Ventilation and Breathing Pattern during Sleep in Duchenne Muscular Dystrophy*

P.E.M. Smith, M.D., M.R.C.P.; R.H.T. Edwards, Ph.D., F.R.C.P.; Peter M.A. Calverley, M.B., M.R.C.P.

Ventilatory data, including timing and partitioning of ventilation, were obtained from six subjects with advanced Duchenne muscular dystrophy, aged 16 to 22 years, during polysomnography on two consecutive nights; the subjects were randomized to breathing air or oxygen. Five of the six patients developed oxygen desaturation exceeding 5 percent during rapid eye movement (REM) sleep while breathing air. Minute ventilation on air (the mean of at least six consecutive minutes) was 6.9±0.7 (SEM) L min⁻¹ but fell, owing to decreases in both tidal volume and frequency, to 4.9±0.3 L min⁻¹ (p<0.05) in slow wave sleep and to 4.5±0.6 L min⁻¹ (p<0.05) in REM sleep. Similar falls were seen on oxygen. The variability of all ventilatory data was significantly greater in REM than non-REM (NREM) sleep. The mean abdominal contribution to breathing was lower than predicted for wakefulness and all sleep stages, and two subjects showed paradoxical abdominal movement in NREM sleep; a correlation (p<0.05) existed between the NREM abdominal (diaphragmatic) contribution and the extent of oxygen desaturation subsequently seen in REM. We conclude that although awake minute ventilation is normal in Duchenne muscular dystrophy, hypventilation occurs in all sleep stages, and those with diaphragmatic dysfunction are especially vulnerable to oxygen desaturation during REM sleep.

We have shown previously that recurrent episodes of central hypopnea and/or apnea with accompanying hypoxemia are common in subjects with advanced Duchenne muscular dystrophy (MD) during rapid eye movement (REM) sleep.¹ There are, however, few reports quantifying the breathing pattern during wakefulness and sleep in patients with respiratory muscle weakness; such data can be obtained noninvasively using respiratory inductance plethysmography (RIP)²⁻⁴ that should help to characterize further the disordered breathing in sleep seen in subjects with Duchenne MD. In addition, the analysis of rib cage and abdominal contributions to breathing during wakefulness and sleep may shed light on the role of diaphragm dysfunction in the mechanism of REM-related oxygen desaturation in Duchenne MD. Accurate and stable quantification of RIP data requires the subject to maintain a single posture and the equipment to be recalibrated following body movement.⁵⁻⁷ During sleep, therefore, reliable quantification is possible only for stationary or paralyzed subjects. Patients with advanced Duchenne MD are capable of only minimal body movement and require assistance to change their sleeping posture; they are thus ideally suited to RIP data analysis. We present ventilatory data obtained during overnight polysomnography from six acclimatized subjects with Duchenne MD randomized to air or oxygen on two consecutive nights.

**Patients and Methods**

Six patients aged 16 to 22 years (mean, 19.2 years) were studied. The diagnosis of Duchenne MD was based on clinical, electrophysiological, and muscle biopsy criteria. None had reported abnormal daytime sleep symptoms and all were free from respiratory tract infection; any scoliosis was either minimal or controlled by segmental spinal surgery. Approval for the studies on air and oxygen had been obtained from the local hospital ethical committee. Pulmonary function measurements made included sitting and lying vital capacity (water spirometer), lung volume estimation (helium dilution technique), maximum inspiratory (MIP) and expiratory (MEF) static mouth pressures (method of Black and Hyatt), and daytime blood gas tensions.

The subjects slept for three nights in the laboratory, the first serving to acclimatize them to the equipment and during which no measurements were made. On the following two nights the subjects were randomized either to room air or nasal oxygen (2 L min⁻¹). Standard overnight polysomnography methods were followed as detailed previously.¹ The variables monitored continuously were electroencephalogram (C4/A2), electro-oculograms (E1/A2, E2/A2), submental electromyogram, electrocardiogram, oxygen saturation (Ohmeda Biox III), oronasal airflow detected by thermistor, and chest and abdominal movement with a combined "sum" signal using RIP (Respirtrace).

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Table 1—Mean ± SD Minute Volume (Ve), Frequency (f), Tidal Volume (VT), Mean Inspiratory Flow (Vr/Ti), Respiratory Duty Cycle Time (TV/Ttot), and Abdominal Contribution (AC) to Breathing During Wakefulness, Stage 2 NREM (S2 NREM), Stage 3-4 NREM (S3/4 NREM), and REM Sleep on Air and Oxygen (Bold Type) in the Six Subjects with Duchenne MD*

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>S2 NREM</th>
<th>S3-4 NREM</th>
<th>REM</th>
</tr>
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<tbody>
<tr>
<td>Ve (L min⁻¹)</td>
<td>6.9±1.8</td>
<td>5.1±0.6</td>
<td>4.9±0.8†</td>
<td>4.5±1.5†</td>
</tr>
<tr>
<td>f (min⁻¹)</td>
<td>6.4±0.9</td>
<td>5.1±0.7</td>
<td>4.7±0.8**</td>
<td>4.3±0.7**</td>
</tr>
<tr>
<td>VT (L)</td>
<td>16.0±3.0</td>
<td>13.5±1.34</td>
<td>13.4±0.9</td>
<td>12.6±3.6</td>
</tr>
<tr>
<td>VT/T (L min⁻¹)</td>
<td>17.5±4.1</td>
<td>14.9±0.9</td>
<td>14.5±1.0</td>
<td>13.0±4.4</td>
</tr>
<tr>
<td>TV/Ttot</td>
<td>0.4±0.1</td>
<td>0.4±0.1</td>
<td>0.3±0.1</td>
<td>0.4±0.1</td>
</tr>
<tr>
<td>AC</td>
<td>0.4±0.4</td>
<td>0.4±0.4</td>
<td>0.35±0.04</td>
<td>0.35±0.1</td>
</tr>
</tbody>
</table>

*Significant differences compared with wakefulness (†), stage 2 NREM (#),and stage 3/4 NREM (+) are denoted as follows: single symbol = p <0.05, 2 symbols = p <0.01.

RIP Calibration

"Respiration" were taped securely to the chest (nipple level) and abdomen (umbilical level and below the costal margins). Immediately before "lights out" and with the patient in his preferred sleeping posture and prepared to sleep, volume-motion (VM) coefficients were obtained using computerized multiple linear regression (MLR) analysis as described by Stradling et al. Briefly, RIP outputs from rib cage (RC) and abdomen (AB) together with the integrated spirometer signal (SP) from a pneumotachograph (Godard et al) previously stabilized to eliminate drift and calibrated against a liter syringe were sampled within 20 ms of each other 150 times during a 20-second fixed period of quiet tidal breathing and were analyzed by MLR using a BBC "B" microcomputer programmed in Basic. The 150 raw data values for RC, AB, and SP were used in each calculation to estimate the VM coefficients (a and b), using the equation described by Armitage, "a + (b × AB) + e = SP" representing errors arising from (1) the different voltages of the three variables, and (2) the offset attributable to the intercept of the plot of RIP volume: spirometer volume). The calibration procedure was repeated at least twice to ensure consistent results. Where poor calibrations occurred (95 percent confidence intervals exceeding 20 percent), these were usually due to insufficient chest wall or abdominal movement and could be improved by repositioning the abdominal belt and/or having patients deliberately hyperventilate during the calibration period. Application of the VM coefficients (each the mean of three acceptable calibrations) allowed the derivation and minute-by-minute update of ventilation frequency (f), tidal volume (VT), mean inspiratory flow (Vr/Ti), fractional inspiratory time (TV/Ttot), and abdominal contribution (AC) to ventilation. Calibration was repeated during the study following any change in the patients' sleeping posture. Ventilatory data during wakefulness were obtained following a period of sleep. Where possible, data from each sleep stage and from wakefulness were obtained from each patient without a change in sleeping position; if the posture were changed (ie, the patient woke and requested to be turned), the instrument was recalibrated before data collection was resumed.

Data Analysis

Data from six to ten representative consecutive minutes of wakefulness, steady stage 2 non-REM (NREM) sleep (S2), stage 3/4 NREM (S3/4), and REM sleep were obtained for both air and oxygen nights and a mean ± SEM derived. The "minute to minute" within-subject coefficient of variation for each sleep stage was also derived from these data. Comparisons between means were made using the Student t test.

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21604/ on 04/18/2017)
Maximum SaO\textsubscript{2} Fall (%)

\[ r = -0.86 \]

**NREM Abdominal Contribution (%)**

*Figure 2.* The relationship between the mean abdominal contribution to breathing (expressed as a percentage) during stage 3/4 NREM sleep and the subsequent maximum fall in oxygen saturation (SaO\textsubscript{2}) during REM sleep. The linear relationship \((y = -0.45x + 22.8)\) shows a significant \((p<0.05)\) correlation.

**RESULTS**

**Daytime Pulmonary Function**

The mean seated vital capacity of the six subjects was 1.48 L (range, 0.8 to 3.0 L) with a mean fall of 6.7 (−3.3 to 20 percent) when supine. The mean total lung capacity was 3.56 L (2.5 to 6.3 L). Residual volume ranged from 1.2 to 3.8 L (mean, 2.18 L) and functional residual capacity from 1.5 to 4.3 L (mean, 2.5 L). Maximum static mouth pressures were low in all subjects, the mean MEP being 37.5 (25 to 65 cm H\textsubscript{2}O) and MEP being 29.2 (15 to 50 cm H\textsubscript{2}O). Daytime blood gas tensions, however, were within normal limits (mean Po\textsubscript{2}, 14.5 kPa [13.2 to 17.9 kPa]; PCO\textsubscript{2}, 5.23 kPa [4.7 to 6.05 kPa]).

**Oxygen Saturation**

The mean saturation in NREM sleep was 95.3 (93.5 to 96.5 percent). The mean frequency of desaturations exceeding 5 percent was 1.92 h\textsuperscript{−1} (0 to 4.2 h\textsuperscript{−1}) of total sleep, the saturation falling to a mean nadir of 80.1 (58 to 93 percent).

**Table 2—Mean (and Range) Values for Coefficient of Variation of the Measurements During Wakefulness, Stage 2 NREM, Stage 3-4 NREM, and REM Sleep in the Six Subjects with Duchenne MD Breathing Air**

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>S2 NREM</th>
<th>S3/4 NREM</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \bar{V}E )</td>
<td>7.7 (1.3-13.1)</td>
<td>4.0 (1.8-7.1)</td>
<td>6.8 (1.3-18.0)</td>
<td>28.8 (12.4-60.3)*###++</td>
</tr>
<tr>
<td>( f )</td>
<td>7.6 (2.6-15.3)</td>
<td>4.6 (2.7-7.5)</td>
<td>2.5 (1.2-4.0)†</td>
<td>16.0 (6.8-20.1)**###++</td>
</tr>
<tr>
<td>( VT )</td>
<td>12.2 (2.8-37.7)</td>
<td>5.5 (2.4-10.0)</td>
<td>4.3 (1.5-7.8)</td>
<td>26.7 (8.0-55.7)+</td>
</tr>
<tr>
<td>( VT/Ti )</td>
<td>11.0 (6.1-28.3)</td>
<td>6.9 (4.0-9.4)</td>
<td>5.8 (1.2-10.0)</td>
<td>35.8 (7.6-65.8)**###++</td>
</tr>
<tr>
<td>( VT/Tot )</td>
<td>6.9 (4.4-8.2)</td>
<td>3.9 (2.5-7.8)</td>
<td>2.8 (1.2-5.7)</td>
<td>23.1 (7.2-50.3)**++</td>
</tr>
<tr>
<td>( AC )</td>
<td>16.6 (6.5-39.9)</td>
<td>14.6 (8.8-27.2)</td>
<td>5.0 (2.9-6.3)†###</td>
<td>24.2 (7.5-61.6)+</td>
</tr>
</tbody>
</table>

*Significant differences compared with wakefulness (†), stage 2 NREM (#), and S3/4 NREM (+) are denoted as follows: single symbol = p<0.05, 2 symbols = p<0.01, 3 symbols = p<0.001.

**Breathing Pattern**

In a previous report\textsuperscript{11} that included data from four of these subjects, sleeping oxygen saturation was shown to improve markedly with oxygen treatment despite a significant overall prolongation of underlying hypopnea/apnea (HA) events by 19 percent. In the present study, no subject desaturated while breathing oxygen, but the mean proportion of REM sleep occupied by HA rose from 31.3 percent (5 to 49 percent) breathing air to 38.2 percent (9 to 54 percent) breathing oxygen. Mean values of \( \bar{V}E, f, VT, VT/Ti, Ti/Tot, \) and AC for the group are given in Table 1. Data from S3/4 usually preceded that from REM sleep, and data from all sleep stages were obtained without a change in patient position. A representative six- to ten-minute consecutive period of stable NREM sleep was available for analysis in all subjects, but the period of REM sleep analyzed was interrupted by NREM sleep in two subjects. Where brief periods of arousal (<20 s) occurred following desaturations in REM sleep, this was still taken to represent a continuous period of REM sleep.

The \( \bar{V}E \) was significantly lower in both S3/4 and REM sleep compared with wakefulness on both air and oxygen owing to falls in both VT and f. The VT/Ti was also reduced from awake values in both S3/4 and REM sleep, but this difference was significant only with oxygen. Abdominal paradoxical movement, present intermittently when awake and persisting into NREM sleep, was observed in one subject, and another had abdominal paradox develop only in NREM sleep (Fig 1). The mean values of abdominal (diaphragmatic) contribution during S3/4 NREM sleep while breathing air ranged between 35 percent and −27 percent (Table 1); a relationship (\( p<0.05 \)) existed between these NREM abdominal contributions and the extent of oxygen desaturation that subsequently occurred in REM sleep (Fig 2).

**Variability of Data**

The within-subject coefficient of variation values were similar on air and oxygen and only those from air are given in Table 2. A marked increase in

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variability of all respiratory measurements occurred in changing NREM to REM sleep, but especially in the frequency of ventilation, and all save VT and AC were more variable in REM than wakefulness.

Comparison to Normal Values

A comparison with normal data, derived using similar MLR calibration of RIP in six restrained young healthy adult males, is presented in Figure 3. This illustrates the mean values of each variable during wakefulness, slow wave (S3/4) sleep, and REM sleep in the six subjects with Duchenne MD studied on air compared to these published normal data. Significant differences between the present data and those of Stradling et al. were noted for VE in NREM sleep (p<0.05) and abdominal contribution during wakefulness (p<0.01), slow wave sleep (p<0.01), and REM sleep (p<0.05). Mean VT/Tf fell by 17.8 percent (air) and 20.9 percent (oxygen) from awake to NREM sleep, but by only 2.9 percent in the published normal results; the further fall from NREM to REM sleep was similar to normal.

Discussion

The immobility of subjects with advanced Duchenne MD allowed a noninvasive analysis of calibrated ventilatory data from six such subjects during wakefulness and sleep. Minute ventilation when awake was similar to that reported in normal subjects but fell in NREM and further in REM sleep to values well below normal. In two subjects, persistent paradoxical abdominal movement was observed in NREM sleep; overall, the abdominal (diaphragmatic) contribution to breathing in NREM sleep was lower than in normal subjects and correlated with the extent of subsequent oxygen desaturation in REM sleep.

We have previously shown that patients with advanced Duchenne MD and only minimal scoliosis usually have no abnormal daytime sleep symptoms and often maintain near normal daytime blood gas tensions despite a severe thoracic restrictive deficit. Although the breathing pattern and oxygen saturation during NREM sleep may appear normal, REM sleep is often accompanied by repeated central hypopneas and/or apneas, with associated significant oxygen desaturation. In a further report that included data from four of these six subjects, we showed that mean hypopnea and apnea duration (usually REM related) was prolonged by oxygen treatment. In the present study, however, mean VE in REM sleep was similar on air and oxygen. Representative mean data obtained over six to ten minutes of each sleep stage give an overall picture of VE rather than an analysis of individual disordered breathing events; minor differences between air and oxygen nights may have been obscured. Nevertheless, it is reassuring that oxygen desaturation can be greatly improved or abolished without an apparent adverse effect on overall ventilation.

Multiple linear regression has been shown to give more accurate VM coefficients (in equivalence to the spirometer) than the isovolume method, and it requires only data obtainable during quiet normal breathing and so is ideally suited to naive subjects. Instability of RIP calibration through "respirand" slippage was minimized by tightly securing the bands to the patient before the study. The awake breathing pattern is influenced by environmental factors, including the polysomnography apparatus and emotional stress. These effects were lessened in our study,
however, by studying patients already acclimatized to the surroundings and by taking a period of wakefulness following sleep as "representative wakefulness" for analysis. Randomizing to air and oxygen on consecutive nights ensured that acclimatization was similar in both parts of the study.

No particular sleeping posture was imposed on the subjects as most were habituated to sleeping for long periods in one chosen position. No allowance was made, therefore, for possible variation in diaphragmatic contribution to breathing or altered tendency to hypoventilate in different postures. Changes in sleep state and, by implication, of respiratory muscle recruitment, may also have influenced these data, but the magnitude of this influence could not be assessed as calibration was possible only in awake subjects. Such problems are shared by all studies in respiratory noninvasive breathing pattern measurements during sleep.

Sampling problems are inevitable when selecting representative data from each sleep stage, particularly from periods of wakefulness and REM sleep. The heterogeneous nature of stage REM, comprising tonic and phasic components and often, in these subjects, brief arousal periods associated with oxygen desaturation, further limits interpretation of its ventilatory data. The heterogeneity is reflected in the measured coefficient of variation of all our measurements and is also seen in normal subjects.6

There have been several attempts to quantify ventilation and its components in normal subjects noninvasively during wakefulness3 and sleep.4,6,14 The RIP data of Stradling et al15 were obtained by MLR from restrained sleeping adult healthy males and so offer an appropriate comparison to the present results. Patients with Duchenne MD have severe generalized respiratory weakness usually without selective diaphragm involvement and, in our subjects, without obesity or significant scoliosis. There have been few reports of quantified ventilatory analysis during sleep in patients with neuromuscular disease and we know of no other such data in Duchenne MD, with or without daytime somnolence or CO2 retention. Patients with selective diaphragm weakness typically show a rapid shallow breathing pattern when awake,15 the frequency of ventilation falling toward normal in sleep.16 A similar awake breathing pattern is observed in interstitial lung disease but the severity of their sleeping ventilatory impairment depends clearly on the inclusion17 or exclusion18 of snorers from the study group, emphasizing the likely importance of upper airway resistance changes to ventilatory morbidity in sleep in these subjects.

Extrathoracic resistance changes normally seen in sleep19 may account for important differences in sleeping ventilation in neuromuscular disease compared with normal, but such data are not available. Airway resistance changes in sleep may have a proportionately greater influence on inspiratory timing (eg, Ti) and VE when the inspiratory musculature is weak, especially when REM sleep further exposes the respiratory muscle dysfunction.40 The large fall in VR/Ti during sleep in these subjects compared with normal subjects, which might normally reflect a fall in central ventilatory drive, may also be attributed to increased inspiratory loading in sleep.

Surface abdominal and rib cage motion reflect diaphragmatic and intercostal contributions to breathing,21 but the relationship of these indexes to diaphragm and intercostal function is more complex. In neuromuscular diseases, the mechanical coupling between muscle activation and rib cage motion may be further distorted. Although the abdominal contribution gives only an indirect index of diaphragm function, more direct measurements such as transdiaphragmatic pressure were avoided in this study to minimize instrumentation of these subjects. Despite these limitations, however, the mean abdominal contributions of our subjects in wakefulness and sleep were well below normal and their relationship in these patients to oxygen desaturation in REM sleep underlines the importance of diaphragm dysfunction in their vulnerability to sleep desaturation. The similarity between the fall in bilateral diaphragm paralysis in dogs lends further support to this view.22

In summary we have found that patients with global muscle weakness due to Duchenne MD can maintain a normal VE when awake, but when confronted with the additional mechanical and neurophysiologic adaptations of sleep, they cannot defend their VE as well as normal subjects. Diaphragm dysfunction reflected by abdominal paradox developed in several patients and the extent of the abnormal diaphragm function in NREM sleep appears predictive of the development of oxygen desaturation during REM periods. Whether this reflects an abnormal increase in upper airway resistance, diaphragmatic weakness, or a combination of the two is unclear. However, the presence of a normal VE when awake does not preclude significant nocturnal hypoventilation in these patients. Oxygen treatment may prolong individual episodes of hypopnea but its effect on overall ventilation and breathing pattern were not significant and should prove a safe way of alleviating episodic nocturnal hypoventilation.

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