Respiratory Medicine (2003) **97**, 1021–1026

ELSEVIER

respiratoryMEDICINE

The effect of treatment on diaphragm contractility in obstructive sleep apnea syndrome

Desiree R. El-Kabir[a,*], Michael I. Polkey[b], Rebecca A. Lyall[c], Adrian J. Williams[a], John Moxham[c]

[a]*Lane Fox Respiratory Unit and Sleep Disorders Centre, St Thomas' Hospital, Guy's King's and St Thomas' School of Medicine, Lambeth Palace Road, London SE1 7EH, UK*
[b]*Respiratory Muscle Laboratory, Royal Brompton Hospital, London SW3 6NP, UK*
[c]*Respiratory Muscle Laboratory, King's College Hospital, Guy's King's and St Thomas' School of Medicine, Bessemer Road, London SE5 9RS, UK*

KEYWORDS
Obstructive sleep apnea syndrome;
Diaphragm;
Low-frequency fatigue;
Nasal CPAP;
Phrenic nerve stimulation

Summary In untreated obstructive sleep apnea syndrome (OSAS) inspiratory efforts are made against an occluded airway and diaphragm fatigue might therefore complicate OSAS. To test this hypothesis we measured twitch transdiaphragmatic pressure (Tw Pdi) in response to bilateral cervical magnetic stimulation of the phrenic nerve roots in nine patients with OSAS before and one month after successful therapy with nasal continuous positive airways pressure (nCPAP). The mean Tw Pdi before therapy was 23.2 cm H_2O and after therapy was 22.8 cm H_2O ($P = 0.59$); the mean change after initiation of nCPAP was 0.4 cm H_2O with 95% confidence intervals of -1.3 cm H_2O and $+2.1$ cm H_2O. We conclude that low frequency diaphragm fatigue does not complicate untreated OSAS.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a common condition[1] which, in mild to moderate disease may result in significant daytime somnolence; however in severe disease ventilatory failure is a recognized complication.[2] During obstructive apneas substantial intrathoracic pressures may be generated and in some patients the pressure time index may exceed the level of 0.18 where diaphragm fatigue may be expected to occur.[3] Previous groups have hypothesized that the load placed on the diaphragm during sleep would generate fatigue. The techniques used to test this hypothesis have included measurement of transdiaphragmatic pressure (Pdi), relaxation rate and power spectral analysis of the diaphragm EMG. However, perhaps because of the variety of methods used, the published data have not conclusively confirmed or refuted the hypothesis.[4–6] Moreover, none of these studies have used methods adequate to detect the presence of low-frequency fatigue, which is the form of fatigue currently postulated to be of clinical relevance.

The method most suitable for clinical studies of diaphragm fatigue is the measurement of twitch transdiaphragmatic pressure (Tw Pdi) in response to single supramaximal bilateral phrenic nerve stimulation.[7] Tw Pdi has been demonstrated to fall when low-frequency diaphragm fatigue is induced in normal humans[8] and recovers over a period of hours.[9] This observation, particularly the long period required for recovery, is consistent with data obtained from other human muscles.[10] In this study we tested the hypothesis that patients with OSAS have low-frequency diaphragm fatigue; if this hypothesis were correct then successful treatment with nasal continuous positive airways pressure

*Corresponding author. Tel.: +44-207-928-9292; fax: +44-207-922-8174.
E-mail address: desielk@cwcom.net (D.R. El-Kabir).

0954-6111/03/$ - see front matter
doi:10.1016/S0954-6111(03)00132-X

(nCPAP) should reverse the fatigue and Tw Pdi should increase.

Methods

Subjects

Nine subjects with moderate OSAS were recruited. None of the patients had clinical evidence of neuromuscular disease, pre-existing respiratory or cardiac disease or other conditions pre-disposing to sleep-disordered breathing. All subjects gave their written informed consent. Ethical approval was granted by the hospital ethics committee.

Diagnosis and management of OSAS

The diagnosis of OSAS for this study required an appropriate history, excessive daytime sleepiness and a diagnostic sleep study. In six cases (Subjects no. 1, 2, 4, 5, 7 and 9) this was a polysomnographic study and in the remaining three subjects overnight oximetry. Polysomnography was performed in a sleep laboratory according to the standards of the American Sleep Disorders Association using the Somnostar Alpha apparatus (Sensormedics Inc, Yorba Linda, CA) and studies were manually scored according to standard criteria.[11] Overnight oximetry was performed in the patients own home using the Ohmeda 3700 Biox oximeter (Ohmeda Inc, CO). All patients had an apnea-hypopnea index (AHI) or oxygen desaturation index (ODI) of greater than 10 events per hour; the mean (SD) AHI being 27.6 (14.6) and the mean ODI 32.8 (10.6) events/h.

The patients were treated with nCPAP; the optimal level of CPAP was determined by an automated titration study (Autoset®, Resmed, Abingdon, UK). All patients accepted nCPAP therapy and obtained satisfactory symptomatic relief with dramatic reduction of symptoms, which in all cases persisted for a minimum of four months at routine follow-up. We also recorded the Epworth sleepiness score (ESS) in all subjects before and after nCPAP therapy; the mean pretreatment value was 16.4 (3.5) and on the day of repeat study was 6.7 (3.2) ($P = 0.001$).

Inspiratory muscle strength tests

Inspiratory muscle contractility was evaluated at the same time each morning (generally 9 am) both before and after at least 1 month of nCPAP treatment. Two balloon-tipped catheters (PK Morgan, Rainham, Kent, UK) 110 cm in length were passed through the nose under topical anesthesia; one was positioned in the mid-esophagus and the other in the stomach. The catheters were connected to differential pressure transducers (Validyne MP45-1; Validyne, Northridge CA), carrier amplifiers (PK Morgan, Rainham, Kent UK), a 12-bit NB-MIO-16 analogue-digital board (National Instruments, Austin, TX) and a Macintosh Quadra Centra 650 personal computer (Apple Computer Inc, Cupertino, CA) running Labview™ software (National Instruments). Signals were sampled at 100 Hz. The subtraction of the esophageal pressure (Pes) from the gastric pressure (Pga) allowed the Pdi to be calculated.

All subjects were rested for 20 min with the catheters in place to minimize twitch potentiation[12] prior to respiratory muscle strength testing. Diaphragm strength was measured as Tw Pdi following cervical magnetic stimulation of the phrenic nerve roots at the back of the neck at the level of the 7th cervical vertebra.[13] A 19-pin, 90-mm circular coil was used powered by a Magstim DEM stimulator (Magstim Co., Whitland, Dyfed, UK). The optimal site for stimulation was first determined with the magnetic stimulator at 70% maximal output, and was then marked. A minimum of five stimulations at 100% output were then performed from relaxed end-expiration judged from Pes with the subject seated and wearing a noseclip. The mean Tw Pdi of these five stimulations was then used for further analysis.

In addition diaphragm strength was assessed volitionally by the measurement of Pdi during a maximal voluntary sniff, sniff transdiaphragmatic pressure (Sn Pdi).[14] The subjects were instructed to perform at least 10 short sharp maximal sniff manoeuvres from FRC and the maximal Sn Pdi value was recorded. Global inspiratory muscle strength was measured as the maximal sniff esophageal pressure (Sn Pes) obtained in this way.[15] During these volitional tests the pressure trace obtained was visible to the subject and the investigator provided verbal encouragement. The pressure measured at the mouth during a maximal static inspiratory effort against an occlusion (PImax) was also recorded. We used a flanged mouthpiece, which was held by the investigator and this test was performed from RV.

Statistics

Paired *t*-tests were used to compare respiratory muscle tests before and after treatment with

nCPAP. The statistical calculations were performed in Stata (Stata Corporation, College Station, TX) and a level of $P<0.05$ was taken as significant.

Results

Clinical data from the nine subjects is shown in Table 1. Eight of the nine subjects were male and the mean (SD) age was 48.0 (10.1) years. The mean (SD) body mass index (BMI) was 36.7 (8.2) and seven subjects were clinically obese ($BMI > 30\,kg/m^2$). Using the criterion of an ESS greater than 10, all subjects were pathologically sleepy, the mean (SD) pretreatment score being 16.4 (3.5). Data from polysomography from five subjects showed a mean (SD) total sleep time of 372.6 (82.0) min. The mean sleep latency was 15.9 (14.4) min and the mean sleep efficiency 78.8 (15.3)%. Mean latency to the onset of rapid eye movement (REM) sleep was 64.3 (47.9) min. The mean distribution of sleep stages was as follows: Stage 1: 8.3 (4.2)%; Stage 2: 54.1 (17.1)%; Stage 3: 11.4 (5.3)%; Stage 4: 0.4 (0.6)% and Stage REM: 10.8 (7.1)%.

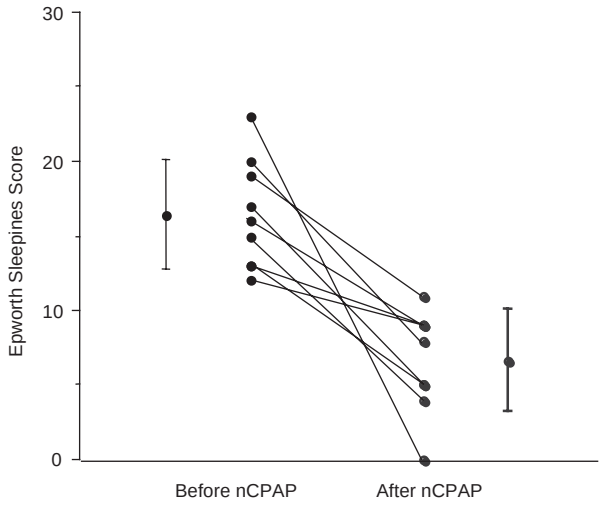

Figure 1 Epworth sleepiness scores (ESS) before and after nCPAP therapy. Individual data are shown together with the means and standard deviation.

Efficacy of therapy was confirmed by the marked improvement in symptoms of nocturnal disturbance and daytime sleepiness in all cases after initiation of nCPAP therapy. This was further demonstrated by a fall in the ESS to a mean (SD) value within the normal range of 6.7 (3.2) ($P = 0.001$) (Fig. 1). Subsequent outpatient review confirmed that all subjects continued to use their nCPAP machines regularly (follow up ranged from 4 months to 5 years).

Tw Pdi was inversely related to BMI ($r^2 = 0.44$, $P = 0.051$) and Sn Pdi ($r^2 = 0.41$, $P = 0.06$) although these trends did not reach statistical significance, presumably because of the small number of subjects studied. There was no relationship between Sn Pdi and BMI ($r^2 = 0.08$, $P = 0.46$).

Respiratory muscle strength before and after nCPAP is shown in Table 2. There was no significant change in inspiratory strength following nCPAP therapy whichever measure was used. In particular for the primary outcome measure (Tw Pdi) the mean value before therapy was 23.2 and 22.8 cm H_2O after therapy ($P = 0.59$); the mean difference was therefore 0.4 cm H_2O with 95% confidence intervals of -1.3 cm H_2O and $+2.1$ cm H_2O (Fig. 2). Thus the greatest rise in Tw Pdi that could have been missed by chance in this study was 1.3 cm H_2O or 5.6%.

Table 1 Clinical data of nine subjects with obstructive sleep apnea syndrome.

Subject no.	Sex	Age (years)	BMI (kg/m^2)	VC (% predicted)	ESS	AHI or ODI (events/h)		nCPAP pressure (cm H_2O)
1	M	54	28.5	121	16	37.4		8
2	M	63	32.9	97	13	22.2		12
3	M	30	36.4	56	19		23.2	14
4	F	59	46.8	44	12	23.0		9
5	M	56	42.9	93	17	20.0		14
6	M	45	32.9	98	20		44.2	14
7	M	42	51.8	95	15	52.0		13.5
8	M	44	32.7	39	23		31.1	12
9	M	39	25.6	115	13	11.0		9.5
Mean (SD)		48(10.1)	36.7(8.2)	84.1(28.7)	16.4(3.5)	27.6(14.6)	32.8(10.6)	11.8(2.2)

ESS, Epworth sleepiness score.AHI/ODI, apnea-hypopnea index/oxygen desaturation index.

Discussion

The present study shows that effective treatment of subjects with OSAS with nCPAP does not result in an increase in Tw Pdi. It is therefore inferred that repeated episodes of upper airway occlusion of the severity seen in obstructive sleep apnea are insufficient to generate diaphragm fatigue. A discussion of the significance of the findings follows a critique of the method.

Critique of the methods

The mean Tw Pdi (22.3 cm H_2O) was slightly less than in previous studies on normal subjects.[16] It is therefore probable that despite stimulation at 100% of magnetic stimulator output, activation was not maximal. Increased soft tissue of the neck and upper back may have reduced that effectiveness of the cervical stimulation. Nevertheless, the critical issue is constancy of stimulation and providing stimulation is reproducible, submaximal stimulation can reliably detect diaphragm fatigue.[10] The variation between pre- and post-treatment values was not greater in the more obese subjects and we doubt therefore that this prevented the observation of a genuine rise in Tw Pdi after the institution of nCPAP.

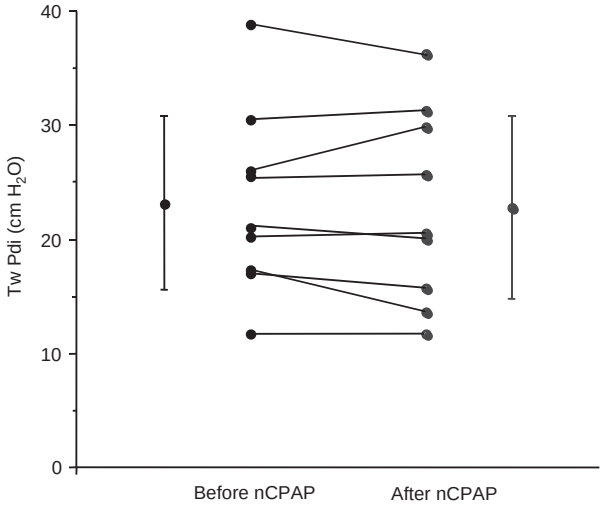

Figure 2 Twitch transdiaphramatic pressure (Tw Pdi) before and after nCPAP therapy. Individual data are shown together with the means and standard deviation.

The validity of the study rests on the patients having OSAS, and on nCPAP successfully treating the OSAS and the patients being compliant with therapy. Diagnostic studies using pulse oximetry are limited by the inability to identify and stage sleep and may also fail to accurately differentiate between obstructive and central apneas. Previous studies have shown that the sensitivity and specificity of oximetry for identifying OSA is dependent on the AHI. When screening patients with an AHI of $\geqslant$10 events/h, a sensitivity of 78% and specificity of 100% has been reported for oximetry.[17] In each of the three cases overnight oximetry revealed the repetitive saw-tooth desaturations characteristic of OSA. Furthermore, the automated nCPAP titration studies performed added confirmatory evidence of the existence of OSAS in all subjects studied.

A potential weakness of the study was the lack of repeat polysomnography and compliance data after the introduction of nCPAP therapy. However, the automated titration studies ensured that the correct pressure of nCPAP was selected which abolished apneic activity altogether. The subjects

Table 2 Respiratory muscle strength before and after nCPAP therapy.

Patient no.	Tw Pdi (cm H_2O)		Sn Pdi (cm H_2O)		Sn Pes (cm H_2O)		PI_{max} (cm H_2O)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	38.9	36.3	151.7	156.6	125.4	122.7	83.0	80.0
2	17.4	13.7	129.5	93.9	101.6	87.2	98.4	153.7
3	25.5	25.7	123.8	136.0	80.9	105.0	74.6	80.3
4	11.8	11.7	102.8	83.5	61.3	47.2	39.1	18.0
5	21.1	20.1	98.6	127.4	74.2	77.0	72.0	76.7
6	30.6	31.4	173.0	206.0	70.8	93.9	92.4	81.3
7	17.1	15.7	122.7	118.0	108.5	102.0	76.9	65.9
8	20.2	20.6	77.0	88.2	60.0	74.1	52.5	12.8
9	26.1	29.9	116.7	130.8	100.7	116.9	84.3	92.9
Mean (SD)	23.2 (7.7)	22.8 (8.1)	121.8 (26.9)	126.7 (36.2)	85.3 (22.3)	88.6 (21.5)	73.6 (18.4)	71.1 (40.9)

Tw Pdi, twitch transdiaphragmatic pressure; Sn Pdi, sniff transdiaphragmatic pressure; Sn Pes, sniff esophageal pressure; PI_{max}, maximum inspiratory mouth pressure. nCPAP pressure of nasal CPAP required to abolish apnoeic activity.

were chosen to participate in the study only if they had been compliant with the nCPAP therapy 1 month after its initiation. In addition, nCPAP therapy in all cases lead to a dramatic reduction in daytime sleepiness and returned the ESS to the normal range. Furthermore, at longer term follow up ranging between 4 months and 5 years, all subjects continued to use nCPAP, supporting the clinical value of the therapy.

We took great care to perform pre- and post-treatment studies at the same time of day because there is some evidence of a diurnal variation in skeletal muscle strength. Morning to evening variation has been measured in limb muscle, and tension found to be up to 8.9% higher in the evening whether measured by twitch, tetanic or maximal voluntary contractions.[18] For the respiratory muscles there are no data on twitch pressures, but mouth pressures were not found to exhibit diurnal variation in 16 healthy men studied by Aguilar et al.[19]

A second concern could be that low-frequency fatigue had resolved by the time the subjects were studied. The time interval between coming off nCPAP and attending the laboratory was approximately 2 h. A previous study from our own laboratory, in which low-frequency fatigue of the diaphragm was induced by 2 min of maximal isocapnic ventilation demonstrated some resolution of Tw Pdi within this time frame.[20] However, in another study, in which fatigue was induced using inspiratory resistive loading (a mechanism perhaps more appropriate to the situation in OSAS) a significant reduction in Tw Pdi was evident even after 24 h.[9]

Significance of the findings

The current data may represent an extension of our understanding of ventilatory failure. Ventilatory failure, as evidenced by carbon dioxide retention, is a recognized sequelae of longstanding severe OSAS.[21] One mechanism for this could be the development of inspiratory muscle fatigue. Our data from subjects with moderate to severe OSAS who have not yet developed ventilatory failure suggest that this is probably not the responsible mechanism in patients with OSAS.

The role of inspiratory muscle fatigue in ventilatory failure is disputed. It is well recognized that the respiratory muscles can show changes consistent with extreme loading (for example slowing of the relaxation rate[22] or EMG power spectrum[23]). Similarly heavy loading in normal subjects, whether in the form of whole body exercise or a task limited to the respiratory system, can lead to overt low-frequency fatigue as judged by a reversible fall in Tw Pdi.[20] It is less clear however whether low frequency fatigue contributes to ventilatory failure in practice. In this context the present data add to our previous studies in COPD[24,25] which also failed to find evidence of diaphragm fatigue in a clinical setting. In the case of COPD we attributed this, in part, to the protective effect of diaphragm shortening on the fatiguability of the muscle. This mechanism could not account for the lack of fatigue in untreated patients with OSAS. A more likely explanation in OSAS is a reduction in central respiratory drive due to abnormalities of central control, for example a blunting of central chemosensitivity. However, the failure to demonstrate low-frequency fatigue in OSAS reinforces the need for future studies of ventilatory failure to use the technique of phrenic nerve stimulation to confirm or refute the presence of low-frequency fatigue in clinical situations such as weaning failure, in which fatigue is currently considered to be relevant.

In summary, in subjects with OSAS treatment with nasal nCPAP despite resolving clinical symptoms failed to result in an increase in Tw Pdi. It is concluded that diaphragm fatigue in this study did not complicate OSAS.

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;**328**:1230–5.
2. Shivaram U, Cash ME, Beal A. Nasal continuous positive airway pressure in decompensated hypercapnic respiratory failure as a complication of sleep apnea. *Chest* 1993; **104**:770–4.
3. Wilcox PG, Pare PD, Road JD, Fleetham JA. Respiratory muscle function during obstructive sleep apnea. *Am Rev Respir Dis* 1990;**142**:533–9.
4. Griggs GA, Findley LJ, Surrat PM, Esau SA, Wilhoit SC, Rochester DF. Prolonged relaxation rate of inspiratory muscles in patients with sleep apnea. *Am Rev Respir Dis* 1989;**140**:706–10.
5. Montserrat JM, Kosmas EN, Cosio MG, Kimoff RJ. Lack of evidence for diaphragmatic fatigue over the course of the night in obstructive sleep apnea. *Eur Respir J* 1997;**10**: 133–8.
6. Cibella F, Cuttitta G, Romano S, Bellia V, Bonsignore G. Evaluation of diaphragmatic fatigue in obstructive sleep apnoeas during non-REM sleep. *Thorax* 1997;**52**:731–5.
7. Anonymous. NHLBI Workshop Summary. Respiratory muscle fatigue. Report of the Respiratory Muscle Fatigue Workshop Group. Am Rev Respir Dis 1990; 142: 474–80.
8. Polkey MI, Kyroussis D, Hamnegard CH, et al. Paired phrenic nerve stimuli for the detection of diaphragm fatigue in humans. *Eur Respir J* 1997;**10**:1859–64.

9. Laghi F, D'Alfonso N, Tobin MJ. Pattern of recovery from diaphragmatic fatigue over 24 h. *J Appl Physiol* 1995; **79**:539–46.
10. Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Quadriceps strength and fatigue assessed by magnetic stimulation of the femoral nerve in man. *Muscle & Nerve* 1996;**19**:549–55.
11. Rechtschaffen A, Kales AE. A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects. Bethesda and Washington: US Government Printing Office, Public Health Service, 1968. p. 1–12.
12. Wragg S, Hamnegard C, Road J, et al. Potentiation of diaphragmatic twitch after voluntary contraction in normal subjects. *Thorax* 1994;**49**:1234–7.
13. Wragg S, Aquilina R, Moran J, et al. Comparison of cervical magnetic stimulation and bilateral percutaneous electrical stimulation of the phrenic nerves in normal subjects. *Eur Respir J* 1994;**7**:1788–92.
14. Miller JM, Moxham J, Green M. The maximal sniff in the assessment of diaphragm function in man. *Clin Sci* 1985;**69**:91–6.
15. Laroche CM, Mier AK, Moxham J, Green M. The value of sniff esophageal pressures in the assessment of global inspiratory muscle strength. *Am Rev Respir Dis* 1988;**138**:598–603.
16. Hamnegard CH, Wragg SD, Mills GH, et al. Clinical assessment of diaphragm strength by cervical magnetic stimulation of the phrenic nerves. *Thorax* 1996;**51**:1239–42.
17. Williams AJ, Yu G, Santiago S, Stein M. Screening foe sleep apnea using pulse oximetry and a clinical score. *Chest* 1991;**100**:631–5.
18. Martin A, Carpentier A, Guissard N, van Hoecke J, Duchateau J. Effect of time of day on force variation in a human muscle. *Muscle & Nerve* 1999;**22**:1380–7.
19. Aguilar X, Fiz JA, Texido A, et al. Maximum inspiratory and expiratory pressures have no daytime variation in healthy men. *Respir Med* 1996;**90**:231–3.
20. Hamnegard CH, Wragg S, Kyroussis D, et al. Diaphragm fatigue following maximal ventilation in man. *Eur Respir J* 1996;**9**:241–7.
21. Berthon-Jones M, Sullivan CE. Time course of change of ventilatory response to CO_2 with longterm CPAP therapy for obstructive sleep apnea. *Am Rev Respir Dis* 1987;**135**:144–7.
22. Goldstone JC, Green M, Moxham J. Maximum relaxation rate of the diaphragm during weaning from mechanical venilation. *Thorax* 1994;**49**:54–60.
23. Pardy RL, Roussos C. Endurance of hyperventilation in chronic airflow limitation. *Chest* 1983;**83**:744–50.
24. Polkey MI, Kyroussis D, Keilty SE, et al. Exhaustive treadmill exercise does not reduce twitch transdiaphragmatic pressure in patients with COPD. *Am J Respir Crit Care Med* 1995;**152**:959–64.
25. Polkey MI, Kyroussis D, Hamnegard CH, et al. Diaphragm performance during maximal voluntary ventilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;**155**:642–8.