Utility of supine spirometry to predict sleep disordered breathing in children with neuromuscular disorders

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Abstract

Aim To explore the relationship between postural changes in lung function and polysomnography (PSG) in the assessment of early sleep disordered breathing in children with neuromuscular disorders [NMD]. Methods In this prospective cross-sectional study, children with NMD performed spirometry in sitting (si) and supine (su) positions. A control group of age and gender matched healthy children also underwent postural lung function testing. PSG was performed within 6 months of spirometry. Spirometry was acceptable according to ATS standards and PSGs scored according to AASM guidelines. Results Forty-one children with NMD, aged 12.3 ±3 years (21 males) performed sitting spirometry. Thirty [73%] performed acceptable spirometry in the supine position. Underlying diagnoses were heterogeneous, with the majority having Duchenne Muscular Dystrophy (n=17). Mean FEV1sit and FVCsit were 78% (SD ±22) and 75% (SD±20.4) respectively, with mean% ΔFVC (sit – sup) 9±11% (range 2% to 20%), and was significantly greater than healthy controls (n=30 SD ±3) (p<0.001). PSG data on these 30 children showed total AHI 6.9 ±5.9/hr (0.3 to 29), obstructive AHI 5.2±4.0/hr (0.2 to 10), and REM AHI 14.1+/-5.3/hr (0.1 to 34.7). A moderate correlation was present between supine FVC% and AHI (r=0.62, p=0.001) in those not using non-invasive ventilation [NIV] in sleep [N=22] but not with the rise in CO2 from non-REM to REM sleep (6 ±1.9 mmHg, range 4 to 11). Conclusion Children with NMD and mild restrictive lung disease showed greater postural changes in spirometry than healthy controls, with changes being greatest in children who required nocturnal NIV.

Introduction

Neuromuscular disorders (NMD) are rare in the general population with an estimated prevalence of approximately 1 in 3000.(1) These conditions predominantly have a genetic basis and often present during childhood. Respiratory morbidity leading to respiratory failure is the common pattern seen in children and adults with neuromuscular weakness.(2) The degree of respiratory involvement in these disorders is variable and can present at differing ages in children.(2) This predominantly depends on the underlying NMD with other factors including lower respiratory illness, scoliosis and pulmonary aspiration having an effect on the age of presentation of respiratory failure.(2-4) Appropriate screening for respiratory failure and subsequent intervention has been shown to reduce unplanned hospital admissions and improve life expectancy.(2, 5-7)

Involvement of respiratory muscles causes significant clinical sequelae, with recurrent respiratory illness and consequently routine respiratory monitoring is recommended in children with NMD.(8) Detailed evaluation relies on additional testing, which includes both invasive tests and non-invasive tests. Amongst the invasive tests the most reliable is the measurement of the oesophageal (P_{oes}) and gastric pressures (P_{gas}). Amongst the non-invasive tests, vital capacity (VC), maximal inspiratory/expiratory pressures (MIP/MEP), sniff nasal inspiratory pressure (SNIP), the peak expiratory flow (PEF) and cough peak flow (CPF) have been studied extensively and are in clinical use in a number of centres.(9) These tests are limited by the need for patient cooperation to achieve the required technical quality standards.(8, 10) Patients with NMD are typically at risk for sleep disordered breathing (SDB) and hypoventilation. SDB is often the first signs

of progressive respiratory decline which can manifest as REM- associated hypoventilation and then into continuous nocturnal hypoventilation.(10)

Spirometry measured in the supine position has been studied in adult patients with NMD. (11, 12) In the seated position it is estimated that the diaphragm contributes to nearly 70% of tidal breathing and the intercostal muscles approximately 30%.(1, 13) However, in the supine position, the diaphragm contributes nearly 90% of breathing done by a normally functioning diaphragm when upright.(14, 15) Studies in adults with amyotrophic lateral sclerosis demonstrated that supine spirometry has a sensitivity of 79% and specificity of 90% to detect diaphragmatic weakness.(14, 15) Supine spirometry has been suggested as a screening test to detect diaphragmatic weakness in children with NMD based on a small number of studies that predominantly involve adults.(11, 16) This screening test has been included in paediatric management guidelines despite being based on data extrapolated from adult studies.(17, 18){, 2012 #449;Wang, 2012 #489} There is a paucity of data on supine spirometry in healthy children, let alone children with neuromuscular disease. The aims of our study were to (1) test the feasibility of supine spirometry in normal children and children with neuromuscular diseases and (2) to correlate the degree of respiratory dysfunction measured by supine spirometry in children with neuromuscular disease with polysomnography derived parameters of the effectiveness of gas exchange.(19-23)

Methods

This was a cross-sectional, prospective study approved by the Human Research Ethics Committee at the Children's Hospital at Westmead (LNR/12/SCHN/280). Patients diagnosed with neuromuscular disorders managed through the Neurogenetics clinic at the Children's Hospital at Westmead were invited to participate in the study. Controls were siblings or friends of neuromuscular patients or children of staff members who had no previous significant respiratory health issues. The inclusion criteria were a proven underlying neuromuscular disease [via genetics, muscle biopsy or nerve conduction studies], age 8 to 18 years, cognitive capacity to perform seated and supine spirometry and willingness to have an overnight polysomnogram [PSG]. Written informed consent was provided by the parent or primary caregiver and children gave their verbal consent to perform the test. The recruitment of patients and healthy controls ran for 24 months,

Data collection was performed during two visits. During the first visit, demographic data was recorded and pulmonary function testing was performed. At the second visit overnight polysomnography parameters were recorded. Demographic information was gathered on the following: (1) diagnosis (2) age at diagnosis, (3) height, (4) weight, (5) BMI, (6) gender, (7) use of wheelchair or walking aids and (8) other medical conditions (e.g. asthma). Testing was offered during their routine clinic visits, scheduled at six monthly intervals. Forced vital capacity (FVC) and Forced Expiratory Volume in one second (FEV_1) were measured with a Lilly type pneumograph (Viasys Healthcare, California) according to ATS/ERS standards.(24) Children were tested in a conventional upright seated position followed by a supine position while wearing a nose clip. As per ATS/ERS guidelines, the best effort, determined as the measurement with the highest sum of FVC and FEV_1, was recorded for the study. (23) Values were expressed as a percentage of predicted normal values (based on healthy children of the same age, gender, and height). Reference values were derived from published data.(24) As there are no published reference standards for supine FVC, percent predicted supine FVC was calculated using predicted values for upright FVC. Children who were unable to produce acceptable and repeatable spirometry in sitting positions according to standardized ATS/ERS criteria were excluded. Children with acceptable and repeatable sitting lung function were asked to perform spirometry in the supine position during the same clinic visit.

Overnight polysomnography was only performed in the children with NMD, and all were undertaken at the David Read Sleep Unit, in The Children's Hospital at Westmead, NSW, Australia, within 6 months of performing pulmonary function tests. Children established on non-invasive ventilation [NIV] previously had their most recent PSG parameters of the diagnostic component of sleep study accessed for this study. Polysomnography was performed in accordance with the 1997 American Thoracic Society (ATS) guidelines using the Sandman Elite® Version 9.2 system (Embla Systems, Broomfield, CO, USA). Data was collected according to standardized recommendations, commenced between 19:30 and 21:00, and ended at 06:00 the

following morning. Data analyses were performed in accordance with the 2007 American Academy of Sleep Medicine guidelines.(25) The modified Epworth Sleepiness Scale (mESS) questionnaire was completed by the child or the parent at the time of the polysomnography.

Respiratory events were scored if they were at least two respiratory cycles long, and significant oxygen desaturations were defined as [?] 3% desaturation from baseline. Children were classified as having sleep disordered breathing [SDB] if polysomnography results showed an apnoea-hypopnoea-index [AHI] >1.0 events/h.(26) The severity of SDB was further classified: mild SDB was defined as an AHI of 1.0 to 4.99 events/h, moderate SDB defined as 5 events/h to 9.99 events/h and severe SDB defined as an AHI > 10 events/h. Nocturnal hypoventilation was defined according to AASM as > 25 % of sleep time with a $TcCO_2$ >50 mmHg or a PCO_2 rise of >10mmHg from baseline (25, 27). (25, 28)

Pearson correlations and linear regression models were used to examine associations between the measures of respiratory function and polysomnography. Sensitivity and specificity results were calculated. Logistic regression was used to examine the ability of change in % FVC to predict a binary outcome of an AHI [?] 5 events/hr. All analyses were conducted in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). There was no adjustment made for multiple statistical comparisons. A p-value of <0.05 was considered statistically significant.

Results

Thirty of the forty-one (73%) patients approached were enrolled and able to perform spirometry in both sitting and supine positions. The mean age at testing was 11.5 years (SD +-3.0). Thirty controls without respiratory or sleep pathology were recruited Characteristics of the two study groups are shown in Table 2.

Specific neuromuscular diagnoses were heterogeneous, with the majority (17/30; 57%) having Duchenne Muscular Dystrophy [DMD] (Table 1). Children with NMD were further categorized as unsupported in sleep (i.e. spontaneously breathing: N=22) or established on nocturnal NIV [N=8].

Pulmonary function testing

An average of 15 minutes was taken to perform reliable supine spirometry after performing sitting spirometry. In the neuromuscular group, the mean sitting FEV_1% and sitting FVC% were 78% (SD +-21.9) and 75% (SD+-20.5) respectively as shown in Table 3. The percentage difference in ΔFVC between sitting and supine in these NMD children was 9%.

Children breathing spontaneously had an FEV_1% of 83% (SD±21.9) and an FVC% of 78% (SD±20.5) and a mean drop in FVC% in the supine position of 7% (SD±17.9). Children on nocturnal NIV had baseline sitting FEV_1% and FVC% values of 72%(SD±17.9) and 70%(SD±24.5), respectively, with a mean drop of 12% in the supine position to an FVC% of 58(SD±18.8). Healthy controls had a baseline sitting lung function of FEV_1 % and FVC% of 95% (SD±5.2) and 98% (SD±4.8), respectively, with a mean drop of 4% in ΔFVC in the supine position, (p<0.001 compared to children with NMD) (Table 3).

Amongst the 11 children who could not do spirometry, 3 children had cognitive delay and were unable to perform acceptable and reproducible spirometry in the sitting position. Another three children were excluded because they did not have acceptable or repeatable spirometry. Five children had severe restrictive lung disease (FVC<40%) and were able to perform sitting spirometry but were excluded because of poor spirometry technique in the supine position.

Polysomnography (PSG) in children with NMD

PSG data were available within 6 months of spirometry for the 30 children with NMD. Mean (±SD) total sleep time was 351±8.8 min. The total AHI was 6.9 ±5.9/hour, obstructive AHI was 5.2±4.2 /hour and REM AHI 14.1±5.3 /hour. Only 2 children [7%] had a normal total AHI [<1/hr].(25) The average baseline SpO_2 was 96 SD±5% and minimum saturation for the entire cohort was 88.4 SD±4.2%. The mean baseline transcutaneous [Tc] CO_2 was 44mmHg (SD±5). The rise in $TcCO_2$ from NREM to REM sleep in the entire cohort was 6 mmHg (SD±2.7) (Table 6).

Eight children with NMD were already established on non-invasive ventilation (NIV) when they were studied. Indications for NIV included recurrent chest infections requiring paediatric intensive care unit admissions (n=2) or evidence of sleep disordered breathing (n=6). The $TcCO_2$ rise from NREM to REM sleep of 5 vs 9 mmHg, for children breathing spontaneously compared to those on nocturnal NIV.

There was no significant correlation between postural changes in spirometry and the rise in $\mathbf{CO_2}$ from NREM to REM sleep on PSG for the group as a whole (r-=0.04, p=0.8), the group spontaneously breathing (r=0.02, p=0.9), or for those established on NIV (r=0.13,p=0.74). The healthy controls did not have polysomnograms.

Discussion

This study demonstrates the feasibility and utility of supine spirometry in children with NMD. To our knowledge this is the first study in children where heathy contemporary controls performed supine spirometry to generate comparative data. The majority of children with NMD (73%) who agreed to participate in this study were able to perform supine spirometry reliably. This study demonstrated a significantly greater decline in spirometry in the supine position in 30 children with NMD compared to 30 healthy controls (9% vs 4%, p=0.03). Supine spirometry also showed greater decline in children NMD who required nocturnal non-invasive ventilation compared to those breathing spontaneously (12% vs 7%, p=0.02). The implications of the postural drop in FVC in children with NMD therefore suggest that its' sensitivity to the level of respiratory muscle compromise occurring in the supine position relates to disease severity.

The falls in supine spirometry for this cohort were relatively mild compared to previous studies, and we speculate that this reflects generalised weakness of respiratory muscles rather than being a measure of early diaphragmatic weakness.(29) Lechtzin et al. showed that in a heterogeneous group of NMD disorders and using invasive measures of diaphragmatic function, a 25% drop in spirometry in the supine position was suggestive of diaphragmatic weakness(14). Certain NMDs, including congenital muscular dystrophy and their subtypes LAMA2-RD and COL6-RD, demonstrate progressive respiratory failure due to disproportionate diaphragmatic involvement.(29) None of the patients in the current cohort dropped their lung function [FVC] by >25% [Maximum change was 20%], as described in previous studies performed on adults with NMD to suggest significant diaphragmatic weakness.(15) From limited studies, performed predominantly in adult patients, an increasing difference between seated and supine spirometry is thought to indicate weakness in a combination of diaphragmatic and other inspiratory muscles, especially the intercostal muscles, resulting in inability to expand the chest wall against the abdominal contents in the supine position. Therefore, we believe the larger postural drop in spirometry demonstrated in the present study in NMD children established on nocturnal NIV suggests more severe generalised respiratory muscle weakness.

This is the first study in children to demonstrate a difference in the postural changes in FVC with NMD breathing spontaneously compared to those established on nocturnal NIV. Previously, Chen et al. compared the relationship of the postural changes in FVC and $FEF_{25-75}$and the need to initiate NIV in patients with neuromuscular disorders in an adult cohort with a heterogeneous group of underlying disorders with the largest subset having ALS.(33) There was a substantial difference in postural FVC between patients who were spontaneously breathing and those on nocturnal NIV. This led to the conclusion that a 14-fold difference in postural change in FVC% is more significant than just the reduction of supine FVC<75% as an indication to start nocturnal NIV. Our paediatric study demonstrated an approximately 2-fold difference in postural change in spirometry between those breathing spontaneously as compared to those on NIV. The findings by Chen et al. were greater than previous studies performed by Schmidt et al. who showed a change of 16% and Varrato et al. who demonstrated a drop of 13%.(30, 31) In the study by Varrato et al. on adults with ALS, patients who experienced breathlessness, orthopnoea and daytime lethargy had a postural drop of 25% as compared to those who did not demonstrate these symptoms. Their study did not compare ALS subjects with other adults established on NIV.

Polysomnography results confirmed that 93% of children in this cohort had SDB, which was predominantly obstructive in nature. The presence of obstructive sleep apnoea may be explained by an abnormal increase in upper airway resistance, muscle weakness, or a combination of the two. The high prevalence of obstructive

sleep apnoea is similar to other published literature which shows that between 30% and 60% of children with DMD had obstructive findings on polysomnography.(19, 20) Our cohort was a heterogeneous group of patients with NMD which may have contributed to the high prevalence of OSA. Other co-morbidities including obesity [related to chronic oral corticosteroid treatment and immobility] may also have played a role in the presence of sleep disordered breathing.

Considering sleep hypoventilation, while we considered the greater rise in the NIV group (9 compared to 6 mmHg) to reflect greater muscular weakness, we found no correlation between this measure and the postural changes in spirometry. REM hypoventilation may be due to loss of intercostal muscle activity in this sleep state.(32) However, it cannot be distinguished from effects of SDB due to upper-airway weakness and reduced pharyngeal tone in this sleep state, as previously reported in studies performed on children with DMD as well as congenital myopathies. (9, 32, 33) Our findings of a poor correlation of supine FVC% as a single measure with the severity of SDB are in agreement with another study performed by Khan et al., on 21 subjects with DMD aged 13 to 23 years.(33)

Limitations

Limitations to our study included involvement of only a single site where children were recruited from one neuromuscular clinic resulting in a small sample size even though all children with NMD who fulfilled inclusion criteria were approached to participate in the study. In addition, ccorrelations between spirometry and PSG parameters may have been apparent if PSG data had been obtained in the control group. Whilst historical cohorts looking at supine spirometry have included similar numbers of patients, we recognize that larger numbers of patients are needed. Children with severe restrictive lung disease (FVC<40%) who were already established on NIV were unable to perform reliable spirometry in both sitting and supine positions. Supine spirometry is therefore not useful in these children on the more severe end of the spectrum where it may be uncomfortable, impractical und unhelpful in predicting SDB. Lastly, the cross-sectional nature of the study did not allow examination of the relationship between supine spirometry and evolution of respiratory weakness over time.

Conclusion

In children with NMD, postural change in spirometry in this cohort of children with neuromuscular disorders was markedly greater than in healthy controls. These postural changes in spirometry were sensitive to the degree of nocturnal respiratory support the children required, but did not correlate with measures of sleep hypoventilation.

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