Postural Change of FVC in Patients with Neuromuscular Disease: Relation to Initiating Non-Invasive Ventilation

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Abstract

**Background:** Forced Vital Capacity (FVC) has been used to assess respiratory muscle strength in patients with Neuromuscular Disease (NMD). However, postural changes to FVC have not been assessed in relation to the start of Non-Invasive Ventilation (NIV). This study aims to assess the changes to postural FVC for indications of NIV.

**Methods:** The records of spirometry performed in seated and supine posture were retrospectively reviewed in 33 patients with NMD [10 breathing spontaneously (SB), 15 receiving NIV]. The change in FVC (in L) between seated (sit) and supine (sup) positions was expressed as %ΔFVC (sit – sup) = [(FVC(L)sit – FVC(L)sup)/FVC(L)sit]. The postural change in forced expiratory flow (FEF), % FEF (sit – sup) was similarly computed.

**Results:** %ΔFVC (sit – sup) in patients receiving NIV exceeded the %ΔFVC (sit – sup) of SB patients by 14-fold (p = 0.001). %ΔFEF (sit–sup) however, did not reach statistical significance between cohorts. There was a negative correlation between %ΔFVC (sit-sup) and VC (% pred) (R = -0.40, p = 0.02), and a direct correlation between %ΔFVC(sit-sup) and %ΔFEF(sit-sup) (R = 0.72, p<0.0001) amongst all patients.

**Conclusions:** Postural change of FVC in patients with neuromuscular disease placed on noninvasive ventilation is significantly greater than in those still able to breathe spontaneously.

A prospective longitudinal study designed to assess the predictive value of ΔFVC (sit – sup), and if possible, a threshold value for initiating NIV may provide a guideline more precise than the seated FVC.

**Keywords:** Postural change in vital capacity; Assisted ventilation; Neuromuscular disorders

Introduction

The forced vital capacity (FVC) and maximal respiratory pressures are commonly used to assess respiratory muscle strength in patients with neuromuscular disorders (NMD) [1-4]. The FVC and lung volumes decrease with progression of the disease, with a drop in FEV1 typically exceeding a drop in FVC [5,6]. Respiratory muscle weakness can also be assessed by measuring the difference in FVC between sitting and supine positions (FVCsit and FVCsup, respectively) [5-14], a more sensitive index than upright FVC. In normal subjects, vital capacity decreases insignificantly (about 5%) upon assuming the supine position [7,8], while greater decreases in VC have been documented in patients with NMD [10-13]. The value of this index as it relates to the need for Non-Invasive Ventilation (NIV) include dyspnea, orthopnea, drowsiness, decreased cognitive function, hypercapnia, and decline in respiratory muscle weakness or paralysis [3]. Indications for initiation of non-invasive ventilation (NIV) include dyspnea, orthopnea, drowsiness, decreased cognitive function, hypercapnia, and decline in FVC to usually below 50% predicted [4]. Respiratory muscle weakness may also be assessed by measuring the difference in FVC between sitting and supine positions (FVCsit and FVCsup, respectively) [5-14], a more sensitive index than upright FVC. In normal subjects, vital capacity changes insignificantly (about 5%) upon assuming the supine position [5-9], while greater decreases in VC have been documented in patients with NMD [10-13]. The value of this index as it relates to the need for NIV, however, has not been assessed. The forced expiratory flow (FEF) has been used to quantify the individual's ability to cough and eliminate airway secretions. Postural change in FEF, however, has also not been assessed in relation to initiating NIV. This retrospective exploratory study aimed to assess the relationship of the postural changes in FVC and FEF with initiation of NIV in patients with NMD.

**Methods**

The records of patients with NMD evaluated in the outpatient respiratory clinic at Keck Medical Center, University of Southern California between January 1998 and June 2011 were reviewed. Spirometric values obtained closest to the time of initiating NIV were recorded. Patients who could not perform spirometry according to ATS/ERS criteria were excluded [14]. Individuals with difficulty in clearing airway secretions and/or who exhibited seated forced expiratory flow rates (FEFRs) less than or equal to 160 L/min were provided cough-assist devices, and their caregivers instructed in the provision of mechanical and manual cough techniques [15]. The study was approved by the Institutional Review Board of the University of Southern California Health Sciences Campus (IRB Proposal #HS-13-00080).

Patients underwent spirometry (Medgraphics Elite Dx, St. Paul, Minnesota) in seated and supine postures while seated comfortably in a reclining chair that could be converted into a horizontal position. Maximal inspiratory and expiratory pressure measurements (Pimax and Pemax, respectively), available in 8 SB and 6 NIV subjects, were measured in seated position according to the method of Black and Hyatt [16,17]. Arterial blood gases were obtained in the seated position while breathing room air (Rapidlab 1265, Siemens, Tarrytown, NY). Reference values for FEV1, FVC were from Morris et al. [18], and Forced Expiratory Flow (FEF) from The National Health and Nutrition Examination Survey (NHANES) III [19].

The change in FVC between seated (sit) and supine (sup) positions was expressed as %ΔFVC(sit – sup) = [(FVC/L)sit – FVC(L)sup]/FVC(L)sit]. The postural change in FEF was expressed as %ΔFEF(sit – sup) = [(FEF(L/sec)sit – FEF(L/sec)sup)/FEF(L/sec)sit].

**Statistical Analysis**

Because of non-normal distribution of subjects, tabulated values were expressed as median and Interquantile Range (IQR). Comparison

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of spirometric variables between seated and supine positions were conducted by paired student t-test. Comparisons of % ΔFVC(sit-sup) and % ΔFEF(sit-sup) between patients who breathed spontaneously and those who required NIV were compared by paired student t-test [20]. Correlations between % ΔFVC(sit-sup) and % ΔFEF(sit-sup) and other selected physiologic variables were by Spearman correlation. A p-value < 0.05 was considered statistically significant.

**Results**

Table 1 shows the anthropometric and functional data in 18 subjects breathing spontaneously (SB) and 15 patients receiving NIV. The diagnoses of the SB patients included the following: amyotrophic lateral sclerosis (ALS) (n=4), post-polio syndrome (n=5), primary lateral sclerosis (n=1), spinal cord injury (n=2), radicular polyneuropathy (n=1), myasthenia gravis (n=2), and diaphragmatic weakness (n=3). The diagnoses of those receiving NIV included: ALS (n=8), post-polio syndrome (n=4), diaphragmatic weakness (n=2), and myasthenia gravis (n=1). The median time interval (IQR) between initiating NIV and the closest recorded pre-NIV spirometric value was 150 (60) days. Ninety percent of patients who received NIV were experiencing exertional dyspnea, orthopnea, or sleep-related discomfort when the closest spirometry was obtained.

The %ΔFVC(sit-sup) in patients receiving NIV exceeded the %ΔFVC(sit-sup) of SB patients by 14-fold (p = 0.0002, Table). Median seated FVC in SB patients, however, exceeded the FVC of those receiving NIV by only 3.6% (NS, Table). By contrast, median seated FEF (in L/s) in SB individuals exceeded those receiving NIV by 34% (p = 0.025). The postural change in FEF in L/s [%ΔFEF(sit-sup)], however, did not differ significantly between cohorts. Median Pimax (in cm H2O) in the 6 NIV and 8 SB subjects in which it was measured exhibited a statistically significant difference between the 2 cohorts (p = 0.008). Pemax, however, did not reach statistical difference between the cohorts.

We assessed the relationships between the postural changes in FVC and selected other variables of respiratory muscle function. Figure 1 shows the negative correlation between %ΔFVC(sit-sup) and FVC sit (% pred) (R = -0.40, p = 0.02). Figure 2 shows a direct correlation between %ΔFVC(sit-sup) and %ΔFEF(sit-sup) in all patients (R = 0.72, p < 0.0001) and amongst those receiving NIV, R = 0.87, p = 0.004, but not amongst the SB group. There was a tendency towards a negative relationship between %ΔFVC(sit-sup) and Pimax, but it did not reach statistical significance (R = -0.6, p = 0.07). Correlations between %ΔFVC(sit-sup) and Pemax, and between %ΔFEF (sit-sup) and Pemax did not reach statistical significance.

**Discussion**

To our knowledge, this is the first study that has assessed the

### Table 1: Anthropometric and physiologic data in patients breathing spontaneously and those started on non-invasive ventilation.

<table>
<thead>
<tr>
<th>Gender (M/F)</th>
<th>Spontaneously breathing (SB)</th>
<th>On non-invasive ventilation (NIV)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/9</td>
<td>9/8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60 (51, 66)</td>
<td>64 (55, 69)</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI</td>
<td>25.2 (21, 29)</td>
<td>27 (22, 32)</td>
<td>0.84</td>
</tr>
<tr>
<td>FVC, L (seated)</td>
<td>3.3 (2.7, 4.3)</td>
<td>3.4 (2.7, 4.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>FVC, % predicted (seated)</td>
<td>70 (55, 96)</td>
<td>67 (27, 88)</td>
<td>0.18</td>
</tr>
<tr>
<td>ΔFVC(sit – sup), %</td>
<td>1.6 (4.9)</td>
<td>22.7 (9, 29.3)</td>
<td>0.0002</td>
</tr>
<tr>
<td>FEF, L/s (seated)</td>
<td>5.8 (4.6, 7.5)</td>
<td>3.8 (1.9, 5.3)</td>
<td>0.025</td>
</tr>
<tr>
<td>FEF, % predicted (seated)</td>
<td>62 (46, 102)</td>
<td>54 (18, 83)</td>
<td>0.46</td>
</tr>
<tr>
<td>ΔFEF (sit – sup), %</td>
<td>10.3 (1.6, 16.7)</td>
<td>8.4 (-2.2, 31.8)</td>
<td>0.54</td>
</tr>
<tr>
<td>Pimax, cm H2O</td>
<td>67 (33, 84) (n = 8)</td>
<td>30 (12, 46) (n = 6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Pimax, % predicted</td>
<td>78 (44, 96)</td>
<td>40 (29, 47)</td>
<td>0.08</td>
</tr>
<tr>
<td>Pemax, cm H2O</td>
<td>91 (43, 120) (n = 8)</td>
<td>62 (32, 104) (n = 6)</td>
<td>0.39</td>
</tr>
<tr>
<td>Pemax, % predicted</td>
<td>58 (26, 83)</td>
<td>34 (26, 53)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Abbreviations: FVC, forced vital capacity; FEF, forced expiratory flow; Pimax, maximal inspiratory mouth pressure; Pemax, maximal expiratory mouth pressure; Values expressed as median (1st and 3rd quantiles); n, numbers of subjects as shown unless otherwise stated. †Differences by 2-tailed t-test.
relationship of the postural differences in FVC and FEF with the need for initiating noninvasive ventilation in patients with neuromuscular disorders. Its main finding is the dramatic difference (on average) in %ΔFVC(sit-sup) between patients who were still breathing spontaneously and those who required initiation of NIV. The 14-fold difference in postural change is considerably greater than the simple reduction in seated FVC usually cited as a criterion for initiation of ventilation (about a 50% reduction in FVC from normal values) [11,12]. By contrast, the postural difference for FEF was not statistically significant between the SB and NIV cohorts.

Normal subjects exhibit a moderate decrease in VC upon assuming the supine position [6], primarily due to an increase in intrathoracic blood volume. Postural change in FVC has been cited as a sensitive indicator of respiratory muscle weakness in patients with ALS [10-14]. Our finding of an AFVC(sit – sup) (in L) of 23% in patients receiving NIV was somewhat higher than that of Schmidt et al. [21] (16%) and Varrato and colleagues [13] (13%) whose patients were not receiving NIV at the time of study enrollment. In the study of Varrato [13], the difference in AFVC(sit – sup) (in L) between patients experiencing dyspnea, orthopnea and daytime fatigue, and asymptomatic patients amounted to as high as 25%, but their study did not include patients on NIV. In healthy subjects, when the diaphragm contracts, abdominal pressure rises and pleural pressure decreases, causing the lungs to expand. In patients with neuromuscular disorders, as the rib cage expands, the fall in pleural pressure is transmitted through the weakened diaphragm, and the abdominal wall moves inward, preventing lung inflation (i.e., paradoxical breathing) [22]. This finding is exaggerated in supine posture. The increasing differences between seated and supine values of FVC are indicative of a weakened diaphragm and other inspiratory muscles unable to expand the thorax against abdominal contents in the supine position. To the extent that inspiratory muscles are unable to generate force, the need for assisted ventilation increases, particularly during sleep, and, as the disease progresses, during wakeful periods, even when erect.

The correlation between %ΔFVC(sit-sup) and %ΔFEF(sit-sup), particularly in patients receiving NIV (that is, those with weaker inspiratory muscles), is not surprising as FEF is volume- (and elastic recoil-) dependent [19]. This relationship was found amongst all patients and those receiving NIV, but not amongst the SB cohort because of the short range of FEF values and smaller numbers. This finding has clinical importance as a decrease in the FEF to less than 3 L/s has been associated with poor cough effort and increased risk for atelectasis and pneumonia [15]. Yet, we found that postural change did not result in a significant decrease in FEF as it did with FVC. The configuration of the flow-volume curve is altered in many patients with NMD. Weakness of the expiratory muscles often leads to a decrease in the slope of the ascending portion of the expiratory limb of the curve, with FEF occurring at a lower percentage VC than in normal subjects, and a reduction in FEF [22]. Hence, a change to the supine position is not likely to result in a decrease in the FEF of the same magnitude as with FVC. FEF is also influenced by airway resistance which is increased due to reduction in lung volume in NMD patients, and probably contributes to absence of a significant difference in postural decline between the two cohorts.

The postural change in FVC in neuromuscular weakness and its association with dyspnea may be considered analogous to changes observed with water immersion [23-25]. Schoenhofer and colleagues [24] found a 34% reduction in FVC in erect patients with severe diaphragmatic weakness (3 with ALS) immersed up to their necks, in contrast to normal subjects who showed no such change. By contrast, they found a 25% increase in the respiratory rate (no change in normal subjects) and a 6.5-fold increase in the mouth occlusion pressure at 0.1 sec (P0.1), a consequence of increase in elastic work of breathing and ventilatory drive. However, time of immersion and water temperature, factors that may have affected intrathoracic blood volume [25], were not described.

The majority of patients who required the initiation of NIV had amyotrophic lateral sclerosis and late effects of poliomyelitis (post-polio syndrome). The decline in FVC may exhibit different patterns in different neuromuscular disorders [26,27], with a slower decline allowing time for “adjustment” and delay before the initiation of NIV. In addition the decline in % predicted FVC is dependent on age (faster than the absolute value of FVC) and presence of spinal deformities [26]. Some patients with ALS experience a rapid decline in FVC from the time of diagnosis, while others with ALS may also exhibit a slow progression of respiratory impairment, only to experience a rapid decrease in function in later stages. Thus the rapidity in the decline of FVC may play a role in determining prognosis and the timing of assisted ventilation. Indeed, while international guidelines list a number of indications for the initiation of long-term NIV, they do not address clinical differences and rapidity of progression of different disorders [28]. A recent study indicates that functional variables such as pulmonary function, blood gases, and maximal respiratory pressures differ amongst specific NMDs when long-term NIV is being considered [29]. We are not aware of studies that followed postural changes in FVC and FEF over time. It is possible that longitudinal assessment of postural change in these variables may prove to be just as predictive of the need for assisted ventilation as the seated FVC, if not more so.

There are a number of limitations in this study. First, it was retrospective, raising the possibility of bias in comparing patients still able to breathe on their own with those receiving assisted ventilation. Indeed, about a fifth of our patients were started on NIV based on a subjective sensation of dyspnea and orthopnea, before their seated FVC fell below the threshold at which assisted ventilation would be recommended (50% from baseline) [11,12]. The median FVC of patients who were started on NIV was 67% predicted, higher than the mean FVC of 40% predicted in the study of Dreher et al. [29]. Second, the time between spirometry and initiation of NIV was long and variable, in part because symptoms of dyspnea and orthopnea, and not just FVC, contributed to the decision to begin assisted ventilation. Nevertheless, the results still clearly exhibited a marked difference in %ΔFVC(sit-sup) between the cohorts regardless of the exact time spirometry was obtained, or of the pattern of functional decline in disease. Third, less than half of our patients had arterial blood gas measurements prior to starting NIV. Nevertheless, PaCO2 was not significantly different in patients who were started on NIV (and in whom arterial blood gases were obtained). Schmidt et al. [21] similarly found a normal mean PaCO2 but with a wide range (32-72 mm Hg) at baseline evaluation of their ALS patients, of whom 60% were eventually prescribed NIV. They concluded that PaCO2 was not a significant predictor of survival. Finally, we did not attempt to separate patients according to diagnosis, in part because there were few individuals with conditions other than ALS and late effects of poliomyelitis. This may be a consideration in disorders with differing rates of decline in respiratory muscle function.

In conclusion, postural change of FVC in this cohort of neuromuscular disease placed on noninvasive ventilation is markedly greater than in those still able to breathe spontaneously.

A larger longitudinal study designed to assess the predictive value of ΔFVC(sit–sup), and if possible, a threshold value for initiating NIV...
may provide a more precise guideline than just the seated FVC. The variable pattern of decline in respiratory function in different disorders may result in differing thresholds of ΔFVC(sit–sup), and this will be variable pattern of decline in respiratory function in different disorders

References