

Oxygen treatment of sleep hypoxaemia in Duchenne muscular dystrophy

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ABSTRACT Patients with Duchenne muscular dystrophy develop progressive ventilatory muscle weakness and often die of respiratory complications. Recurrent, often profound, hypoxaemia has been shown in a previous study by this group to occur during rapid eye movement (REM) sleep in these patients before they develop sleep symptoms. In this study the efficacy and physiological effects of nocturnal oxygen in such patients have been assessed. Seven patients with Duchenne muscular dystrophy (age range 16-22 years; mean vital capacity 1.37 litres) with normal arterial blood gas tensions when awake were investigated by standard overnight polysomnography on an acclimatisation night followed by two successive nights on which they received room air and nasal oxygen (2 litres/min) respectively in random order. Total sleep time, proportion of REM and non-REM sleep, and frequency and duration of arousals were similar on the two nights. When breathing air six of the seven subjects developed oxygen desaturation of more than 5% during REM sleep. With oxygen only one subject showed any oxygen desaturation exceeding 2.5%. Oxygen desaturation was associated with periods of hypopnoea or cessation of respiratory effort. The mean duration of episodes of hypopnoea and apnoea was prolonged during oxygen breathing by 19% and the mean duration of episodes during REM sleep by 33% (the proportion of REM sleep associated with hypopnoea and apnoea increased in all subjects). Heart rate in non-REM sleep fell by 9.3%; heart rate variation in REM and non-REM sleep was unchanged. These acute studies show that oxygen reduces the sleep hypoxaemia associated with respiratory muscle weakness; whether long term treatment will be possible or desirable is not clear as oxygen potentiates the underlying ventilatory disturbance.

Introduction

Patients with Duchenne muscular dystrophy die prematurely, usually before the age of 25 years and usually from respiratory muscle failure.¹ We have shown² that profound hypoxaemia is common during rapid eye movement (REM) sleep in patients with advanced Duchenne muscular dystrophy, despite normal arterial blood gas tensions when they are awake and in the absence of sleep symptoms. The prognostic importance of this degree of sleep hypoxaemia is not established, but prevention may be beneficial. Aggressive management of respiratory failure with assisted ventilation in patients with progressive neuromuscular disease may prevent hypoxaemia but it poses ethical problems.³ Oxygen treatment is a logical choice to prevent sleep hypox-

aemia, being non-invasive and readily acceptable. We have used overnight polysomnography to study whether low flow nocturnal oxygen given to abolish sleep hypoxaemia in patients with advanced Duchenne muscular dystrophy is beneficial.

PATIENTS

We studied seven patients with Duchenne muscular dystrophy aged 16-22 (mean 19) years. The diagnosis had been made on the basis of clinical, electrophysiological, and muscle biopsy findings. None had appreciable obesity or scoliosis; five had undergone operative spinal stabilisation. The study was approved by the hospital ethical committee.

LUNG FUNCTION MEASUREMENTS

Lung function measurements included vital capacity on a water spirometer, total lung capacity (TLC) and its components determined by the helium dilution technique, and maximum static inspiratory and expiratory mouth pressures (MIP and MEP) obtained by

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the method of Black and Hyatt.⁴ Predicted normal values for MIP and MEP were taken from Wilson *et al.*⁵ Blood gas tensions were measured from radial artery blood obtained when the patients were awake and supine.

POLYSOMNOGRAPHY

Standard polysomnographic methods were used.⁶ The following recordings were made on an EEG pen monitor (SLE 100T; paper speed 15 mm/s): electroencephalogram (EEG; C4/A1), electro-oculogram (E1/A1 and E2/A1), submental electromyogram (EMG), chest and abdominal wall excursion measured by respiratory inductance plethysmography (Respirace) together with a combined "sum" signal, and oronasal airflow detected by a thermistor secured below the nares. Oxygen saturation (Sao₂) was recorded from an ear oximeter (Ohmeda Biox III) on a separate chart recorder (paper speed 30 mm/h).

The patients slept in the laboratory for three nights, the first to acclimatise them to the surroundings and equipment. In most cases a parent slept near to the sleep laboratory and attended to the patients' positional needs as required during the night. Recordings were made on the second and third nights, the subjects receiving, in random order, nasal oxygen (2 l/min) on one night and room air on the other.

SLEEP STAGING AND MEASUREMENTS

Sleep was staged manually in 20 second epochs according to standard criteria.⁵ Arousal was defined as an increase in EMG amplitude accompanied by either a change to a lighter sleep stage or the appearance of alpha rhythm on the EEG, with at least 20 seconds between arousals. Awakening was defined as more than three consecutive epochs (> 1 minute) of stage W (awake) with at least one minute of sleep between awakenings. Hypopnoea was defined as a fall in the thoracoabdominal movement signal amplitude ("sum") to less than 50% of the preceding stable level over one minute of sleep, persisting for more than 10 seconds. Episodes with apnoea contained periods exceeding 10 seconds of zero "sum" and airflow signal ("central" apnoea) or diminished "sum" but absent airflow ("obstructive" apnoea). Desaturation was defined as a fall in oxygen saturation of more than 5% from the preceding stable (usually non-REM) value. The mean heart rate during REM and non-REM sleep was derived from three one minute periods of REM and of stage 3 non-REM sleep in each subject. The heart rate in nine consecutive 20 second epochs during REM and non-REM sleep was also obtained to derive the coefficient of variation for heart rate.

STATISTICS

Statistical comparisons of means (SEM) were performed by means of Student's *t* test.

Results

The estimated mean body mass index (weight/arm span²) of the seven patients was 18.8 (range 13.1–21.8) kg/m². Pulmonary function tests showed a very restrictive pattern with profound respiratory muscle weakness. Mean vital capacity was 1.37 (range 0.7–3.0) l and TLC 3.34 (2.02–6.33) l. MIP was reduced to between –25 and –65 (mean –36) cm H₂O (normal 107 (11.7) cm H₂O) and MEP to 15–50 (mean 25) cm H₂O (normal 139 (10.6) cm H₂O). Arterial blood gas tensions with the patient breathing air were normal, PaO₂ ranging from 12.5 to 15.6 (mean 14.4) kPa, and PaCO₂ from 4.7 to 6.1 (mean 5.3) kPa.

Oxygen was administered on the first study night to three subjects, and on the second study night to four. All subjects completed the study, with a minimum total sleep time of 352 minutes with both air and oxygen. The study time, total sleep time, and proportions of REM and non-REM sleep are given in table 1. The mean sleep onset latency was 25.7 minutes with air and 33.6 minutes with oxygen; mean REM sleep onset latency (excluding periods of awakening) was 111.5 minutes with air and 106.5 minutes with oxygen.

OXYGEN DESATURATION

Arterial oxygen saturation changes are shown in table 2. Mean Sao₂ was greater with the subjects breathing oxygen rather than air, by 1.5% when they were awake (*p* < 0.05) and by 2.2% during non-REM sleep (*p* < 0.01). While breathing air, six of the seven subjects developed from 6 to 102 oxygen "desaturations" (> 5%) per night; five subjects had from 2 to 68 desaturations that exceeded 10%. Desaturation of more than 5% was limited to periods of REM sleep (figure) in all but the most severely affected patient, who also showed desaturation during non-REM sleep; this subject was alone in showing any desaturation exceeding 2.5% while breathing oxygen.

BREATHING PATTERN

The dominant feature of the sleep disordered breathing in these patients was diminished chest wall movement, especially during REM sleep; this was

Table 1 Mean (SEM) [range] study and sleep duration on air and oxygen nights with percentages of the different sleep stages

	Air (n = 7)		Oxygen (n = 7)	
Study time (min)	521	(21.2) [475–639]	483	(7.6) [464–512]
Total sleep time (min)	417	(20.8) [352–520]	395	(13.6) [352 ± 461]
% stage REM	19	(2.5) [10–28]	20	(2.3) [11.0–27]
% stages 1 and 2 non-REM	57	(2.3) [53–69]	53	(3.0) [41–67]
% stages 3 and 4 non-REM	24	(3.4) [11–37]	27	(2.3) [19–37]

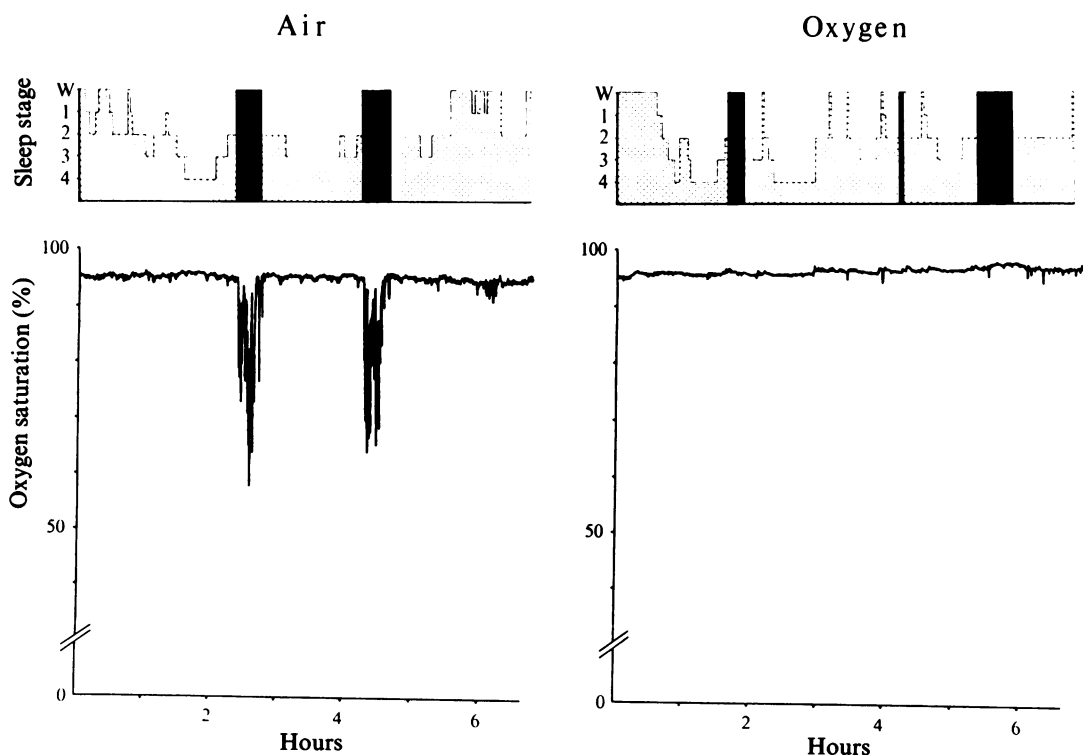
Table 2 Oxygen saturation (SAO_2) on air and oxygen nights (mean (SEM) [range] values)

	Air (n = 7)	Oxygen (n = 7)	p*
Awake SAO_2 (%)	96.0 (0.25) [95–97]	97.5 (0.57) [95–100]	< 0.05
Non-REM SAO_2 (%)	95.2 (0.38) [93.5–96.5]	97.4 (0.60) [95–100]	< 0.01
REM SAO_2 (range)	58–96	86–100	
No of dips/h			
> 5%	4.0 (2.1) [0–16.1]	0.1 (0.11) [0– 9.1]	NS
> 10%	2.3 (1.5) [0–10.7]	0.04 (0.04) [0– 0.26]	NS
Largest SAO_2 fall (%)	16.4 (4.4) [3–39]	2.5 (1.6) [0– 12.2]	< 0.02

*Paired *t* test.

occasionally associated with apnoea of the “central” type. When subjects were breathing air there were 44 (6.0) episodes of hypopnoea and apnoea an hour during REM sleep compared with 3.5 (1.5) episodes an hour during non-REM sleep. Oxygen did not affect the frequency of such events but the character changed and the percentage of abnormal sleep occupied by apnoea (as opposed to hypopnoea) rose from 42 (15) when they were breathing air to 50 (12) with oxygen. The proportion of total sleep occupied by hypopnoea and apnoea was higher with oxygen than with air in six of the seven subjects, the mean (range) percentage for

the seven subjects rising from 7.9 (1.9–17.5) with air to 10 (5.0–17.1) with oxygen. The percentage of REM sleep occupied by hypopnoea and apnoea episodes increased in all subjects when breathing oxygen (from a mean (SEM) of 32 (6.8) to 42 (5.7)). These changes reflected an increase in duration rather than frequency of hypopnoea (549 episodes with oxygen, 520 with air) or apnoea (259 with oxygen, 202 with air). The mean duration of the hypopnoea episodes was 19% greater with oxygen than with air (oxygen 30.9 (1.22) seconds, air 25.9 (0.66) s; $p < 0.01$). This difference in mean duration was greater during REM sleep (air (n = 388)



Overnight oxygen saturation with air and with oxygen in a 16 year old patient with Duchenne muscular dystrophy (vital capacity 1.0 litre, maximum static inspiratory mouth pressure – 30 cm H_2O) showing repeated oxygen desaturation during REM sleep corrected by oxygen. Light shaded areas represent wakefulness (W) and stages 1–4 of non-REM sleep; REM sleep is represented by the solid bars.

28.0 (0.8) s, oxygen (n = 383) 37.1 (1.62) s; $p < 0.001$). The episodes during REM sleep were significantly longer ($p < 0.001$) during REM sleep than during non-REM sleep (mean duration of non-REM episodes: air (n = 132) 20.1 (0.92) s; oxygen (n = 166) 16.8 (0.75) s.

HEART RATE

Mean heart rate was 76 beats/min with air and 69.4 beats/min with oxygen. During non-REM sleep the difference in heart rate between the air and the oxygen night ranged from +3.5% to -18.1%. The coefficient of variation (%) of heart rate was greater during REM than non-REM sleep, both for air (REM 9.3 (1.6), non-REM 2.6 (0.4) ($p < 0.01$)) and for oxygen breathing (REM 7.2 (1.3); non-REM 2.5 (0.6) ($p < 0.01$)), but did not differ between air and oxygen.

AROUSALS

The frequency of arousals and awakenings combined was similar on the air and oxygen nights, being 10.4 (2.3)/h and 10.3 (1.8)/h respectively. Arousal frequency was high during REM sleep (22.2 (4.9)/h). There were significant ($p < 0.01$) differences in arousal and combined arousal and awakening frequency between REM and non-REM sleep with both air and oxygen. Most of the arousals and awakenings from REM sleep were associated with a documented episode of hypopnoea or apnoea of more than 10 seconds' duration—100% when subjects were breathing air and 99% when they were breathing oxygen. By contrast, during non-REM sleep only 11.5% of arousals or awakenings with air and 22% with oxygen followed documented hypopnoea. There was no relation between the number of oxygen desaturation episodes and either the arousal frequency or the sleep quality whether subjects were breathing air or oxygen.

Discussion

Duchenne muscular dystrophy provides a useful example of a condition where severe chronic respiratory weakness is uncomplicated by any obvious central ventilatory disorder when patients are awake⁷ or, in our subjects, by substantial scoliosis or obesity. Previous short reports of oxygen therapy in neuromuscular disease have provided little polysomnographic detail^{8,9} and sleep studies of oxygen therapy in Duchenne muscular dystrophy have not been reported. We have shown that low flow overnight oxygen is effective in reducing or abolishing sleep hypoxaemia in patients with Duchenne muscular dystrophy, despite an associated prolongation of underlying hypopnoea and apnoea events. The mean proportions of each sleep stage were similar with no differences in the

numbers of arousals or awakenings between the air and the oxygen nights. Although the age range of our subjects was narrow (16–22 years), they represented a wide range of respiratory disability and tendency to sleep hypoxaemia yet had a consistent pattern of oxygen desaturation related to REM sleep. All but one of the seven subjects showed oxygen desaturation exceeding 5% during REM sleep when breathing air; only one subject had desaturation of more than 5% during non-REM sleep. Randomisation of the order in which subjects received air and oxygen after initial acclimatisation ensured that any alteration in sleep disordered breathing from improved acclimatisation was not attributed to oxygen. Carbon dioxide tensions were not measured during sleep and so we cannot comment on whether carbon dioxide retention was a complicating factor.

The term central apnoea requires qualification in the context of neuromuscular disease. The distinction between central and obstructive apnoea depends on thoracic and abdominal wall movement, which may be diminished if very weak patients make an inadequate response to normal or increased ventilatory drive. Our earlier studies showed that apparently central apnoea could occur despite persisting phasic EMG inspiratory bursts in the submental muscles.² Episodes of central apnoea without apparent persisting muscle activity are shortened by oxygen,¹⁰ possibly by relief of hypoxic suppression of the respiratory centre; obstructive apnoea is usually little changed,^{11,12} but may deteriorate¹³ or improve.¹⁴ It has been suggested that oxygen may promote the obstructing mechanism, perhaps converting central to obstructive apnoea, by suppression of upper airway tone.¹³ Thus the prolongation of hypopnoea and apnoea during oxygen breathing in muscular dystrophy supports an obstructive contribution (rather than a truly central mechanism) for these events.

Our earlier studies have shown that sleep quality, as assessed by the percentage of each EEG sleep stage present, is well preserved in these patients irrespective of whether REM related hypoxaemia is present.² Unlike older patients with severe chronic obstructive lung disease, whose disturbed sleep pattern can be improved by relief of their nocturnal hypoxaemia,¹⁶ oxygen had little impact on the sleep of patients with Duchenne dystrophy whether assessed by the distribution of sleep stages, arousal frequency, or number of epochs of complete wakefulness.

The clinical and prognostic importance of sleep hypoxaemia in this and other chronic neuromuscular diseases is not established. Hypoxaemia is likely to be responsible for the pulmonary hypertension seen in the terminal stages of Duchenne muscular dystrophy¹⁷ and may have an important role in precipitating sudden unexpected deaths in this condition.¹⁸ REM

related hypoxaemia is commonly seen in Duchenne dystrophy with no associated somnolence² (presumably because non-REM restorative sleep is of normal duration and quality), implying that sleep hypoxaemia is more common among patients with neuromuscular problems than is clinically apparent. Although oxygen potentiates the underlying ventilatory disorder and theoretically may raise carbon dioxide tension, it was effective in reducing nocturnal arterial oxygen desaturation and deserves further investigation as a long term measure to prevent the complications of recurrent hypoxaemia in neuromuscular disease.

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References

- 1 Smith PEM, Calverley PMA, Edwards RHT, Evans GA, Campbell EJMI. Practical considerations of respiratory care of patients with muscular dystrophy. *N Engl J Med* 1987;316:1197-205.
- 2 Smith PEM, Calverley PMA, Edwards RHT. Hypoxemia during sleep in Duchenne muscular dystrophy. *Am Rev Respir Dis* 1988;137:884-8.
- 3 Rideau Y, Delaubier A. Management of respiratory neuromuscular weakness. *Muscle Nerve* 1988;11:407.
- 4 Black LF, Hyatt RE. Maximum static respiratory pressures in generalised neuromuscular disease. *Am Rev Respir Dis* 1971;103:641-50.
- 5 Wilson SH, Cooke NT, Edwards RHT, Spiro SG. Predicted normal values for maximum respiratory pressures in caucasian adults and children. *Thorax* 1984;39:535-8.
- 6 Rechtschaffen A, Kales A. *A manual of standardised terminology, techniques, and scoring system for sleep states in human subjects*. Bethesda: US Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Institute of Neurology Disease and Stroke, Neurological Information Network, 1968:1-12.
- 7 Begin R, Bureau M-A, Lupien L, Lemieux B. Control of Breathing in Duchenne's muscular dystrophy. *Am J Med* 1980;69:227-34.
- 8 Fischer DA. Poliomyelitis: Late pulmonary complications and management. In: Halstead LS, Wiechers DO, eds. "Late effect of Poliomyelitis". Miami, Florida: Symposia Foundation, 1985:185-92.
- 9 Martin RJ, Sufit RL, Ringel SP, Hudgel DW, Hill PL. Respiratory improvement by muscle training in adult onset acid maltase deficiency. *Muscle Nerve* 1983;6:201-3.
- 10 McMicholas WT, Carter JL, Rutherford R, Zamel N, Phillipson EA. Beneficial effect of oxygen in primary alveolar hypoventilation with central sleep apnea. *Am Rev Respir Dis* 1982;125:773-5.
- 11 Smith PL, Haponik EF, Bleecker ER. The effects of oxygen in patients with sleep apnea. *Am Rev Respir Dis* 1984;130:958-63.
- 12 Gold AR, Smith PL, Haponik EF, Bleecker ER. Effect of low flow oxygen on central sleep apnea [abstract]. *Am Rev Respir Dis* 1984;129:A274.
- 13 Hudgel DW, Hendricks C, Dadley A. Alteration of apnea time in obstructive sleep apnea by O₂ and CO₂ inhalation [abstract]. *Am Rev Respir Dis* 1987;135:A185.
- 14 Martin RJ, Sanders MH, Gray BA, Pennock BE. Acute and long-term ventilatory effects of hyperoxia in the adult sleep apnea syndrome. *Am Rev Respir Dis* 1982;125:175-80.
- 15 Staats BA, Bonekat HW, Harris CD, Offord KP. Chest wall motion in sleep apnea. *Am Rev Respir Dis* 1984;130:59-63.
- 16 Fleetham J, West P, Mezon B, Conway W, Roth T, Kryger M. Sleep, arousals and oxygenation in chronic obstructive pulmonary disease. The effect of oxygen therapy. *Am Rev Respir Dis* 1982;126:429-33.
- 17 Yoshitake S, Aoyagi T, Izhikawa K, Sugita H. Haemodynamic study of the terminal Duchenne muscular dystrophy patients [abstract]. *Muscle Nerve* 1986;9(5S):205.
- 18 Rideau Y, Gatin G, Bach J, Gines G. Prolongation of life in Duchenne's muscular dystrophy. *Acta Neurol (Napoli)* 1983;5:118-24.