Domiciliary investigation of sleep-related hypoxaemia in Duchenne muscular dystrophy


ABSTRACT: In Duchenne muscular dystrophy (DMD) nocturnal oxygen desaturation occurs during rapid eye movement (REM) sleep. Polysomnography, which requires hospital admission, will detect sleep-related breathing abnormalities. In order to avoid the inconvenience of hospital admission for the disabled patient, we investigated overnight oxygenation in ten boys with DMD by domiciliary oximetry. In four boys the results of oximetry were compared with those of a polysomnographic recording. The "repeatability" of domiciliary oximetry was assessed in six boys by performing oximetry on two non-consecutive nights.

Older boys with DMD may develop a cardiomyopathy. In order to assess cardiac rhythm and ST segment changes we performed simultaneous Holter monitoring and oximetry in seven boys with overnight hypoxaemia.

Six of the initial ten boys studied demonstrated episodic nocturnal hypoxaemia and there was a strong correlation between minimum oxygen saturation overnight and daytime arterial oxygen and carbon dioxide tensions (Paco$_2$ r=-0.87). Despite adequate REM time during polysomnography, greater oxygen desaturation was found during domiciliary oximetry. No difference was found in the severity of desaturation recorded in the boys who were studied on two separate occasions. Five boys demonstrated marked heart rate variation during hypoxaemic episodes and more serious arrhythmias occurred overnight in the three most hypoxaemic boys.

Domiciliary oximetry is a simple, repeatable method of assessing overnight oxygenation and compares well with polysomnography. In boys with advanced DMD and severe nocturnal hypoxaemia, 24 h electrocardiographic monitoring may detect potentially life-threatening arrhythmias.

Keywords: Arrhythmias; Duchenne muscular dystrophy; hypoxaemia; sleep

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Duchenne muscular dystrophy (DMD) is associated with respiratory muscle weakness and cardiomyopathy which may lead to both cardiac and respiratory failure and early death [1]. The respiratory abnormalities seen in DMD include impaired respiratory muscle strength, gradual reduction in lung volumes [2], and the development of a scoliosis [3]. The clinical management of these patients involves physiotherapy, prevention of obesity and the early treatment of respiratory infections. More recently attention has turned to the detection and treatment of nocturnal oxygen desaturation in older boys with more advanced DMD [4] and nocturnal ventilatory support has been offered to those who develop chronic respiratory failure [5, 6].

Sleep-related symptoms are unusual until the disease is very advanced [1], but nocturnal hypoxaemia, occurring during rapid eye movement (REM) sleep, may be seen without the presence of daytime hypersomnolence or early morning headache [5]. It has proved difficult to predict the severity of nocturnal oxygen desaturation from daytime measurements of pulmonary function, although "desaturating" patients tend to be rather older and fatter, with lower lung volumes and significantly lower maximal expiratory mouth pressures (Pemax) than those who do not desaturate during sleep [7].

Whilst it is rare for boys with DMD to be symptomatic of cardiac abnormalities even in their late teens, cardiac abnormalities can be detected early in life.
Electrocardiographic (ECG) abnormalities are common even in the young [8, 9] and the incidence of echocardiographic evidence of cardiomyopathy increases with age, until present in all patients by the age of eighteen [10]. In other clinical settings arrhythmias are common in patients with cardiomyopathy and may be exacerbated by hypoxia.

The physiological abnormalities leading to oxygen desaturation overnight in DMD have been defined by polysomnography but it is not known whether hospital based studies are essential in order to assess the severity of nocturnal desaturation. It is also not known whether this episodic nocturnal hypoxaemia is associated with cardiac arrhythmias or ST segment changes.

We have therefore studied a group of older boys with DMD by domiciliary pulse oximetry, to determine the severity of nocturnal hypoxaemia and, by using simultaneous ECG monitoring, we have looked for cardiac abnormalities that could be temporally related to periods of nocturnal oxygen desaturation.

**Methods**

**Study 1 (in hospital)**

Full polysomnography was performed in four boys aged 15–20 yrs (median 19 yrs) in the sleep laboratory. None had symptoms of nocturnal hypventilation but they were chosen because they were older boys in whom we might expect nocturnal hypventilation to be present. The patients slept in their usual position for two consecutive nights, the first serving as an acclimatization night with all recording electrodes attached, but with data recorded on the second night only. The electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG) and electrocardiogram (ECG) were monitored continuously and recorded on an 8 channel EEG pen recorder (SLE 100T) together with oronasal airflow, chest and abdominal wall movement (measured by inductance plethysmography) and arterial oxygen saturation (Sao2). An Ohmeda Biox 3700 pulse oximeter was used to measure oxygen saturation continuously. Sleep was staged using standard criteria [11]. The overnight oxygenation recorded during polysomnography was subsequently compared with that obtained during domiciliary oximetry performed a few months later in the same four boys (as described in study 2).

**Study 2 (at home)**

Ten boys aged 14–24 yrs (median 18.5 yrs) were studied, none had symptoms of nocturnal hypventilation or evidence of daytime respiratory failure. Six of the ten had previously undergone spinal stabilization using a Luque procedure [12]. Daytime pulmonary function was assessed during a short hospital visit. Forced vital capacity (FVC) was measured in the sitting position, using a Vitalograph respirometer. Maximal inspiratory (Pimax) and maximal expiratory (Pemax) static mouth pressures were measured using the technique of BLACK and HYATT [13]. Arterial blood gas tensions were measured by sampling blood from the radial artery.

An Ohmeda Biox 3700 pulse oximeter and a pen recorder (Rikadenki model R-03) were then taken to the patient’s home, and the ear probe was attached to the patient at their usual bedtime. The patients slept in their normal position and were turned as necessary during the night by their parents, with any change in sleeping position or episodes of snoring being noted on the recording. The ear probe was removed on awakening the following morning and the oxygen saturation trace subsequently analysed.

“Desaturation” was defined as a fall in Sao2 by more than 4% from the awake value. Statistical analysis using linear regression by the least squares method was used to determine the relationship between daytime measures of respiratory function and nocturnal oxygen desaturation.

**Study 3 (repeat study at home)**

To test the “repeatability” of domiciliary oximetry, six of the boys aged 16–24 yrs (median 19 yrs) were studied on a second occasion approximately 3 mths after the first study. The patients were again monitored at home using the methods described above. The two oxygen saturation recordings were later compared using a paired Student’s t-test.

**Study 4 (24 h ECG and oximetry at home)**

To assess whether there is any relationship between nocturnal hypoxaemia and cardiac arrhythmias or electrocardiographic ST segment abnormalities in patients with DMD, seven boys (aged 16–24 yrs; median 19 yrs) who demonstrated nocturnal hypoxaemia in Study 2 were studied on a further occasion using overnight domiciliary oximetry and simultaneous Holter monitoring of the ECG. After careful skin preparation a modified V5 lead position was chosen and skin impedance was checked (Oxford Medical Systems XI-1) to ensure a reading of less than 5 kΩ. To control for any ST segment changes that might occur secondary to positional changes, one minute each was recorded with the patient supine, in the left lateral and in the right lateral position at the start of each Holter monitor recording. Both the ear oximeter and the Holter monitor were attached to the patient at their usual bedtime but only the oximeter was removed on awakening. Electrocardiographic monitoring was continued for the full 24 h, the daytime recording therefore providing a control for the night time results. The magnetic tapes (TDK AD60 cassettes) were replayed (Oxford 4500 system) to produce a hard copy report of
the ST segment and heart rate trends and to allow electrocardiogram strips to be examined at times of interest. The presence of arrhythmias was noted together with the oxygen saturation at that time. The baseline ST level was determined after taking into account the maximum ST change during initial postural manoeuvres. Episodes of ST depression were identified by scanning the ST trend, printed out as real time electrocardiogram strips and then validated by examining each point of interest using a ×8 magnifying lens [14].

Results

Study 1 (in hospital)

During polysomnography the median total sleep time was 444 min (range 307–483 min) and the median percentage time spent in REM sleep was 24.5% (range 16–27.6%). The median awake Sao2 was 96% (range 95–97%) and the median minimum Sao2 overnight, which invariably occurred during REM sleep, was 88% (range 79–93%). The median Sao2 during non-REM (NREM) sleep being 95%. Desaturation overnight was classified as falls in Sao2 of either 4–10%, or >10%. The median number of 4–10% dips per hour was 0.86 (range 0–2.6) and the median number of >10% dips per hour was 0.46 (range 0–1.23). Desaturation was associated with either central apnoeic or hypopnoeic events. No obstructive episodes were noted. The sleep disordered breathing was almost exclusively seen in REM sleep as shown by a median total sleep hypopnoea/apnoea index (H/A) of 10 (range 5.7–13.7) with a median H/A duration of 20 s (range 13.7–25 s); but the REM sleep H/A index was 45 (range 18.7–47.6) with a median duration of 23.5 s (range 16.4–25.6 s).

More detailed information from these studies has previously been reported as part of a larger "in hospital" study of ventilatory abnormailities during sleep in Duchenne muscular dystrophy [15]. The polysomnographic record was then compared with the results of domiciliary oximetry in the same four patients. During domiciliary oximetry the median awake Sao2 was 95.5% (range 95–96%), with a median minimum Sao2 of 78% (range 71–86%) which was rather lower than that seen during polysomnography (fig. 1).

Study 2 (at home)

Patient characteristics are given in table 1. Respiratory measurements and arterial blood gas tensions were measured in the early afternoon in all subjects. The median FVC was low at 1.1 l (range 0.35–2.5 l) and maximal respiratory pressures were reduced with a median Pmax of 45 cmH2O (range 20–70 cmH2O), and a median Pmax of -40 cmH2O (range -10 to -60 cmH2O). Predicted values for boys of this age are Pmax 158–167 cmH2O, P1max -117 to -128 cmH2O [16]. Daytime arterial blood gas tensions were well-preserved with a median arterial oxygen tension (Pao2) of 11.7 kPa (range 8–14.4 kPa) and a median arterial carbon dioxide tension (Paco2) of 5.0 kPa (range 4.5–9.7 kPa). Only two boys demonstrated daytime arterial hypercapnia (Paco2 >6.4 kPa). Sleep quality on the study night was reported as normal by all boys and none were noted to snore during the study. Six boys demonstrated arterial oxygen desaturation overnight lasting 15 min or more (fig. 2) Three boys did not desaturate, and one boy desaturated for only 5 min. Desaturation occurred as repetitive discrete episodes of hypoxaemia (between 1 and 7 episodes per night) each lasting 10–60 min. Between these episodes the Sao2 was maintained at, or very close to, waking values. The median awake oxygen saturation (Sao2) was 96% (range 90–97%) with a median nadir overnight of 86% (range 53–97%). The median time spent with an Sao2 <4% below the awake value was 17 min (range 0–620 min), with a median total monitoring time of 600 min (range 420–720 min). There was no relationship between sleeping position and the presence of oxygen desaturation.

Statistical analysis revealed a strong correlation between the minimum oxygen saturation overnight and awake Paco2 (r=0.89, p<0.001), awake Paco2 (r=0.87, p<0.001), and age (r=0.65, p<0.05) with a weaker correlation with Pmax (r=0.63, p<0.05). There was no relationship, of statistical significance, between oxygen desaturation overnight and Pmax or FVC (r=0.48 and r=−0.47, respectively).
SLEEP-RELATED HYPOXAEMLA IN DMD

Table 1. - Patient age, FVC, respiratory muscle strength and daytime arterial blood gas tensions

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age yrs</th>
<th>FVC l</th>
<th>Pemax cmH₂O</th>
<th>Pimax cmH₂O</th>
<th>Pao₂ kPa</th>
<th>Paco₂ kPa</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>0.5</td>
<td>N/A</td>
<td>N/A</td>
<td>11.7</td>
<td>5.6</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>1.25</td>
<td>+50</td>
<td>-45</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>1.45</td>
<td>+35</td>
<td>-15</td>
<td>11.3</td>
<td>5.0</td>
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<tr>
<td>4</td>
<td>24</td>
<td>0.35</td>
<td>+20</td>
<td>-10</td>
<td>8.0</td>
<td>9.7</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>0.2</td>
<td>+20</td>
<td>-15</td>
<td>11.3</td>
<td>6.5</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>0.8</td>
<td>+30</td>
<td>-20</td>
<td>11.2</td>
<td>5.9</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>1.3</td>
<td>+60</td>
<td>-60</td>
<td>14</td>
<td>4.8</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>2.0</td>
<td>+70</td>
<td>-30</td>
<td>14.4</td>
<td>4.5</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>2.0</td>
<td>+40</td>
<td>-70</td>
<td>12.5</td>
<td>4.9</td>
</tr>
<tr>
<td>10</td>
<td>19</td>
<td>0.9</td>
<td>+40</td>
<td>-40</td>
<td>11.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Median</td>
<td>18.5</td>
<td>1.1</td>
<td>+45</td>
<td>-40</td>
<td>11.7</td>
<td>5.0</td>
</tr>
</tbody>
</table>

FVC: forced vital capacity; Pemax and Pimax: maximal expiratory and inspiratory static mouth pressure, respectively; Pao₂ and Paco₂: arterial oxygen and carbon dioxide tension, respectively; N/A: not available.

Table 2. - Results of overnight oximetry in six boys studied on two nights (I and II) at home, separated by at least three months

<table>
<thead>
<tr>
<th>Subject</th>
<th>Awake</th>
<th>Minimum</th>
<th>Monitoring time mins</th>
<th>Time Sa₀₂ &lt;4% below awake value min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>96</td>
<td>86</td>
<td>660</td>
<td>20</td>
</tr>
<tr>
<td>II</td>
<td>95</td>
<td>82</td>
<td>720</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>96</td>
<td>88</td>
<td>420</td>
<td>15</td>
</tr>
<tr>
<td>II</td>
<td>96</td>
<td>87</td>
<td>420</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>96</td>
<td>71</td>
<td>720</td>
<td>150</td>
</tr>
<tr>
<td>II</td>
<td>96</td>
<td>84</td>
<td>780</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>95</td>
<td>71</td>
<td>630</td>
<td>80</td>
</tr>
<tr>
<td>II</td>
<td>94</td>
<td>65</td>
<td>600</td>
<td>140</td>
</tr>
<tr>
<td>6</td>
<td>95</td>
<td>85</td>
<td>510</td>
<td>60</td>
</tr>
<tr>
<td>II</td>
<td>95</td>
<td>81</td>
<td>600</td>
<td>60</td>
</tr>
</tbody>
</table>

Sao₂: arterial oxygen saturation.

Fig. 2. - Examples of the oxygen saturation trace obtained overnight from two boys with DMD. A) Subject 6, with normal daytime arterial blood gas tensions. B) Subject 4, who demonstrates daytime arterial hypoxaemia and hypercapnia.

Study 3 (repeat study at home)

Oxygen saturation overnight in the six boys studied on two separate nights is given in table 2. For the group as a whole, no statistical difference was found between the severity of nocturnal oxygen desaturation on each occasion. Patient 3, however, spent 150 min desaturated during the first study and only 10 min during the second study during which the desaturation was less severe.

Study 4 (24 h ECG and oximetry at home)

All seven boys demonstrated episodic oxygen desaturation overnight from a median awake Sao₂ of 95% (range 94-96%) to a median nocturnal nadir of 78% (range 54-92%). The median total monitoring time was
Fig. 3. — A comparison of the electrocardiographic (ECG) records obtained in one boy during the daytime (a) and during an episode of nocturnal hypoxaemia (b), showing marked variation in heart rate at night compared with the smaller variation in rate seen during the day.

600 min (range 420–780 min) and the median time during which \( \text{Sao}_2 \) was >4% below the awake baseline was 30 min (range 0–720 min). Twenty four hour Holter monitoring did not demonstrate any arrhythmia during the daytime in any boy, but five boys developed a marked variation in heart rate during episodes of hypoxaemia overnight (fig. 3). More serious arrhythmias were seen in three boys. One suffered an episode of rapid atrial fibrillation and the second had two sinus pauses each lasting for two seconds. The third boy demonstrated four episodes of non-sustained ventricular tachycardia. These episodes occurred in the boys who suffered the most severe nocturnal hypoxaemia (minimum \( \text{Sao}_2 \) overnight 81%, 54% and 65%, respectively) but these arrhythmias did not necessarily occur at the most hypoxic time of the night. No significant ST segment depression or elevation occurred during any 24 h recording in any boy even during periods of hypoxaemia.

Discussion

Hospital admission for forty eight hours for two overnight sleep studies is uncomfortable and disruptive for the disabled patient and his family. Sleep quality, as assessed in the sleep laboratory, may be poor because of the change in environment imposed upon the patient, and therefore the first night in the sleep laboratory is not used for data collection. Domiciliary oximetry is a simple, safe technique which provides reproducible results with the minimum of discomfort to the patient, and because the patient is studied in their usual environment acclimatization factors are of minor importance. In the present study the severity of desaturation obtained during domiciliary oximetry was greater than that seen in the same patients during polysomnography despite adequate amounts of REM sleep, suggesting that possibly an even greater amount of REM sleep was experienced on monitoring in the home environment, thus allowing more marked oxygen desaturation. Domiciliary oximetry is more likely, therefore, to define the extent of nocturnal hypoxaemia in these patients.

During study 3, there was a disparity between the proportion of the monitoring time spent desaturated on the two monitoring nights in only one patient. It is possible that the patient spent an uncomfortable and restless second night, thus reducing REM sleep time and, therefore, remaining well-saturated. There was no evidence of artefact on the domiciliary recordings obtained from these boys who are unable to move spontaneously during sleep because of peripheral muscle weakness.

We found the dominant feature of the sleep disordered breathing pattern during polysomnography to be diminished chest wall movement during REM sleep. The majority of the desaturated episodes were due to hypopnoic events although apnoeic episodes of the “central” type did occur. The distinction between central and obstructive apnoea depends on thoracic and abdominal wall movement which may be severely diminished in the very weak patient. The use of inductance plethysmography in study 1 indicated that the events observed in our patients were central in origin but it may be impossible to differentiate between obstructive and central events in such patients without the use of gastric and oesophageal pressure monitoring.

Sleep-related hypoxaemia can occur without daytime symptoms in DMD. We found that the minimum oxygen saturation overnight is related to increasing age, daytime arterial blood gas tensions and reduction in maximal expiratory mouth pressure. Those boys with the most
abnormal daytime arterial blood gas tensions are the most likely to suffer REM-related hypoxaemia. Although vital capacity is considered a useful prognostic indicator in DMD [17], we found no correlation between forced vital capacity and the severity of oxygen desaturation overnight. In addition, no relationship was seen between nocturnal oxygen desaturation and Pimax reflecting the relative preservation of diaphragm function during wakefulness in DMD.

Daytime hypercapnia can be predicted in patients with pure respiratory muscle weakness when the respiratory muscle strength (mean of Pmax and Pimax) is <30% of normal or when the vital capacity is <55% of the predicted value [18], and in this study the two boys with daytime hypercapnia were those with the most severely impaired lung volumes and respiratory muscle strength.

REM-related hypoxaemia is associated with a transient increase in pulmonary arterial pressure and may contribute to the development of cor pulmonale. In addition, in patients with a cardiomyopathy, the stress of episodic hypoxaemia might increase the risk of developing myocardial ischaemia and/or arrhythmias. No significant ST segment depression was seen in any boy in this study despite the presence of nocturnal hypoxaemia. It is unlikely, therefore, that the arrhythmias seen were primarily related to myocardial ischaemia. Although serious arrhythmias occurred in the three boys with the most severe desaturation overnight, in only one case was the arrhythmia associated with the nadir of oxygen saturation. Overnight oxygenation can be improved by the use of nocturnal mechanical ventilatory support which is now in widespread use for a variety of neuromuscular disorders [19], and indeed one group advocates the use of intermittent positive pressure ventilation (IPPV) via a tracheostomy in boys with DMD with an FVC of <600 ml or evidence of carbon dioxide retention before the onset of respiratory support failure [20]. The use of intermittent positive pressure ventilation delivered by a nasal mask (NIPPV) is an effective form of nocturnal ventilatory support [21, 22] and is superior to the use of negative pressure ventilation [23] or to the delivery of IPPV via a tracheostomy.

In summary, we found that domiciliary oximetry adequately detects nocturnal oxygen desaturation in boys with DMD, some of whom were also found to have potentially dangerous arrhythmias overnight (but not during the daytime). Studies using NIPPV to abolish nocturnal hypoxaemia in such patients are underway and the effect of this treatment on daytime cardiorespiratory function and on cardiac rhythm are awaited. Such treatment is difficult practically and requires ethical consideration. For both of these reasons symptomatic and objective evidence of improvement would be required before ventilatory support could be recommended for these patients.

References


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RÉSUMÉ: Dans la dystrophie musculaire de Duchenne (DMD), les désaturations nocturnes en oxygène se développent pendant le sommeil à mouvement oculaire rapide (REM). La polysomnographie, qui exige une admission hospitalière, permet de détecter les anomalies respiratoires en rapport avec le sommeil. Pour éviter les inconvénients de l’admission hospitalière chez des patients handicapés, nous avons investigué l’oxygénation nocturne chez 10 enfants atteints de DMD, grâce à une oxymétrie réalisée au domicile. Chez quatre garçons les résultats de l’oxymétrie ont été comparés à ceux obtenus pendant l’enregistrement polysomnographique. La “reproductibilité” de l’oxymétrie au domicile a été appréciée chez six garçons par l’exécution de mesures oxymétriques lors de 2 nuits consécutives.

Des garçons plus âgés, atteints de DMD, peuvent développer une cardiomyopathie. Afin d’apprécier le rythme cardiaque et les modifications du segment ST, nous avons pratiqué un monitoring au Holter et une oxymétrie simultanés chez sept garçons atteints d’hypoxémie nocturne.

Six des dix garçons repris initialement avaient des épisodes d’hypoxémie nocturne, et l’on a noté chez eux une forte corrélation entre la saturation oxygénée minimale nocturne et les tensions artérielles des gaz du sang diurnes (Pao₂, r=0.89; Paco₂, r=-0.87). Malgré une durée de REM adéquate au cours de la polysomnographie, des désaturations oxygénées plus importantes ont été observées au cours de l’oxymétrie à domicile. L’on n’a trouvé aucune différence dans la sévérité de la désaturation enregistrée chez les garçons qui ont été examinés à deux occasions séparées. Chez cinq garçons, l’on a noté des variations marquées du rythme cardiaque au cours des épisodes hypoxémiques, et des arythmies plus sérieuses ont été observées pendant la nuit chez les trois garçons les plus hypoxémiques.