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# 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 [18 breathing spontaneously (SB), 15 receiving NIV]. The change in FVC (in L) between seated (sit) and supine (sup) positions was expressed as $\%\Delta FVC$ (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:** $\%\Delta FVC$ (sit – sup) in patients receiving NIV exceeded the $\%\Delta FVC$ (sit – sup) of SB patients by 14-fold (p = 0.001). $\%\Delta FEF$ (sit–sup) however, did not reach statistical significance between cohorts. There was a negative correlation between $\%\Delta FVC$ (sit-sup) and $FVC_{sit}$(% pred) (R = -0.40, p = 0.02), and a direct correlation between $\%\Delta FVC$(sit-sup) and $\%\Delta FEF$(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 $\Delta FVC$ (sit – sup), and if possible, a threshold value for initiating NIV may provide a guideline more precise than the seated FVC.

## 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. Orthopnea is associated with diaphragmatic 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 can also be assessed by measuring the difference in FVC between sitting and supine positions ($FVC_{sit}$ and $FVC_{sup}$, 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 (FEFs) 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, Tarreytown, NY). Reference values for $FEV_1$ and 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 $\%\Delta FVC(sit – sup) = [\{FVC(L)_{sit} – FVC(L)_{sup}\}/FVC(L)_{sit}]$. The postural change in FEF was expressed as $\% \Delta FEF(sit – sup) = [\{FEF(L/sec)_{sit} – FEF(L/sec)_{sup}\}/FEF(L/sec)_{sit}]$.

## Statistical Analysis

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

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.
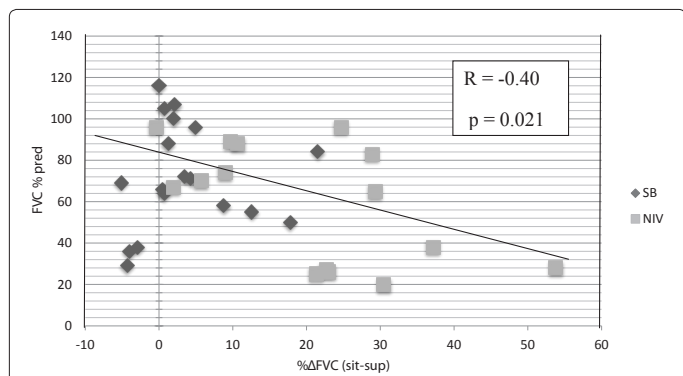


**Figure 1:** Relationship between % ΔFVC(sit-sup) and $FVC_{sit}$ (% predicted). ♦ = spontaneously breathing subjects; ■ = patients receiving noninvasive ventilation.
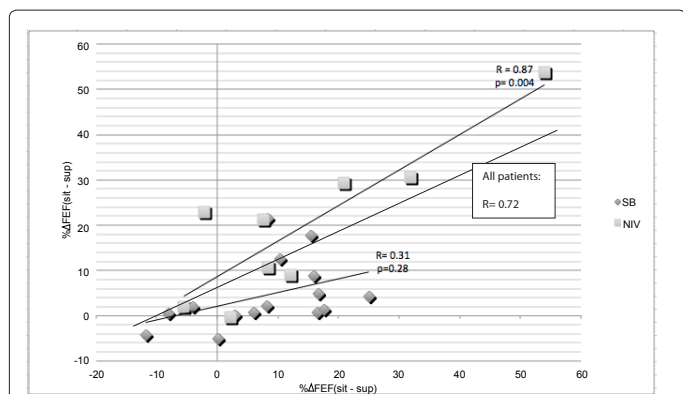


**Figure 2:** Relationship between %ΔFVC(sit-sup) and %ΔFEF(sit-sup). Symbols same as in Figure 1.

## 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 solitary diaphragmatic weakness (n=3). The diagnoses of those receiving NIV included: ALS (n=8), post-polio syndrome (n=4), solitary 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 $H_2O$) 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 Pimax, 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

| | Spontaneously breathing (SB) | On non-invasive ventilation (NIV) | P-value† |
|---|---|---|---|
| Gender (M/F) | 9/9 | 7/8 | |
| Age (yr) | 60 (51, 66) | 64 (55, 69) | 0.11 |
| BMI | 25.2 (21, 29) | 27 (22, 32) | 0.84 |
| FVC, L (seated) | 3.3 (2.7, 4.3) | 3.4 (2.7, 4.2) | 0.27 |
| FVC, % predicted (seated) | 70 (55, 96) | 67 (27, 88) | 0.18 |
| ΔFVC(sit – sup), % | 1.6 (0, 4.9) | 22.7 (9, 29.3) | **0.0002** |
| FEF, L/s (seated) | 5.8 (4.6, 7.5) | 3.8 (1.9, 5.3) | **0.025** |
| FEF, % predicted (seated) | 62 (46, 102) | 54 (18, 83) | 0.46 |
| ΔFEF (sit – sup), % | 10.3 (1.6, 16.7) | 8.4 (-2.2, 31.8) | 0.54 |
| Pimax, cm $H_2O$ | 67 (33, 84) (n = 8) | 30 (12, 46) (n = 6) | **0.008** |
| Pimax, % predicted | 78 (44, 96) | 40 (29, 47) | **0.08** |
| Pemax, cm $H_2O$ | 91 (43, 120) (n = 8) | 62 (32, 104) (n = 6) | 0.39 |
| Pemax, % predicted | 58 (26, 83) | 34 (26, 53) | 0.22 |

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.

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

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 a ΔFVC(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 ΔFVC(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 airflow 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 ($P_{0.1}$), 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, $PaCO_2$ 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 $PaCO_2$ 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 $PaCO_2$ 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 relevant for future studies.

## References

1. Baydur A (1991) Respiratory muscle strength and control of ventilation in patients with neuromuscular disease. Chest 99: 330-338.

2. Ambrosino N, Carpenè N, Gherardi M (2009) Chronic respiratory care for neuromuscular diseases in adults. Eur Respir J 34: 444-451.

3. Nightingale S, Bates D, Bateman DE, Hudgson P, Ellis DA, et al. (1982) Enigmatic dyspnoea: an unusual presentation of motor-neurone disease. Lancet 1: 933-935.

4. Hill NS, Liesching T, Kwok H (2005) Indications for Non-invasive Ventilation: Update in Intensive Care Medicine: Mechanical Ventilation.

5. McMichael J, McGibbon JP (1940) Postural changes in in the lung volume. Clin Sci 4:175-183.

6. Tenney SM (1959) Fluid volume redistribution and thoracic volume changes during recumbency. J Appl Physiol 14: 129-132.

7. Hanson JS, Tabakin BS, Caldwell EJ (1962) Response of lung volumes and ventilation to posture change and upright exercise. J Appl Physiol 17: 783-786.

8. Allen SM, Hunt B, Green M (1985) Fall in vital capacity with posture. Br J Dis Chest 79: 267-271.

9. Baydur A, Behrakis PK, Zin WA, Jaeger MJ, Weiner JM, et al. (1987) Effect of posture on ventilation and breathing pattern during room air breathing at rest. Lung 165: 341-351.

10. Cho DH, Kang SW, Park JH, Yoo TW (2004) Postural change of vital capacity in patients with neuromuscular disease. J Korean Acad Rehabil Med 28: 454-457.

11. Fromageot C, Lofaso F, Annane D, Falaize L, Lejaille M, et al. (2001) Supine fall in lung volumes in the assessment of diaphragmatic weakness in neuromuscular disorders. Arch Phys Med Rehabil 82: 123-128.

12. Lechtzin N, Wiener CM, Shade DM, Clawson L, Diette GB (2002) Spirometry in the supine position improves the detection of diaphragmatic weakness in patients with amyotrophic lateral sclerosis. Chest 121: 436-442.

13. Varrato J, Siderowf A, Damiano P, Gregory S, Feinberg D, et al. (2001) Postural change of forced vital capacity predicts some respiratory symptoms in ALS. Neurology 57: 357-359.

14. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, et al. (2005) Interpretative strategies for lung function tests. Eur Respir J 26: 948-968.

15. Tzeng AC, Bach JR (2000) Prevention of pulmonary morbidity for patients with neuromuscular disease. Chest 118: 1390-1396.

16. Black LF, Hyatt RE (1969) Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis 99: 696-702.

17. Black LF, Hyatt RE (1971) Maximal static respiratory pressures in generalized neuromuscular disease. Am Rev Respir Dis 103: 641-650.

18. Morris JF, Koski A, Johnson LC (1971) Spirometric standards for healthy nonsmoking adults. Am Rev Respir Dis 103: 57-67.

19. National Health and Nutrition Examination Survey. 2009 - 2010 Data Documentation, Codebook, and Frequencies. Spirometry - 1st Test & 2nd Test Bronchodilator Studies.

20. Dixon WJ, Massey FJ Jr (1983) Introduction to statistical analysis, (4th Edn), McGraw-Hill,New York.

21. Schmidt EP, Drachman DB, Wiener CM, Clawson L, Kimball R, et al. (2006) Pulmonary predictors of survival in amyotrophic lateral sclerosis: use in clinical trial design. Muscle Nerve 33: 127-132.

22. De Troyer, Estenne M (1995) The respiratory system in neuromuscular disorders: The Thorax. Part C: Disease, Ed. Ch Roussos, (2nd Edn), Marcel Dekker, New York.

23. McCool FD, Mead J (1989) Dyspnea on immersion: mechanisms in patients with bilateral diaphragm paralysis. Am Rev Respir Dis 139: 275-276.

24. Schoenhofer B, Koehler D, Polkey MI (2004) Influence of immersion in water on muscle function and breathing pattern in patients with severe diaphragm weakness. Chest 125: 2069-2074.

25. Leal JC, Mateus SR, Beraldo PS (2005) Water immersion effects on severe diaphragm weakness. Chest 127: 2286-2287.

26. Rideau Y, Jankowski LW, Grellet J (1981) Respiratory function in the muscular dystrophies. Muscle Nerve 4: 155-164.

27. Inkley SR, Oldenburg FC, Vignos PJ Jr (1974) Pulmonary function in Duchenne muscular dystrophy related to stage of disease. Am J Med 56: 297-306.

28. [No authors listed] (1999) Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation--a consensus conference report. Chest 116: 521-534.

29. Dreher M, Rauter I, Storre JH, Geiseler J, Windisch W (2007) When should home mechanical ventilation be started in patients with different neuromuscular disorders? Respirology 12: 749-753.