Indicators for ventilator use in Duchenne muscular dystrophy

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KEYWORDS
Duchenne muscular dystrophy; Noninvasive ventilation; Spirometer; Noninvasive parameter; RR/VC

Summary
Background: Noninvasive mechanical ventilation is being used up to continuously by patients with Duchenne muscular dystrophy (DMD). Invasive and noninvasive tests are used to assess ventilatory function but there are few reports relating them to extent of ventilator dependence for which simple and cost effective parameters are needed.
Objective: To investigate the relative efficacy of noninvasive lung function parameters for determining extent of need for ventilator use.
Materials and methods: 83 DMD patients were divided into three groups: no ventilator use (asymptomatic) (n = 26) [Group 1], nocturnal ventilator use (symptomatic) (n = 20) [Group 2], and full-time ventilator dependence (n = 37) [Group 3]. Tidal volume (TV), vital capacity (VC), respiratory rate (RR), inspiratory time (Ti), respiratory cycle time (Ttot), rapid shallow breathing index (RSBI [RR/TV]), breathing intolerance index (BITI), ventilator requirement index (VRI) and a new parameter RR/VC were monitored and compared. Data were analyzed with receiver-operating-characteristic curves (ROC) and the area under the curve (AUC) was calculated.
Results: In group 2 and 3, patients used NIV for 3.3±2.1 and 11.2±4.7 years, respectively. By ROC comparison, RR/VC (RR/VC ≥ 0.024 [AUC, 0.921] and ≥ 0.071 [AUC, 0.935]), RR/TV (RR/TV ≥ 0.024) and ventilation intolerance index (BITI) (BITI ≥ 0.024 [AUC, 0.921]) were the best parameters for detecting ventilator requirement.

Abbreviations: ANOVA, Analysis of Variance; AUC, The area under the curve; BITI, Breathing intolerance index; DMD, Duchenne muscular dystrophy; NMD, Neuromuscular disorders; NIV, Noninvasive ventilation; PEmax, Maximal expiratory pressures; Plmax, Maximal inspiratory pressure; PSG, Polysomnography; ROC, Receiver-operating-characteristic; RR, Respiratory rate; RSBI, Rapid shallow breathing index; SD, Standard deviation; Ti, Inspiratory time; TTmusc, The tension–time index of the inspiratory muscles; Ttot, Respiratory cycle time; TV, Tidal volume; VC, Vital capacity; VRI, Ventilator requirement index.

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Introduction

Duchenne muscular dystrophy (DMD) is an X-linked progressive neuromuscular disease due to the absence of dystrophin in the subsarcolemmal cytoskeleton that occurs in about 1 in 3600–6000 males.\(^1\) Respiratory muscle weakness is progressive and results in symptomatic sleep hypoventilation usually in the late teens. Respiratory complications, including lower tract infections, atelectasis, and retained secretions are the main causes of morbidity and mortality. FVC of <1L is a predictor of poor outcome, with a 5-year survival rate of only 8% if assisted ventilation is not provided.\(^3\) Without ventilator support, the life expectancy in DMD has been reported to be about 19 years\(^3\) but with it can exceed 4 decades.\(^3\) Besides managing acute and chronic ventilatory failure, it is useful in cardioprotection by preventing cor pulmonale.\(^7\) Despite therapeutic advances in assisting inspiratory and expiratory muscle function to prolong survival,\(^3,4\) there is no general consensus on what parameters should indicate initiation and extent of ventilator use.\(^9,10\) In 2004, the American Thoracic Society recommended nocturnal polysomnography (PSG) and/or pulse oximetry with carbon dioxide monitoring to indicate introduction of noninvasive ventilation (NIV) for DMD.\(^11\) However, PSG is not universally available, is time consuming, expensive, and not available during routine evaluations when decisions about NIV need to be made.\(^12\) and PSG is programmed to attribute apneas and hypopneas only to central and obstructive events rather than to inspiratory muscle dysfunction. In addition, appreciation of symptoms of inspiratory muscle dysfunction is often delayed in DMD patients.\(^13\) Thus, prescription of ventilatory assistance can be delayed despite severe lung dysfunction.

Despite therapeutic advances for DMD, there has been no significant change over the past 20 years in the time from symptom onset to diagnosis.\(^9,10\) Moreover, the frequency and circumstances of childhood mortality are geographically and socio-economically dependent\(^14\) and the main causes of mortality are from complications of respiratory muscle weakness. Therefore, basic and low cost indicators for institution of NIV are needed. Baydur A et al.\(^16\) and a consensus conference\(^32\) reported that it is considered to require NIV when VC decreased to 500–700 ml and below 50% predicted, respectively. Hahn et al. reported that noninvasive determination of the tension–time index of the inspiratory muscles (TT\(_{MLIS}\)) can help to justify the extent of need for NIV.\(^15\) Fauroux et al. studied the correlation between several volitional and non-volitional parameters and the need for NIV.\(^16\) We proposed a breathing intolerance index (BITI)\(^17\) and ventilator requirement index (VRI)\(^18\) as noninvasive indicators. BITI was defined as multiplying Ti/Ttot by TV/VC, while VRI was obtained by multiplying BITI by RR. But these require a digital spirometer with specific software. We now consider RR/VC. The purpose of this study was to investigate the relative efficacy of these noninvasive lung function parameters for determining extent of need for ventilator use.

Materials and methods

A retrospective analysis was undertaken of 83 DMD patients followed up at National Yakumo Hospital since 2003 with diagnosis established by dystrophin absence on muscle biopsy or by DNA analysis. All patients were wheelchair-bound by age 12. We introduced nocturnal NIV when patients had symptoms of nocturnal hypoventilation including increasing nocturnal awakenings, daytime sleepiness, morning headaches, and palpitations. Patients extended use to around-the-clock and were provided with a simple 15 mm angled mouth piece for daytime use when dyspnea developed upon cessation of NIV in the morning and as a result of daytime hypercapnia. The patients were divided into three categories: Group 1 patients were asymptomatic and not using ventilators; Group 2 patients used nocturnal NIV for relief of symptoms; and Group 3 required both nocturnal and daytime ventilator use. A Meteor digital spirometer with a liquid crystal diode monitor (Cardio-Pulmonary technologies, Sussex, WI) was used with custom-prepared software for a Windows-based personal computer (FMV-660 MC/W, A Fujitsu Corporation, Tokyo, Japan). The computer selected the six most consistent tidal TV waveforms with the patient supine and at rest and it averaged them for the Ti, Ttot, and TV data. With this equipment, TV, VC, RR, inspiratory time (Ti), and respiratory cycle time (Ttot) were analyzed. Then, RSBI [RR/TV], BITI, and VRI were analyzed along with RR/VC. We calculated RR/VC by multiplying TV/VC by RR/TV. All measurements were performed with the patients at supine since some patients could not sit. Absolute VC values were used because comparing percentage of predicted normal is not meaningful when lung volumes are very small and these are difficulties in translating absolute volumes to percentage of predicted for patients with severe back deformity.\(^19\) One technician performed all measurements. Arterial blood gas analysis was not done because 30% of people hyperventilated because of the pain of the arterial puncture, temporarily decreasing carbon dioxide tensions.\(^34\)

Statistical analysis

Data were analyzed by one-way analysis of variance (ANOVA). For all post-ANOVA intergroup comparisons, we used Tukey-Kramer test. Sensitivity and specificity were calculated, and the data were also analyzed with receiver-operating-characteristic (ROC) curves, in which the proportions of true positive results and false positive results were...
plotted against each other for threshold values and the area under the curve (AUC) to reflect the accuracy of the index. Threshold cut-off values were calculated by providing the best compromise between the optimal sensitivity and specificity.

## Results

Eighty-three patients were included in the study. Twenty-six patients were not ventilated (Group 1). Twenty patients were treated with nocturnal NIV, and used essentially nocturnal-only NIV for 3.3 ± 2.1 years (Group 2). Thirty-seven patients extended use to around-the-clock, and used NIV for 11.2 ± 4.7 years (Group 3).

Demographic data and pulmonary data are in Table 1. Along with ventilator dependency, RR progressively increased ($p < 0.05$). VC and TV progressively decreased for all three groups.

Table 2 illustrates the cut-off values to introduce nocturnal ventilator use. VC, RR/TV, and RR/VC had AUCs of 0.896, 0.905, and 0.921, respectively, indicating good diagnostic accuracy. Cut-offs of VC ≤ 770 ml, RR/TV ≥ 0.024, and RR/VC ≥ 0.024 had sensitivities of 85%, 81%, and 85%, respectively, and specificities of 89%, 90%, and 89%, respectively. Table 3 shows the cut-off values to introduce continuous ventilator use. VC, RR/TV, and RR/VC had AUCs of 0.898, 0.905, and 0.935, respectively, indicating good diagnostic accuracy. Cut-offs of VC ≤ 370 ml, RR/TV ≥ 0.153, and RR/VC ≥ 0.071 had sensitivities of 78%, 81%, and 86%, respectively, and specificities of 85%, 90%, and 95%, respectively. Fig. 1 illustrates ROC curves of RR/VC values that indicate nocturnal (Fig. 1A) and continuous ventilator use (Fig. 1B) with AUC 0.921, and 0.935, respectively.

## Discussion

Lung volumes are used to gauge the severity of respiratory muscle impairment in DMD. It is recommended that VC, peak cough flow, and maximal inspiratory (PImax) and expiratory pressures (PEmax) should have to be routinely evaluated. But, in patients with facial muscle weakness or general bulbar-innervated muscle dysfunction, technical difficulties and leak problems may limit PImax and PEmax accuracy. Furthermore, low values of these parameters can also be difficult to interpret. Sniff nasal inspiratory pressure correlates with inspiratory muscle strength, is easy to perform, and is generated during a ballistic maneuver. However, tachypneic DMD patients may not be able to perform a rapid sniff maneuver. Invasive parameters including sniff esophageal pressure, sniff transdiaphragmatic pressure, twitch transdiaphragmatic pressure, twitch T10 gastric pressure, and cough gastric pressure have been used. However, because of their invasive nature these tests cannot be routinely performed. Although Nicot et al. reported that these invasive tests were easier to perform for neuromuscular disorders, they analyzed only young and relatively strong patients. Nevertheless, neither the invasive nor the noninvasive parameters mentioned above are quantitative indicators for extent of need for ventilatory assistance.

There are three reports relating lung function parameters to NIV dependence. Fauroux et al. correlated several

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cut-off</th>
<th>AUC</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
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<tbody>
<tr>
<td>VC, ml</td>
<td>≤770</td>
<td>0.896</td>
<td>85</td>
<td>89</td>
</tr>
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<td>TV/VC</td>
<td>≥0.3</td>
<td>0.806</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>RR/TV, breaths/ml</td>
<td>≥0.024</td>
<td>0.905</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>B1T1</td>
<td>≥0.144</td>
<td>0.835</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>VRI</td>
<td>≥3.04</td>
<td>0.863</td>
<td>70</td>
<td>89</td>
</tr>
<tr>
<td>RR/VC, breaths/ml</td>
<td>≥0.024</td>
<td>0.921</td>
<td>85</td>
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volitional and non-volitional parameters with need for NIV\textsuperscript{16} but noted only that the test results were lower in children using NIV. Hahn et al. reported that noninvasive determination of the tension–time index of the inspiratory muscles (TT\textsubscript{MUS}) might help to justify the extent of need for NIV.\textsuperscript{15} TT\textsubscript{MUS} surpassed 0.23 and 0.37 in 95% of subjects ventilated 8–20 h per day and >20 h per day, respectively. Bach et al. reported that a VC < 50% or a VRI > 1.2 had a 95% sensitivity for the justification of a ventilator for nocturnal use, while a VC < 1100 ml or VRI > 2.5 was 93% sensitive for predicting need for a second ventilator but ROC curves were not analyzed.\textsuperscript{18} VRI is calculated by multiplying BITI by RR and BITI by multiplying Ti/Ttot by TV/VC. In reevaluating our earlier BITI and VRI data, Ti/Ttot did not vary significantly with the extent of ventilator need.\textsuperscript{17,18} Therefore, it does not seem to be necessary to include Ti/Ttot measurements (that require a specific spirometer) to evaluate this.

This study investigated the relative sensitivity and specificity of noninvasive lung function parameters for determining extent of need for ventilator use and found that the RR/VC and VC were the most sensitive and specific parameters. RR/VC was most sensitive and specific for indicating the need to initiate full-time NIV. RR/TV and TV/VC have been reported to correlate with dyspnea.\textsuperscript{26} RR/TV reflects rapid shallow breathing, is a ventilator weaning predictor.\textsuperscript{27} Furthermore, high value of RR/TV can cause hypercapnia.\textsuperscript{28} Interestingly, Toussaint et al. stated that TV/VC > 0.33 accurately predicted daytime hypercapnia (ROC, 0.923) but RR/TV could not (ROC, 0.604).\textsuperscript{12} VC decreases at 200–250 ml (5–10%) per year following plateau between ages 9 and 16 before the rate of decrease tapers off below 400 ml.\textsuperscript{31} VC measurements have become popular for assessing respiratory muscle weakness and to predict respiratory failure in neuromuscular disease.\textsuperscript{12,29} It was reported that nocturnal and full-time NIV were required when VC was 500–700 ml and about 300 ml, respectively.\textsuperscript{30} Toussaint et al. suggested that DMD patients were at high risk for diurnal hypercapnia when VC decreased below 680 ml. Hahn et al. also suggested that VC was sensitive in recognizing subjects who need NIV. Our results suggest that VC ≤ 770 and ≤ 370 ml are predictive for nocturnal and full-time ventilator use, respectively. In addition, RR/VC was the most appropriate screening parameter because it yielded the lowest proportion of false negative results. VC can be analyzed with a simple, portable spirometer. RR is also easily obtained. In predicting full-time NIV need, VC alone yielded a relatively high false negative rate because patients’ NIV dependence varies greatly once VC decreases below 400 ml. Therefore, we suggest that RR/VC is the simplest and most accurate parameter for indicating extent of need for long-term ventilator use.

Limitations of this study include its retrospective nature and the small numbers of subjects. We also did not correlate lung function and overnight and/or awake CO\textsubscript{2} measurement. Prospective studies are warranted.

We conclude that RR/VC ≥ 0.024 and 0.071, respectively, are most useful screening parameters to justify the need for sleep NIV and continuous NIV. RR/VC, thereby, can

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<tbody>
<tr>
<td>VC, ml</td>
<td>≤370</td>
<td>0.898</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td>TV/VC</td>
<td>≥0.48</td>
<td>0.789</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>RR/TV, breaths/ml</td>
<td>≥0.153</td>
<td>0.905</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>BITI</td>
<td>≥0.246</td>
<td>0.717</td>
<td>59</td>
<td>85</td>
</tr>
<tr>
<td>VRI</td>
<td>≥6.96</td>
<td>0.825</td>
<td>62</td>
<td>90</td>
</tr>
<tr>
<td>RR/VC, breaths/ml</td>
<td>≥0.071</td>
<td>0.935</td>
<td>86</td>
<td>95</td>
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Table 3  Pulmonary function parameter sensitivity and specificity for DMD full-time ventilator use requirement. Area under the curve (AUC): 1 = perfect discrimination between Group 2 and 3; 0.5 = poor discrimination with 50% chance of error.

Figure 1  The ROC curves of RR/VC for indicating need for ventilator use (Fig. 1A) and full-time ventilator use (Fig. 1B). Fig. A: AUC 0.921, Fig. B AUC 0.935.
best justify the need for a second ventilator for daytime use and as a back-up for NIV dependent patients.

**Conflict of interest**

All authors have no conflicts of interest to declare in relation to this work.

**References**


