>
<td>20</td>
<td>28</td>
<td>0.211</td>
</tr>
<tr>
<td>7</td>
<td>13.4</td>
<td>M</td>
<td>SMA</td>
<td>+</td>
<td>13.4</td>
<td>52</td>
<td>14</td>
<td>28</td>
<td>0.194</td>
</tr>
<tr>
<td>8</td>
<td>25.7</td>
<td>M</td>
<td>SMA</td>
<td>-</td>
<td>16.9</td>
<td>35</td>
<td>N/A</td>
<td>56</td>
<td>0.129</td>
</tr>
<tr>
<td>9</td>
<td>11.4</td>
<td>M</td>
<td>Prune belly</td>
<td>-</td>
<td>34.8</td>
<td>&lt;15</td>
<td>73</td>
<td>32</td>
<td>0.342</td>
</tr>
<tr>
<td>10</td>
<td>12.4</td>
<td>M</td>
<td>SMA</td>
<td>+</td>
<td>15.5</td>
<td>N/A</td>
<td>31</td>
<td>34</td>
<td>0.279</td>
</tr>
<tr>
<td>11</td>
<td>13.3</td>
<td>F</td>
<td>SMA</td>
<td>-</td>
<td>9.5</td>
<td>N/A</td>
<td>15</td>
<td>11</td>
<td>0.437</td>
</tr>
</tbody>
</table>

Table 3. Breathing pattern, inspiratory muscle function, and respiratory mechanics data

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>NMD Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/Ttr</td>
<td>0.44 ± 0.03</td>
<td>0.46 ± 0.04</td>
<td>0.14</td>
</tr>
<tr>
<td>P1 h0, cmH2O</td>
<td>1.9 ± 0.9</td>
<td>2.9 ± 1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>P1, cmH2O</td>
<td>12.1 ± 4.9</td>
<td>15.2 ± 4.4</td>
<td>0.12</td>
</tr>
<tr>
<td>MIP, cmH2O</td>
<td>98.8 ± 20.7</td>
<td>43.0 ± 22.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P1/MIP</td>
<td>0.1 ± 0.05</td>
<td>0.44 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TTmus</td>
<td>0.054 ± 0.02</td>
<td>0.205 ± 0.12</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means ± SD. T/Ttr, duty cycle; P1 h0, occlusion pressure measured at the mouth 100 ms after onset of inspiration; P1, mean inspiratory pressure.

Fig. 3. Isobar plot of tension-time index of respiratory muscles (TTmus) in control subjects (●) and neuromuscular disease (NMD) patients (○). Each isopleth represents an identical product of the ratio of mean inspiratory pressure to maximal inspiratory pressure (P1/MIP) and duty cycle (T/Ttr, where Ttr is inspiratory time and Tr is respiratory cycle time). Higher values of TTmus are associated with increasing likelihood of fatigue.
tions of all the inspiratory muscles, measurement of TT_{mus} may be preferable to measurement of TTI. Although respiratory muscle strength (MIP) is the most commonly used method to assess NMD patients, a more integrated analysis that includes breathing pattern, strength, and mechanical load provides a more thorough assessment of the respiratory pump.

Our results are consistent with those of Matecki et al. (15). In their study of 10 DMD patients (mean age 11.5 ± 1.5 yr) and 10 healthy children (mean age 12 ± 1 yr), they measured the maximal time (T_{lim}) that a fixed threshold load (35% of the individual's MIP) could be tolerated until exhaustion. T_{lim} was significantly shorter in the DMD children (4.45 ± 1.45 min) than in the controls (>30 min) and seemed to be reproducible. Such measures of endurance time require adherence to a challenging protocol, and it remains unclear whether termination of the test is truly due to muscle fatigue or other reasons. The use of TT_{mus} integrates assessments of T/Tr, MIP, and P_{100} during tidal breathing.

Therefore, compared with T_{lim} and TTI, TT_{mus} is a simple test for patients to perform that may be easily incorporated into the clinical setting.

Patients with NMD often adopt a breathing strategy to avoid respiratory muscle fatigue, such as decreasing T/T_{r}, to balance the increased P/P\textsubscript{MIP} (2). Although we did not observe this strategy in our subjects, we have observed tidal breathing below FRC to allow chest wall recoil to aid in inspiration (19).

TT_{mus} provides an objective parameter that may predict worsening respiratory muscle function and impending respiratory failure independently from routine clinical assessment or traditional pulmonary function measurements. Earlier recognition of impending respiratory failure would allow for more timely institution of therapies such as noninvasive ventilation. Additionally, assessment of other therapies (pharmacological and gene transfer) for neuromuscular diseases (e.g., spinal muscular atrophy and DMD) and their effects on respiratory muscle fatigue might be evaluated using TT_{mus}. Although TT_{mus} was <0.1 in all our control subjects and >0.1 in nearly all NMD patients, it is unclear at which value of TT_{mus} respiratory muscle fatigue occurs. Three of our subjects with TT_{mus} ~0.2 were receiving assisted ventilation. Because they were not studied before they received assisted ventilation, it is unknown whether their TT_{mus} values were affected by this therapy. Two subjects with very high TT_{mus} (0.342 and 0.437) were not receiving assisted ventilation at the time of study but are under consideration for respiratory muscle support.

In conclusion, we have shown that TT_{mus} is elevated in children with NMD. Such a measure would be useful for monitoring the progression of respiratory muscle dysfunction in patients with NMD. Therapeutically, TT_{mus} may help identify worsening respiratory muscle fatigue and impending respiratory failure, thereby aiding in the decision to institute therapies such as mechanical ventilation or respiratory muscle training.
APPENDIX

Calculation of $P_t$ from $P_{100}$. $P_t$ was calculated from $P_{100}$ as follows (Fig. 5)

$$P_t = \text{mean inspiratory pressure} = \text{area } \Delta abc + T_1$$

$$\text{Area } \Delta abc = \frac{1}{2} \times \text{length} \times \text{height}$$

$$= \frac{1}{2} \times T_1 \times \text{pressure at point } c$$

If it is assumed that pressure increases linearly from point $a$

Pressure at point $c = \text{slope } \times T_1$

$$\text{Slope} = \frac{\Delta y}{\Delta x} = P_{100} / 0.1 \text{ s}$$

$$= 10 \times P_{100}$$

$\therefore \text{Pressure at point } c = 10 \times P_{100} \times T_1$

$$\text{Area } \Delta abc = \frac{1}{2} \times T_1 \times (10 \times P_{100} \times T_1)$$

$$= 5 \times P_{100} \times T_1^2$$

$\therefore P_t = 5 \times P_{100} \times T_1^2 + T_1 = 5 \times P_{100} \times T_1$

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