Patterns and predictors of sleep disordered breathing in primary myopathies

R Ragette, U Mellies, C Schwake, T Voit, H Teschler

Background: Sleep disordered breathing (SDB) is common in neuromuscular diseases but its relationship to respiratory function is poorly defined. A study was undertaken to identify distinct patterns of SDB, to clarify the relationships between SDB and lung and respiratory muscle function, and to identify daytime predictors for SDB at its onset, for SDB with continuous hypercapnic hypventilation, and for diurnal respiratory failure.

Methods: Upright and supine inspiratory vital capacity (IVC, % predicted), maximal inspiratory muscle pressure (PImax), respiratory drive (P0.1), respiratory muscle effort (P0.1/PImax), and arterial blood gas tensions were prospectively compared with polysomnography and capnometry (Picco2) in 42 patients with primary myopathies.

Results: IVC correlated with respiratory muscle function and gas exchange by day and night. SDB evolved in three distinct patterns from REM hypopnoeas, to REM hypopnoeas with REM hypventilation, to REM/non-REM (continuous) hypventilation, and preceded diurnal respiratory failure. SDB correlated with IVC and Pmax which yielded highly predictive thresholds for SDB onset (IVC <60%, Pmax <4.5 kPa), SDB with continuous hypventilation (IVC <40%, Pmax <4.0 kPa), and SDB with diurnal respiratory failure (IVC <25%, Pmax <3.5 kPa).

Conclusion: Progressive ventilatory restriction in neuromuscular diseases correlates with respiratory muscle weakness and results in progressive SDB which, by pattern and severity, can be predicted from daytime lung and respiratory muscle function.

Sleep disordered breathing (SDB) is common in patients with neuromuscular diseases and respiratory muscle weakness. The primary mechanism involves reduction of alveolar ventilation (as normally occurs during sleep due to a fall in central respiratory drive), blunted arousal thresholds, and reduced respiratory muscle activity. Disproportionate loss of upper airway muscle tone and diaphragm weakness may add additional loads, particularly during REM sleep, the time of maximal muscle hypotonia. Imbalance between respiratory load, drive and muscular capacity predisposes to SDB with desaturations, hypopnoeas, obstructive and central apnoeas, and hypercapnic hypventilation which occur preferentially in REM sleep.

SDB is rarely apparent from daytime clinical assessment, but may develop early in the course of disease and progress as ventilatory restriction worsens. Hypercapnic hypventilation is the most significant of the sleep induced breathing disorders, signalling a critical imbalance between ventilatory demand and capacity and a high risk of life threatening decompensations. Hypercapnic hypventilation is a reflection of nocturnal respiratory failure which precedes and probably contributes to the development of daytime respiratory failure. Timely recognition requires a high index of suspicion and evaluation with polysomnography and nocturnal capnometry. Non-invasive ventilation provides effective treatment and may improve survival.

Because polysomnography is time consuming, expensive and not universally available, daytime predictors of SDB have been sought; however, relationships between nocturnal respiratory variables and daytime lung function have been highly variable. Although forced expiratory volume in 1 second (FEV1) <40% was recently reported as a predictor of nocturnal hypventilation, hypventilation was defined as desaturations under 90% during more than 2% of total sleep time and is likely to have included transient episodes of limited relevance.

We have conducted a detailed study of daytime lung and respiratory muscle function and nocturnal respiration in a large group of patients with primary myopathies to test the hypothesis that SDB evolved in distinct patterns that were directly related to lung and respiratory muscle function. We were particularly interested to identify predictive thresholds for (1) SDB at its onset, (2) SDB involving hypercapnic hypventilation during more than 50% of total sleep time, a degree of hypventilation likely to require non-invasive ventilation, and (3) daytime respiratory failure.

METHODS

Subjects

Forty two patients (17 women) of mean (SD) age 28.7 (15.8) years (range 14–63) and body mass index (BMI) 18.7 (5.4) kg/m2 with primary myopathies were studied: 10 Duchenne muscular dystrophy, 10 congenital muscular dystrophy, seven limb girdle dystrophy, 12 acid maltase deficiency, one nemaline myopathy, one myotonic dystrophy, and one non-classified myopathy. A neurologist had assessed all patients and the diagnosis had been confirmed by histology and, where possible, by cell molecular biology. Twenty three patients were ambulatory, 19 were wheelchair bound. Thirteen patients (10 Duchenne muscular dystrophy, three congenital muscular dystrophy) had severe kyphoscoliosis, seven had bad stabilisation surgery. No patient was using ventilatory support.

Lung function

Inspiratory vital capacity (IVC), forced expiratory volumes (FVC, FEV1), and flow-volume loops were measured with a

Abbreviations: IVC, inspiratory vital capacity; Pmax, maximal inspiratory muscle pressure; P0.1, Pmax, measure of respiratory muscle effort; Paco2, arterial carbon dioxide tension; PaO2, arterial oxygen tension; Picco2, mean transcutaneous carbon dioxide tension; SaO2, mean nocturnal oxyhaemoglobin saturation.
was derived as \( \frac{P_{0.1}}{P_{\text{Imax}}} \).

Automated blood gas analyser (AVL 500, AVL LIST GmbH) was used for comparative analysis with nocturnal respiratory variables. Arterial blood gas tensions were determined. Predicted values for adolescents were derived from the data of Zapletal et al. Diaphragm weakness was defined as >20% postural fall in diaphragm function and is less affected by isolated expiratory muscle weaknesses. IVC\% was used synonymously with IVC\% for ventilatory capacity as it more directly reflects diaphragm function and is less affected by isolated expiratory muscle weaknesses. IVC\% was used synonymously with IVC\% predicted. Predicted values for adolescents were derived from the data of Zapletal et al\(^{16}\) and for adults from the data of the European Community of Steel and Coal.\(^{17}\) Supine measurements were used for comparative analysis with nocturnal respiratory variables. Arterial blood gas tensions were determined from radial artery or arterialised ear lobe blood in an automated blood gas analyser (AVL 500, AVL LIST GmbH Medizintechnik, Graz, Austria).

Maximal inspiratory muscle pressure (P\(_{\text{Imax}}\), best of three efforts) and mouth occlusion pressure at 0.1 s of tidal breathing (\( P_{0.1} \), mean of 8–10 consistent measurements) were determined using a computerised manometer allowing for online graphic display and quality control of pressure curves (ZAN Meßgeräte, Oberthulba, Germany). Respiratory muscle effort was derived as \( \frac{P_{0.1}}{P_{\text{Imax}}} \).\(^{14}\)

Diaphragm weakness was defined as >20% postural fall in IVC combined with development of either dyspnoea, thoracoabdominal paradox, or accessory muscle activity.\(^{15}\)

**Polysomnography (PSG)**

PSG was performed according to the standards of the American Academy of Sleep Medicine.\(^{18}\) No oxygen was supplemented. Electroencephalogram, electrooculogram, submental electromyogram and microphone, single lead electrocardiogram, oronasal flow and respiratory movement sensors (thermistor and piezoelectrical crystal; ProTech, Woodville, WA), oxyhaemoglobin saturation (INVIVO Pulse Oximeter 4500, INVIVO Research Inc, Orlando, FL USA), and transcutaneous \( \text{PCO}_2 \) (Ptco\(_2\)) (Radiometer, Copenhagen, Denmark) were recorded onto a computerised work station (Compumedics, Melbourne, Australia). Sleep stages and respiratory parameters were scored manually. Apnoeas were defined as >10 s cessation of airflow and respiratory effort (central) or >10 s cessation of airflow with persisting effort (obstructive). Hypopnoeas were defined as >10 s discernible reduction in airflow or thoracoabdominal effort accompanied by >3% oxyhaemoglobin desaturation or EEG arousal of >3 s. SDB was considered present if the respiratory disturbance index (RDI) was >5 events per hour of total sleep or 10 per hour of REM sleep. Hypoventilation was defined as \( \text{Ptco}_2 >6.67 \text{kPa} (50 \text{mm Hg}) \) for >50% of REM sleep alone (REM hypoventilation) or during both REM and >50% of non-REM sleep (continuous hypoventilation). Diurnal respiratory failure (DRF) was defined as daytime hypercapnia on arterial blood gas testing (\( \text{Paco}_2 \geq 6.0 \text{kPa} (45 \text{mm Hg}) \)) obtained before PSG, and nocturnal alveolar hypoventilation.

**Statistical analysis**

Analysis was performed with Statistica 6.0 software package (StatSoft Inc, Tulsa, OK, USA). Interrelationships between vital capacity, respiratory muscle function, polysomnographic parameters, and gas exchange were analysed using the Spearman’s rank test. Group comparisons were performed using the Mann-Whitney U test. Multiple linear regression analysis was performed with SDB as the dependent variable and IVC, \( P_{\text{Imax}}, \) age, and BMI as the independent variables. Predictive values of IVC and \( P_{\text{Imax}} \) were computed by applying bidimensional analysis at equal sensitivity to specificity ratio to the respective receiver operator curves (ROC). The dependent variable with the maximal area under the curve (AUC) was considered to be the strongest predictor. All results are presented as mean (SD) values, p values of <0.05 were considered statistically significant.

**RESULTS**

**Lung and respiratory muscle function**

Upright IVC was normal in nine patients, 60–79% in five, 40–59% in seven, 20–39% in 14, and <20% in seven patients. Daytime hypercapnia was present in 12 patients (\( \text{Paco}_2 \geq 6.0 \text{kPa} (45 \text{mm Hg}) \)). Diaphragm...
weakness was found in 11 patients (26%) and occurred at any
degree of ventilatory restriction. It resulted in a supine fall in
IVC of 32.6 (10.8)% and a supine fall in P\textsubscript{Imax} of 18.2 (13.8)%. IVC correlated with P\textsubscript{Imax} (R=0.67, p<0.0001), P\textsubscript{tcCO2}/P\textsubscript{Imax} (R=–0.68, p<0.0001), and P\textsubscript{co2} (R=–0.50, p=0.001; fig 1). The relationship was
curvilinear with both P\textsubscript{co2} and P\textsubscript{tcCO2}/P\textsubscript{Imax}, however, did not interrelate (R=0.51, p<0.001).

**Sleep disordered breathing**

SDB was found in 33 patients. Obstructive apnoeas were
found in only six patients, two with Duchenne muscular dyn-
strphy, two with limb girdle dystrophy, and two with acid
maltase deficiency. The predominant finding in all subjects
were hypopnoeas which lacked terminating snorts and lost
maltase deficiency. The predominant finding in all subjects

### DISCUSSION
This study of daytime and nocturnal respiratory function in
primary myopathies has shown close relationships between
lung function, respiratory muscle function, and SDB, and has
identified highly predictive thresholds for SDB onset, SDB
with hypercapnic hyperventilation, and daytime respiratory
failure which, because it is invariably associated with noctur-
nal hyperventilation, was classified as diurnal respiratory fail-
ure. We confirmed that vital capacity related directly to respira-
tory muscle strength, a finding previously reported in
polymyositis and Duchenne muscular dystrophy but not
noted in other studies of neuromuscular diseases. We have
expanded the existing data by showing for the first time that
P\textsubscript{tcCO2} and P\textsubscript{co2}/P\textsubscript{Imax} increased progressively with declining
respiratory muscle strength, a finding likely to reflect the

**Predictors of SDB**

Predictive thresholds of IVC (fig 4) and P\textsubscript{Imax} were computed for
SDB onset, SDB with continuous hyperventilation, and
diurnal respiratory failure. Sensitivities, specificities and AUC
values are summarised in table 1.
compensatory rise in respiratory drive and muscle effort in an attempt to maintain alveolar ventilation. The close relationship between vital capacity and respiratory muscle function underlines the role of respiratory muscle weakness in the development of restrictive ventilatory defect and implies that intrinsic lung disease was absent. Indeed, our patients had no evidence of parenchymal lung disease and gas exchange was maintained in the near normal range until IVC fell to <25%.

Acute on chronic respiratory failure was the presenting feature in three patients with IVC <25% and accounts for the disproportionate degree of hypoxaemia and hypercapnia seen in this setting.

Assuming that the same pathophysiology was present during sleep, we hypothesised that SDB would primarily depend on respiratory muscle function and ventilatory restriction. Sleep, because of its detrimental effects on respiratory muscle activity, drive and load, represents a significant stress test to the respiratory system, particularly in the setting of decreased respiratory muscle capacity. The severity of SDB is therefore likely to provide a good index of functional respiratory muscle reserve. Indeed, we found a significant correlation between vital capacity, respiratory muscle function, and SDB severity graded empirically by hypopnoea pattern and degree of hypercapnia. As expected, SDB occurred predominantly in REM sleep, a period of relative muscle hypotonia or atonia. SDB differed from the central or obstructive sleep apnoea/hypopnoea syndromes previously reported and the RDI did not correlate with IVC. Hypopnoeas predominated in early restrictive disease but, as restriction worsened, changed into poorly circumscribed and ever more prolonged hypoventilatory phases that did not enter the hypopnoea score. RDI was therefore increased in the early phase but was normal in advanced restrictive disease. 

Table 1  Predictors of sleep disordered breathing (SDB) and diurnal respiratory failure

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC (%)</th>
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<tbody>
<tr>
<td>IVC (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60: SDB onset</td>
<td>91</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td>&lt;40: continuous HV</td>
<td>94</td>
<td>79</td>
<td>98</td>
</tr>
<tr>
<td>&lt;25: dRF</td>
<td>92</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td>PImax (kPa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4.5: SDB onset</td>
<td>82</td>
<td>89</td>
<td>85</td>
</tr>
<tr>
<td>&lt;4.0: continuous HV</td>
<td>95</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>&lt;3.5: dRF</td>
<td>92</td>
<td>55</td>
<td>81</td>
</tr>
</tbody>
</table>

IVC=inspiratory vital capacity; PImax=maximal inspiratory pressure; HV=hypercapnic hypoventilation; dRF=diurnal respiratory failure; AUC=area under the curve.
We wanted to identify predictive thresholds for SDB at its onset, for SDB with continuous hypercapnic hypoventilation, and for diurnal respiratory failure as they represent turning points in the course of a patient with progressive myopathic disease. The predictors have important implications for the practical management of these patients whose respiratory limitations may escape attention because of desynchronous involvement of peripheral and respiratory muscle groups, minimal dyspnoea because of adaptation and a sedentary lifestyle, and normal blood gases until very late in the course of the disease. With severe muscle weakness life threatening complications may be triggered by minor increases in respiratory demands, such as occur with fever, respiratory infection, or surgical interventions. It is paramount to identify the patients at risk. Sitting/supine bedside spirometric testing at 6–12 month intervals provides a low cost, reproducible, and easy to perform test that allows stratification of patients into distinct risk groups. Those with IVC >60% are unlikely to have SDB, indicating good respiratory reserve and minimal risk of respiratory complications. Those with IVC <60% are predisposed to SDB, indicating reduced respiratory reserve and the need for polysomnography for assessment. At IVC <40% continuous hypercapnic hypoventilation becomes the major concern and capnometry is warranted for proper evaluation. As continuous hypercapnic hypoventilation indicates barely compensated respiratory failure and a high risk of acute respiratory deterioration, non-invasive ventilation might be considered at this point.28

ACKNOWLEDGEMENTS
C Schwake was supported by an interdisciplinary research grant from the University of Essen, grant # 107505-0/IFORES.

Authors’ affiliations
R Ragette, U Mellies, C Schwake, H Teschler, Ruhrlandklinik, Department of Pneumology and Sleep Medicine, Essen, Germany
T Voit, University of Essen, Department of Neurupediatrics, Essen, Germany

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Thorax 2002 57: 724-728
doi: 10.1136/thorax.57.8.724

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