SLEEP DISORDERED BREATHING

Continuous Positive Airway Pressure and Breathlessness in Obese Patients with Obstructive Sleep Apnea: A Pilot Study

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Study Objectives: Continuous positive airway pressure (CPAP) is an effective treatment for obstructive sleep apnea (OSA). However, long-term compliance with CPAP is limited. We tested the hypothesis that CPAP levels routinely used during sleep increase neural respiratory drive (NRD) and breathlessness, which may discourage compliance.

Methods: This was an observational physiological cohort study in a respiratory physiology and sleep unit, University Hospital. Patients with a body mass index (BMI) > 25 kg/m^2 and confirmed OSA were studied supine and awake on CPAP (4–20 cm H_2O, increments of 2 cm H_2O/3 min). We measured NRD during awake CPAP titration in obese subjects to quantify the response to the load of the respiratory system and compared it to the CPAP used for nocturnal treatment, with the modified Borg Scale (mBorg) for dyspnea recorded (from 0 to 10 points, with higher numbers indicating more breathlessness).

Results: Fifteen patients (age 48 ± 10 years, 12 male, BMI 38.9 ± 5.8 kg/m^2) with OSA (AHI 32.2 ± 21.1/h, 95th percentile of CPAP 14.1 ± 3.8 cm H_2O) were studied and NRD (electromyogram of the parasternal intercostals, EMGpara; EMG of the external oblique, EMGabdomen) was recorded (awake, supine). Awake, EMGpara declined from baseline to 70.2% ± 17.1% when CPAP of 10.7 ± 3.4 cm H_2O (P = 0.026) was applied. Further increase in CPAP led to a rise in EMGpara and increased breathlessness (P = 0.02). CPAP compliance (nights used) correlated negatively with mBorg scores (r = −0.738, P = 0.006).

Conclusions: Awake, the respiratory system is maximally offloaded with lower than therapeutic CPAP levels in obese patients with OSA. Levels of NRD observed at effective CPAP levels while asleep are associated with breathlessness which may limit long-term CPAP compliance.

Keywords: neural respiratory drive, electromyography, parasternal intercostals

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Significance

The measurement of Neural Respiratory Drive (NRD) is helpful to determine optimal chest inflation when using Continuous Positive Airway Pressure (CPAP) therapy in awake and obese patients with Obstructive Sleep Apnea (OSA). However, pressures required for effective CPAP control while asleep can cause breathlessness in the awake patient and this might affect long-term compliance. Further work needs to be undertaken to understand whether non-obese subjects respond in a similar way to obese patients and if the adjustment of CPAP to optimize chest inflation and reduce levels of NRD can improve long-term compliance.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by recurring episodes of upper airway collapse, causing intermittent hypoxia, and fragmented sleep.[1] The prevalence of OSA is increasing, as many cases are linked to the obesity epidemic,[2] requiring effective long-term treatment strategies.

Continuous positive airway pressure (CPAP) is an effective treatment for OSA, maintaining upper airway patency while asleep.[3] Long-term therapeutic control of OSA requires good compliance, and the long-term uptake of CPAP is limited due to various factors. Although the numbers differ depending on the definition of compliance, roughly a quarter of patients on CPAP stop its usage within weeks, and at one-year follow-up less than half of the patients continue with regular use.[4,5]

OSA is associated with obesity which, in turn, can affect total lung capacity (TLC) and functional residual capacity (FRC), leaving morbidly obese subjects breathing close to the residual volume.[6] In obese subjects, CPAP helps to inflate the chest, increase functional residual capacity, decrease airway resistance and offload the respiratory muscles, particularly in the supine posture, and reduce neural respiratory drive (NRD), in addition to maintaining upper airway patency at night.[7]

Neural respiratory drive (NRD), as measured by the electromyogram (EMG) of the diaphragm or the parasternal muscles, reflects the response to the load on the respiratory system and is closely associated with breathlessness.[8–10]

In this study, obese patients with OSA were studied in the supine posture while awake to determine the point at which CPAP maximally offloads the respiratory system, as measured by the lowest levels of NRD and breathlessness. We hypothesized that the effective nocturnal CPAP level is higher than that required to maximally offload the respiratory system while awake due to the state-dependent contribution of the upper airway, which could result in breathlessness and impact on long-term compliance.

METHODS

Subjects

Overweight and obese subjects (> 18 years) with a body mass index (BMI) > 25 kg/m^2 and confirmed OSA were recruited from the Sleep Disorders Centre at Guy's & St Thomas' NHS Foundation Trust, London, UK. The study was approved by the local Research Ethics Committee and informed written consent was obtained from each patient.

Demographics

Patients were included if they had either an apnea-hypopnea index (AHI) > 15/h, or if they were symptomatic (Epworth Sleepiness

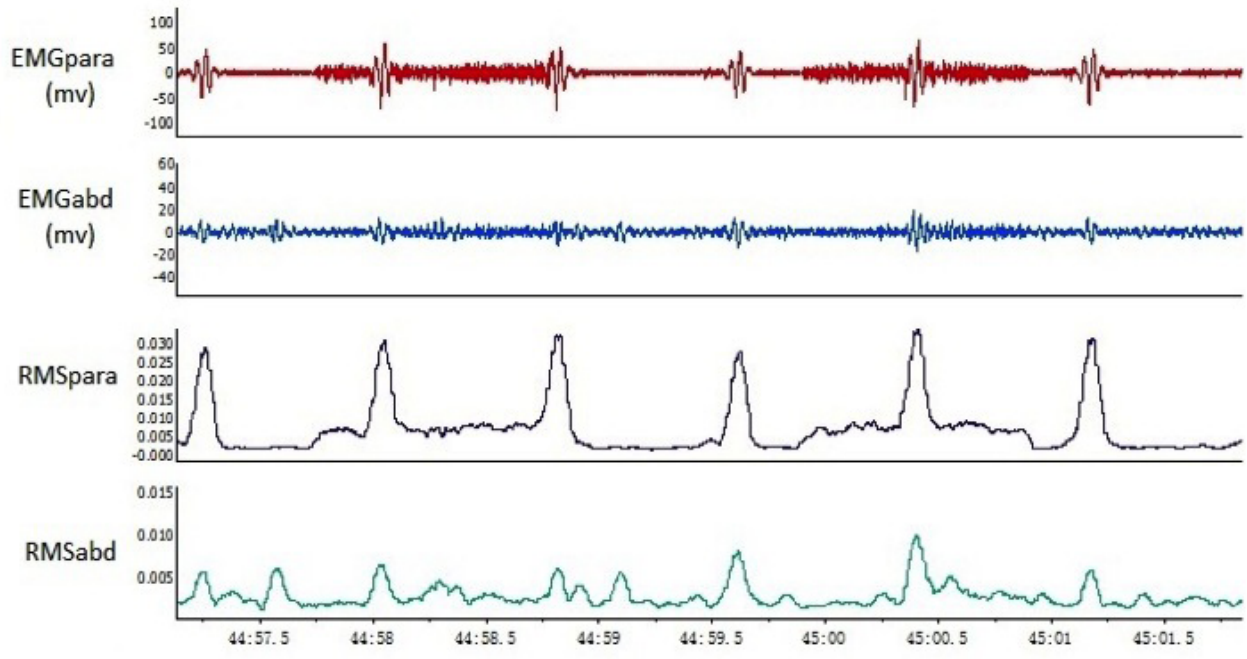

Figure 1—Screenshot of two inspiratory efforts. Channel 1 and 2 are the raw EMG signals of parasternal muscle and abdomen muscle activity (mV). Raw EMG signals are converted to root-mean-square (RMS) and shown in channel 3 and 4. The peak value of the RMS (time constant 100 ms) in each respiratory cycle during the final minute of each CPAP level was measured and the mean value among all of the cycles averaged, resulting in the mean value reported as "Neural Respiratory Drive" of the parasternal intercostals for the respective CPAP level.

Scale > 10 points) and had an AHI > 5/h. Anthropometric measurements included age, sex, height, weight, body mass index (BMI), neck, waist, and hip circumference, Mallampati score, and smoking history. The Epworth sleepiness scale was administered before the overnight polysomnography on CPAP titration.

CPAP Measurements, Asleep and Awake

CPAP during the titration night was determined by expert sleep technicians, as defined by the 95th percentile of CPAP level that was required to avoid upper airway occlusion (CPAP-*sleep*).[11] The next morning, the surface electromyogram of the parasternal muscles (EMG_{para}) and abdominal muscles ($EMG_{abdomen}$) was measured, as previously described.[6,7,12] For recording of the surface EMG_{para}, electrodes were placed on each side of the sternum 3 cm from the midline in the second intercostal space[12]; for the surface $EMG_{abdomen}$, one electrode was placed in the middle of a vertical line connecting the lower rib cage with the anterior superior iliac spine, with the subject standing. The other electrode was placed approximately 4–5 cm anterior to that location using surface electrodes (Kendall Arbo, Tyco Healthcare Neustadt, Germany).[6,7] Patients were then asked to rest on a bed to measure EMG activity during baseline breathing and titrate pressures, while awake.

Prior to any measurements, patients were asked to lie on a bed in a standardized supine position (legs straight and uncrossed, hands by their side with their palms facing down, and head/shoulders supported using a pillow so that the patient felt no effort to maintain head and neck posture) for 5 minutes. The surface EMG (EMG_{para}; $EMG_{abdomen}$) was then recorded for 3 minutes at baseline (without a CPAP mask). A further 3 minutes were recorded breathing with a CPAP mask (ResMed Mirage Quattro full face mask, ResMed Ltd, Oxfordshire, UK), open to air. After that, the surface EMG signal was recorded while the mask was attached to a CPAP machine (CPAP S8, Resmed Ltd, Oxfordshire, UK) and CPAP levels were changed stepwise from 4 cm H_2O to 20 cm H_2O, using increments of +2 cm H_2O, every level being recorded for at least 3 minutes, analyzing the EMG signals of the last minute of settled and stable breathing at each pressure level once a steady state was achieved (Figure 1). At the end of each level, patients were asked to score their perceived degree of breathlessness on a modified Borg Scale (mBorg) for dyspnea (from 0 to 10 points, with higher numbers indicating more breathlessness; see the supplemental material).[13] The protocol finished either when patients had reached a CPAP of 20 cm H_2O for > 3 min or when they felt that the pressures were unpleasant or caused significant breathlessness.

Data Analysis

The EMG data were amplified and band-pass filtered between 20 Hz and 1 kHz (Yinghui Medical Equipment Scientific Ltd, Guangzhou, China), saved, and analyzed using LabChart (Version 7.3.7, ADInstruments, Colorado Springs, CO, USA). Raw EMG signals were converted to root-mean-square (RMS), and all of the RMS of EMG was normalized to baseline RMS of the EMG recorded when the patients were breathing at rest, without mask, in the supine posture; the results were expressed as percent of baseline activity (%EMG, *baseline*). The mean value of RMS (time constant 100 ms) in the final minute of each pressure level (0–20 cm H_2O) was calculated to define NRD (Figure 1). Following daytime CPAP titration, the

Table 1—Demographics of patients.

Subject	Age (years)	Gender (F:M)	BMI (kg/m²)	Neck (cm)	Waist (cm)	Hip (cm)	W:H (ratio)	AHI (events/h)
1	34	M	32.6	45	110	115	0.96	28
2	38	M	37.2	43	127	129	0.98	23
3	54	F	49.7	41	160	145	1.10	10
4	57	M	27.9	43	122	97	1.26	51
5	54	M	40.4	51	138	130	1.06	77
6	54	M	42.6	47	133	130	1.02	19
7	49	M	36.7	46	126	109	1.16	23
8	48	M	38.7	48	139	115	1.21	20
9	37	F	37.3	38	110	120	0.92	52
10	53	M	30.8	44	114	124	0.92	40
11	62	M	41.5	47	127	126	1.01	16
12	46	F	36.4	41	119	118	1.01	20
13	60	M	44.7	52	128	130	0.98	25
14	31	M	44.9	54	148	127	1.17	69
15	37	M	42.1	50	126	124	1.02	9
Mean	**47.6**	**3:12**	**38.9**	**46.0**	**128.4**	**122.6**	**1.05**	**32.2**
SD	**9.9**		**5.8**	**4.5**	**13.8**	**11.1**	**0.10**	**21.1**

The group was predominantly male, middle-aged; all but two patients suffered with moderate-to-severe obstructive sleep apnea. F:M female and male participants. Neck, waist, and hip are reported as circumference, W:H is the waist-hip ratio.

pressure that led to the lowest level of NRD, as defined by the surface EMG_{para} and $EMG_{abdomen}$, was marked (CPAP-*awake*); this value was compared with CPAP-*sleep*.

Statistical Analysis

Data were statistically analyzed using SPSS (SPSS, Chicago, IL, USA). Following testing for normality, mBorg scale and surface EMG during CPAP titration in individual cases were expressed as mean ± SD. A one-way ANOVA was applied when mBorg scale and surface EMG were compared to baseline and maximal pressures, respectively. CPAP-*sleep* and CPAP-*awake* were compared using paired t-test; post hoc corrections were used for multiple comparisons. Statistical level of significance was defined with a P value < 0.05.

RESULTS

Fifteen patients with a confirmed diagnosis of OSA were studied. The patients were middle-aged and predominantly male (80%), and obese, with one patient being in the overweight category (number 4). The neck, waist, and hip circumference were elevated, with a waist-hip ratio > 1. Two patients had mild (number 3 and 15) and all others had moderate-severe obstructive sleep apnea (Table 1). Patients had relatively preserved lung function, as expressed by the age-, gender-, and height-adjusted percent predicted values (Table 2).

All but one patient completed the study protocol, reaching a CPAP level of 20 cm H_2O; subject number 2 stopped at 14 cm H_2O due to breathing "discomfort." Except for subject number 9, we observed in all patients that increasing levels of CPAP initially offloaded the respiratory system resulting in a clear reduction of EMG_{para} from baseline. Thereafter there was a substantial increase in EMG_{para} and/or $EMG_{abdomen}$ once the pressure levels for optimal chest inflation, as defined in the method section as CPAP-*awake*, had been exceeded (Figure 2A, 2B).

Table 2—Spirometry results.

Subject	FEV1 (L/%pred)	FVC (L/%pred)	FEV1/FVC (%)
1	3.49 / 81	4.66 / 89	75
2	4.13 / 102	5.09 / 103	81
3	1.43 / 70	1.59 / 65	90
4	3.64 / 106	4.13 / 96	88
5	3.09 / 86	3.80 / 84	81
6	3.00 / 83	3.85 / 85	78
7	2.77 / 76	3.53 / 79	79
8	2.35 / 62	3.79 / 80	62
9	1.88 / 83	2.68 / 101	70
10	3.16 / 99	3.60 / 91	88
11	2.45 / 75	3.62 / 86	68
12	1.53 / 63	2.25 / 80	68
13	3.13 / 93	4.01 / 93	78
14	4.28 / 90	5.49 / 95	78
15	3.57 / 92	4.50 / 95	79
Mean	**2.9 / 84.1**	**3.8 / 88.1**	**77.5**
SD	**0.9 / 13.3**	**1.0 / 9.8**	**8.0**

FEV1, forced expiratory volume in 1s in liters (L) and percent predicted (%pred); FVC, forced vital capacity in liters (L) and percent predicted (%pred); FEV1/FVC, ratio in percent.

The effect of CPAP on $EMG_{abdomen}$ was variable, but there was clear recruitment of abdominal muscles with higher pressures in 9/15 participants (number 4, 6–11, 14, and 15; Figure 2B).

CPAP-*awake*

The optimal level of chest inflation, as defined in the method section as CPAP-*awake*, achieved a reduction in EMG_{para} to 70.2% ± 17.7% of baseline activity (P = 0.026). At the end of the protocol (CPAP of 20 cm H_2O) EMG_{para} returned to 103.3 ± 49.3% of baseline activity.

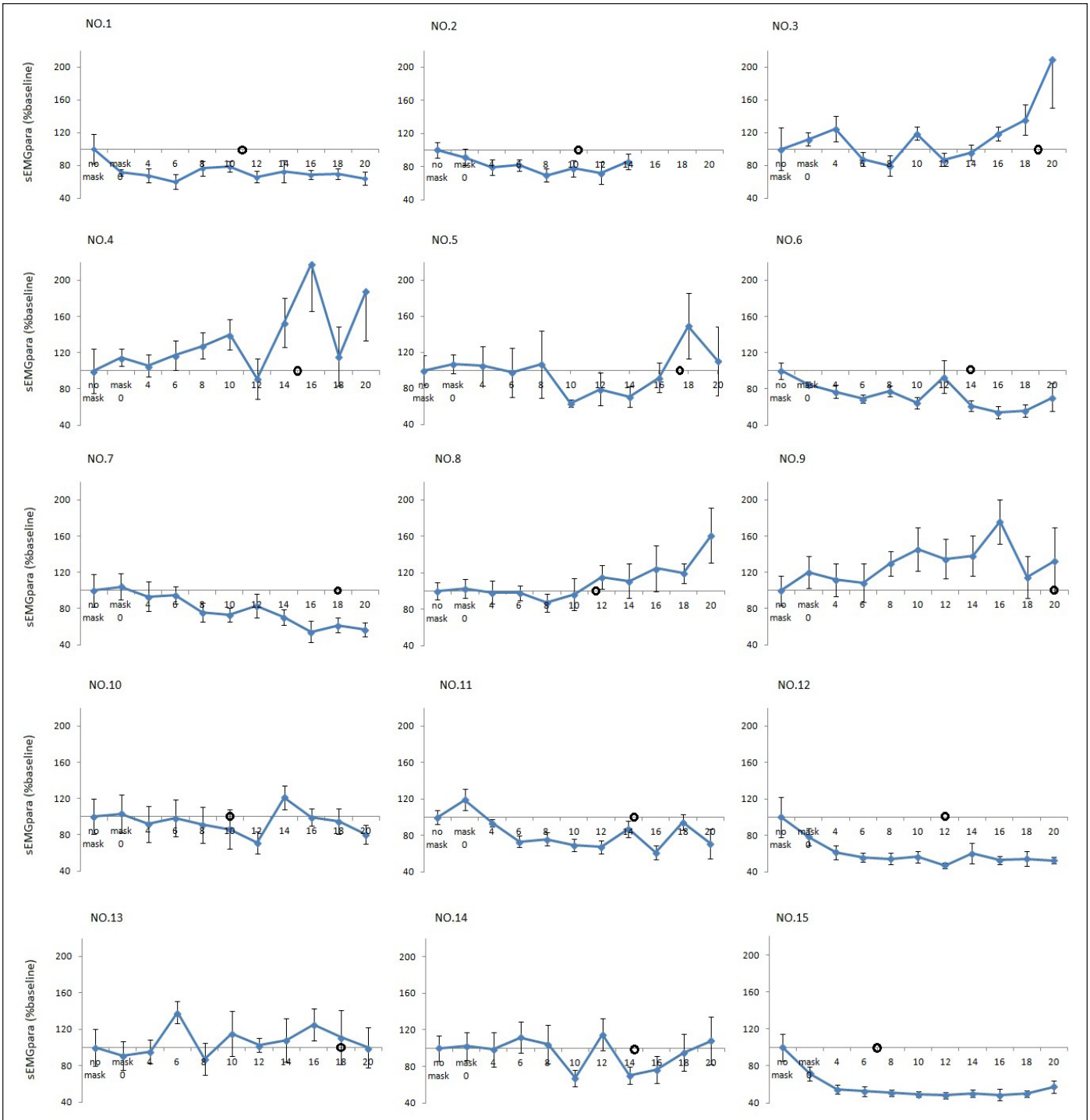

Figure 2A—Individual plots for the pressure titration up to a level of CPAP of 20 cm H_2O while awake. The surface EMG_{para} is plotted as percent of baseline activity (mean ± SD). Data are presented as percent of baseline activity (100%), breathing without CPAP mask, supine. The effective nocturnal CPAP level (95th percentile; CPAP-*sleep*) is indicated for each patient with an open circle on the x-axis. Subject No. 2 did not tolerate pressures above 14 cm H_2O.

$EMG_{abdomen}$ was significantly lower at CPAP-*awake* with 93.8% ± 9.3% of baseline activity (P < 0.001). At higher CPAP levels (20 cm H_2O), $EMG_{abdomen}$ increased and became highly variable (Figure 2B).

When CPAP pressures were increased above 6 cm H_2O, patients slowly started to feel more breathless, and with CPAP approaching 20 cm H_2O, the mBorg scale was significantly higher than at the beginning of the protocol, although there was high variability (Figure 3).

CPAP-*sleep*

The comparison of CPAP-*sleep* vs CPAP-*awake* revealed significant higher sleep pressures (P = 0.026). The mBorg scores recorded during daytime CPAP titration were compared with

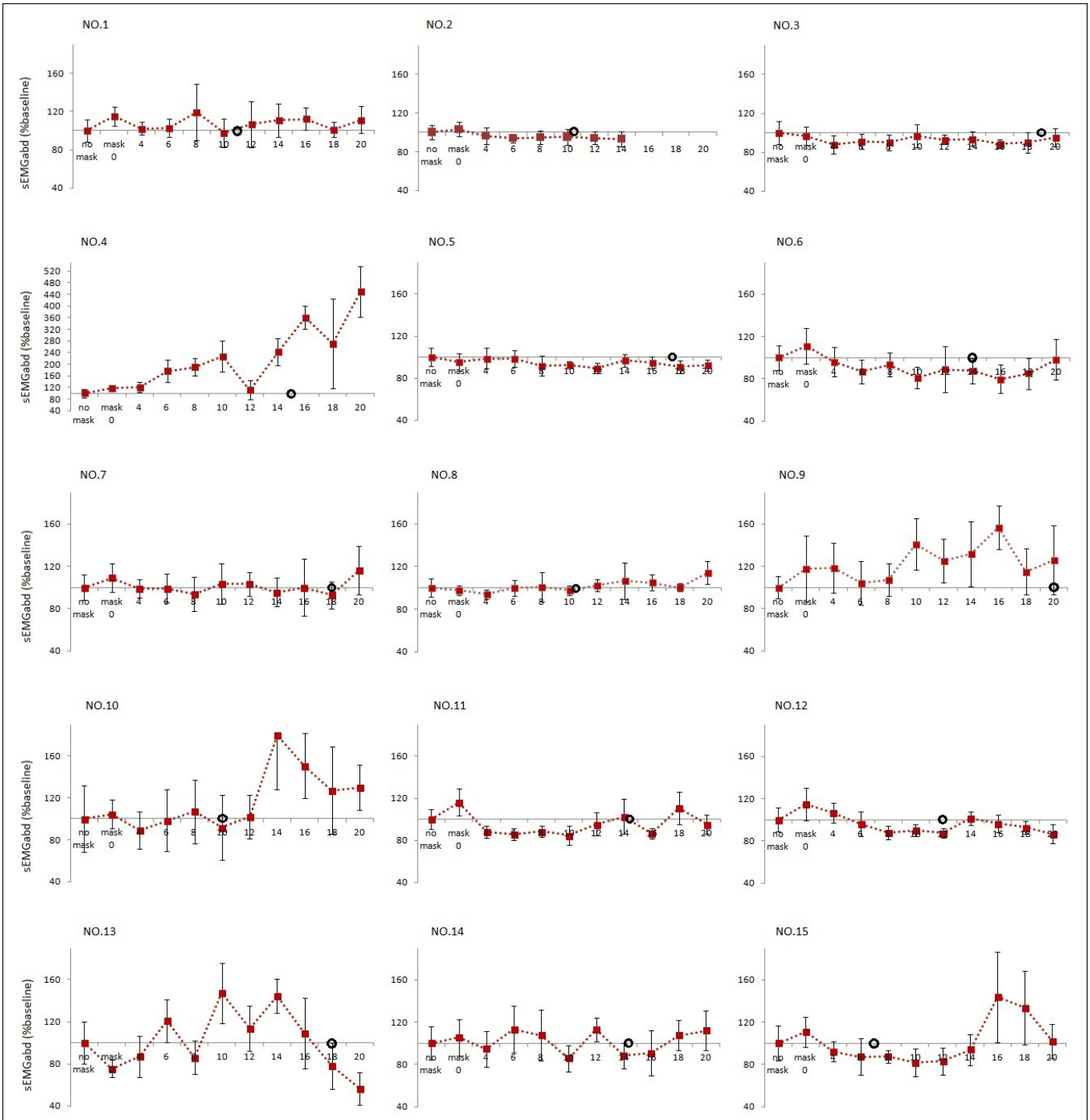

Figure 2B—Individual plots for the pressure titration up to a level of CPAP of 20 cm H_2O while awake. $EMG_{abdomen}$ is plotted as percent of baseline activity (mean ± SD). Data are presented as percent of baseline activity (100%), breathing without CPAP mask, supine. The effective nocturnal CPAP level (95th percentile; CPAP-*sleep*) is indicated for each patient with an open circle on the x-axis. The highly variable response in the $EMG_{abdomen}$ of subject No. 4 (430% of baseline activity) required an adjustment of the y-axis; subject No. 2 did not tolerate pressures above 14 cm H_2O.

CPAP-*sleep* and at effective nocturnal pressures patients scored higher than at CPAP-*awake* (P = 0.045; Table 3) although there was a variable response.

Changes in Inspiratory NRD during the Awake CPAP Titration

Responses in EMG_{para} with an increase in CPAP levels were:

1. EMG_{para} decreased (patient number 1, 2, 6, 7, 11, 12, & 15),
2. EMG_{para} increased (patient number 3, 4, 8, 9), or
3. EMG_{para} fluctuated with CPAP changes (patient number 5, 10, 13, 14; Table 4).

The group with a clear decrease in EMG_{para} had the lowest mBorg scores. In contrast, the group with an increase in EMG_{para} during CPAP titration expressed the highest levels

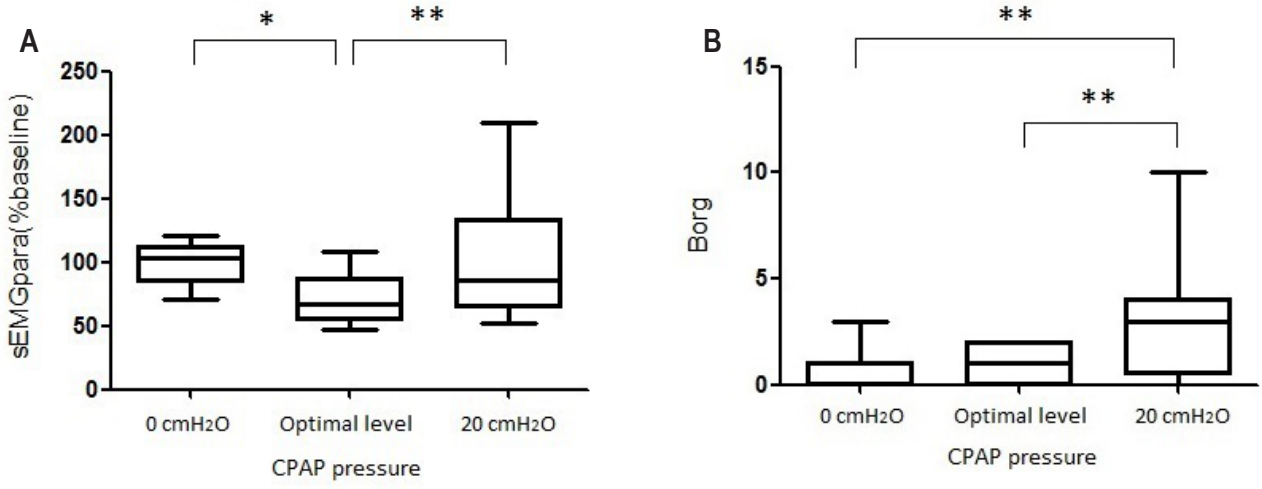

Figure 3—Box Whisker Plots for the whole cohort indicating the **(A)** EMG_{para} and **(B)** mBorg score at 0 cm H_2O, CPAP-*awake* and maximal pressures of 20 cm H_2O. The initial increase in CPAP results in a lower neural respiratory drive (NRD), but when the optimal level of chest inflation has been reached any further increase in CPAP leads to higher EMG activity (EMG_{para}) and breathlessness. *P < 0.05, **P < 0.01

Table 3—CPAP levels and breathlessness.

Subjects	CPAP-*awake* (cm H_2O)	Borg at CPAP-*awake*	CPAP-*sleep* (cm H_2O)	Borg at CPAP-*sleep*
1	6	0	10.9	0
2	8	1	10.4	2
3	8	1	18.8	6
4	12	2	15.0	3
5	10	1	17.5	3
6	16	2	14.0	2
7	16	0	18.0	0
8	8	1	10.5	1
9	6	2	20.0	3
10	12	0	10.1	0
11	16	1	14.6	1
12	12	0	12.0	0
13	8	0	17.9	1
14	10	2	14.6	3
15	12	1	7.0	0.5
Mean	**10.7**	**0.9**	**14.1**	**1.7**
SD	**3.4**	**0.8**	**3.8**	**1.7**

CPAP-*awake* and CPAP-*sleep* for each subject and the level of breathlessness they scored when being exposed to the respective pressure. Nocturnal pressures were higher (P < 0.026), and so were mBorg scores at CPAP-*sleep* compared to CPAP-*awake* (P < 0.05).

of breathlessness. The mBorg score for the group with a fluctuating change in EMG_{para} was between the other 2 groups. The group with the highest mBorg score had also the highest $EMG_{abdomen}$ (Table 4).

CPAP Compliance

The average CPAP compliance at 6-week follow-up was 2.8 ± 2.5 h of nocturnal usage during 46.5% ± 43.4% of the nights. Three patients (20%) were lost to follow-up during this period and eventually returned their CPAP machines. In order to determine whether CPAP compliance was associated with breathlessness, we compared those patients who had an increased mBorg score with higher CPAP levels (subject numbers = 2,3,4,5,9,13,14; Table 3) with those who did not. Patients were generally more breathless when tested on higher CPAP (r = 0.746, P = 0.001); higher CPAP levels were also correlated with an increased response in the mBorg scale (r = 0.561, P = 0.030). CPAP compliance, as measured by the number of nights used, correlated negatively with breathlessness scores at lower CPAP (CPAP-*awake*) levels (r = −0.738, P = 0.006).

DISCUSSION

This is the first study that has measured NRD and breathlessness during CPAP titration in overweight and obese patients with OSA while awake and related the findings to the effective CPAP level required to maintain airway patency when

Table 4—EMG subgroup analysis.

	CPAP 0 cm H_2O			CPAP-*awake*			CPAP 20 cm H_2O		
Subjects	**EMG_{para}**	**$EMG_{abdomen}$**	**Borg**	**EMG_{para}**	**$EMG_{abdomen}$**	**Borg**	**EMG_{para}**	**$EMG_{abdomen}$**	**Borg**
Group 1									
1	71.3	114.9	0	60.2	102.9	0	64.0	111.4	2
2	91.3	103.1	1	69.8	94.6	1	86.0	93.0	5
6	84.9	110.8	0	54.0	79.7	2	70.9	98.1	2
7	104.2	109.1	0	54.4	99.9	0	56.9	116.2	0
11	119.3	116.2	3	61.5	86.7	1	70.9	95.2	0
12	78.4	114.9	0.5	47.3	87.6	0	52.7	86.6	0
15	71.8	110.9	0	48.3	83.2	1	57.6	101.8	3
Mean	**88.7**	**111.4**	**0.6**	**56.5**	**90.7**	**0.7**	**65.6**	**100.3**	**1.7**
SD	**17.8**	**4.5**	**1.1**	**8.0**	**8.7**	**0.8**	**11.4**	**10.4**	**1.9**
Group 2									
3	112.1	96.6	3	79.8	90.0	1	209.3	95.4	10
4	114.4	118.0	0	91.5	111.6	2	188.3	449.5	3
8	102.8	97.6	0	87.3	100.8	1	160.8	114.1	4
9	120.3	117.8	0	108.8	104.3	2	133.3	126.0	3
Mean	**112.4**	**107.5**	**0.8**	**91.9**	**101.7**	**1.5**	**172.9**	**196.2**	**5.0**
SD	**7.3**	**12.0**	**1.5**	**12.3**	**9.0**	**0.6**	**33.0**	**169.3**	**3.4**
Group 3									
5	107.1	95.2	2	63.5	92.6	1	110.4	92.2	3
10	103.3	104.3	0	71.0	102.1	0	80.4	130.0	0.5
13	91.2	75.5	0.5	87.7	85.9	0	99.8	56.4	1
14	102.2	105.5	1	67.3	85.6	2	108.2	111.9	6
Mean	**101.0**	**95.1**	**0.9**	**72.4**	**91.6**	**0.8**	**99.7**	**97.6**	**2.6**
SD	**5.9**	**12.0**	**0.7**	**9.2**	**6.7**	**0.8**	**11.8**	**27.3**	**2.2**

Differences between three groups of responders, (1) reduction in EMG_{para}, (2) increase in EMG_{para}, and (3) fluctuating response. The lowest levels of breathlessness were observed in the group with lower EMG activity (group 1), while the group with high EMG_{para} also had a high $EMG_{abdomen}$ activity (group 2). EMG data were reported as percent of baseline activity (100%).

asleep (CPAP-*sleep*). CPAP effectively offloads the respiratory system in obese subjects, when awake, and reduced NRD by 30%. Breathlessness is not experienced when NRD is reduced. However, when CPAP was increased to higher pressures, NRD, as reflected by activity of the parasternal intercostals and the expiratory muscles, increased and patients became breathless.

There is a discrepancy between CPAP levels associated with lowest levels of NRD and breathlessness while awake and the level of CPAP required to control of the upper airway when asleep. This makes it likely that breathlessness develops when using CPAP at higher than comfortable levels, influencing long-term compliance. This mismatch between comfortable and required pressures could explain the low adherence to CPAP therapy at six weeks. Breathlessness is likely to be a problem before sleep onset and when patients periodically wake during the night.

The standard way to titrate CPAP, either by manual titration or via an automated algorithm, is to abolish the physiological correlate of upper airway obstruction and to reduce apneas and hypopneas.[11] This results in pressures being increased until upper airway patency is restored and airway resistance remains low. This approach does not consider the impact of high CPAP levels on sleep quality. In contrast, adjusting CPAP by daytime to lower pressures results in residual apneas and hypopneas with an elevated apnea-hypopnea index (AHI) which also leads to increased sleep fragmentation. However, with lower pressures sleep quality might be less disturbed, sleep onset and wake after sleep onset could be diminished, and some patients may symptomatically benefit due to better CPAP adherence. Considering that the alternative to optimizing CPAP levels to acceptable pressures might be non-compliance, there may be an argument to consider daytime CPAP titration to subjectively better tolerated pressures.

Clinical Implications

CPAP therapy remains the treatment of choice for patients with moderate-severe OSA.[14] Non-CPAP alternatives are predominantly available for mild OSA,[15] but with the increase in prevalence of OSA,[2] alternative solutions are needed to meet the need of patients with moderate-severe OSA who fail long-term CPAP therapy. Patients on CPAP are likely to stop their treatment the longer the intervention is delivered. Depending on the definition of compliance and the system used approximately a quarter of patients are noncompliant after 6 weeks and more than half do not use CPAP after 1-year.[4] Investigators have sought to understand the problem behind the reluctance of patients to continue with CPAP therapy and different interventions to improve adherence have been tried, patient education is considered important.[16]

Hitherto the importance of breathlessness has not been studied in the context of CPAP compliance in OSA. Obese subjects breathe at low lung volumes, often close to residual

volume.[6] Employing CPAP to stent the upper airway inflates the chest, abolishes intrinsic positive end-expiratory pressure (PEEPi) in the supine posture[7,17] and shifts the tidal volume to a more-favorable part on the pressure-volume (PV) curve thereby improving compliance of the respiratory system and reducing the work of breathing and NRD.[7] With CPAP the initial response in obese patients is to shift functional residual capacity (FRC) to volumes normal for their age, gender, and height, but when pressures are further increased the chest is inflated beyond normal levels of FRC. With hyperinflation the work of breathing increases, reflected by an increase in EMG_{para}. At this stage, patients also recruit expiratory muscles to exhale towards a lower and more normal FRC, as we observed with higher levels of CPAP and abdominal muscle EMG activity ($EMG_{abdomen}$). In this situation, neural respiratory drive (NRD) and the sensation of breathlessness increase. As a consequence, patients who have their CPAP levels set at pressures higher than those well tolerated when awake (CPAP-*sleep* > CPAP-*awake*) experience discomfort and breathlessness. It is plausible that patients who try to fall asleep or wake up at night feeling breathless because of high CPAP levels will stop treatment in the long term, and we have shown that CPAP compliance is associated with breathlessness. To solve this problem, would a lower level of CPAP, potentially at a subtherapeutic level, improve compliance? Could an autotitrating CPAP device avoid breathlessness by adjusting pressure downwards in these patients who wake at night? It would be of interest to understand whether CPAP adherence could be improved by adjusting pressures according to the level of breathlessness and/or NRD. The fact that we found different physiological responses with CPAP titration also raises the question of what defines different phenotypes; the measurement of esophageal and gastric pressures could aid understanding of different responses.

Neural Respiratory Drive and Different Respiratory Muscle Groups

To understand the complexity of EMG activity in sleep, it is important to address specific activity of different muscle groups (cranial *vs* spinal innervation, respiratory *vs* non-respiratory, antigravity muscles) and differentiate between tonic and phasic EMG. Loss of neuromuscular tone in sleep affects various muscle groups in different ways; of the respiratory muscles the diaphragm is least affected by atonia while pharyngeal dilator muscles are highly sensitive. EMG of the parasternal intercostals, although closely related to the diaphragm EMG activity,[8] is not interchangeable with the activity of other respiratory muscles. However, it is a marker for disease severity in chronic respiratory conditions like cystic fibrosis,[8] COPD,[9] and asthma,[12] or obesity-related respiratory conditions,[7] and there is a high correlation with the EMG of the diaphragm and modified Borg scores.[8] The easy access and reproducibility of the surface signal make the EMG of the parasternal intercostals a useful target muscle for noninvasive monitoring of respiratory muscle activity.

In normal subjects neural respiratory drive, as measured by the diaphragm EMG, and ventilation fall at sleep onset.[18] In NREM sleep the respiratory muscles that are active when awake continue to be active, although less so than when awake. However, in REM sleep ventilation is predominantly supported by the diaphragm in normal healthy subjects and other inspiratory muscles (e.g., intercostals) are relatively silent.[19,20] The relative contribution of state-dependent airway resistance shifts when subjects fall asleep, particularly with upper airway obstruction. In the awake state, upper airway patency is usually well maintained and most of the work of breathing is related to the lower respiratory system, compliance and degree of chest inflation, posture, and ventilatory demand. However, in OSA patients, upper airway occlusion in sleep leads to a complex interaction of upper airway dilator tone, NRD to the diaphragm and, usually, arousal from sleep associated with a peak of EMG activity. Upper airway dilator muscles are more affected by the loss of neuromuscular tone in sleep than the diaphragm, but breathing against a high resistance (occluded airway) triggers a central inhibitory reflex that limits inspiratory muscle activity.[21–23]

Consequently, it is difficult to define a stable state of sleep in which CPAP would achieve a minimization of NRD to the inspiratory muscles other than during upper airway patency in the asleep OSA patient. However, the level of CPAP-*sleep* can be compared against CPAP-*awake* which identifies "optimal" levels of NRD at the nadir, as patients will become aware of unfavorable levels of NRD when they try to fall asleep/wake up—a sensation that will affect their decision to continue with treatment or remove the interface.

Breathlessness and Sleep: A Hypothetical Construct

"Breathlessness" is a subjectively reported symptom. However, the physiology, in the case of OSA during sleep, follows the sensation and without sensation during sleep, in theory, there is no breathlessness. Hypothetically, breathlessness is not compatible with sleep as it requires the subject to report the symptom,[24] and this is impossible. Consequently, physiological parameters associated by daytime with the sensation of breathlessness usually settle when the patient is asleep—although respiratory disturbance due to afferent feedback of increased respiratory demand may continue in the case of OSA. It is therefore not possible to take a firm view on whether patients feel breathless while asleep, but it is not unthinkable that certain parameters, airway resistance leading to increased work of breathing, hypoxia, or hypercapnia could lead to an increased afferent feedback when asleep which could trigger arousal from sleep, influence sleep stages, and lead to a more superficial and fragmented sleep architecture and reduced sleep quality.

Limitations

Multidimensional Sensation of Breathlessness

Breathlessness is not only a unidimensional sensation resulting from a singular function, in this case the respiratory muscles. The current standard to assess breathlessness is described in the "Multidimensional Dyspnea Profile."[25] The American Thoracic Society (ATS) statement defines dyspnea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity," and that dyspnea "*per se* can only be perceived *by the person*

experiencing it."[24] It is therefore important to define the way that patients report the symptom, as clinical assessment and tests usually do not correlate well.[26] There are at least three domains—sensory-perceptual experience, affective distress, and symptom impact or burden—interfering with the perception of the symptom, and data on brain-imaging technology demonstrate that dyspnea activates cortico-limbic structures.[24] In the current setting—a physiology laboratory-based assessment of a group of patients with OSA wearing a full-face mask—the modified 10-point Borg scale was chosen, consistent with latest studies evaluating intensity of this symptom.[27,28] Despite potential limitations and biases due to subjective reports the measurement of breathlessness requires the patient-reported symptom to be quantified.[26] In this context, respiratory muscle activity as a marker for intensity of dyspnea falls into the sensory dimension ("physical breathing effort," "air hunger").[25]

Lower vs Higher CPAP

This was a relatively small pilot study, exploring the hypothesis that NRD could be used to optimize CPAP levels for obese patients with OSA. Despite insights into optimal inflation of the respiratory system, breathlessness and potential explanations why patients are less likely to have good long-term adherence, these data demonstrate the need for further investigation. It remains unclear whether non-obese patients show a similar pattern of breathlessness. Whether long-term compliance with CPAP can be improved using optimal levels of NRD is another hypothesis that needs to be tested. In this context, it is crucial to understand what impact lower therapeutic CPAP levels would have on the long-term compliance and outcomes in OSA. Could a slightly lower therapeutic pressure with improved compliance be superior to an effective CPAP level with lower compliance? Furthermore, it has to be considered that manually titrated CPAP levels can be lower than autotitrated pressures,[29] and prospective studies could address the efficacy following measurement of NRD to differentiate between lower therapeutic and sub-therapeutic CPAP.

It is difficult to obtain good quality EMG signals in routine clinical setting. This technique requires expertise, equipment (hardware and software) and is time-intense. It is unlikely that EMG measurements of the respiratory muscles will become a feasible method to adjust CPAP in the usual clinical setting, but this method could be considered for the assessment in tertiary referral centers to support patients who have failed standard CPAP therapy.

Lung Volume Measurements

We have previously shown that CPAP reduces the response to the load of the respiratory system, effectively reducing neural respiratory drive.[7] Obese subjects breathe at low lung volumes, close to residual volume.[6] Using CPAP is likely to improve chest compliance, work of breathing, and NRD by placing the respiratory system on a more compliant portion of the PV curve. Consequently, very high pressures of CPAP are likely to push the functional residual capacity further up the pressure-volume (PV) curve and closer to total lung capacity (TLC). This, again, is a less compliant lung volume with consequences for the work of breathing. However, in this pilot study we have not measured lung volumes and future work should include these measures (e.g., by spirometry, Respitrace, or magnetometers) as well as markers for the work of breathing (e.g., esophageal pressures, transdiaphragmatic pressures), as the individual lung volume can be highly variable.

Contribution of Volitional Breathing

Volitional activity of respiratory muscles, particularly the expiratory muscles, might have, in part, contributed to EMG activity recorded during CPAP titration. In order to minimize the volitional component, EMG signals were recorded at each level of pressure for at least 3 minutes, until a stable and reproducible breathing pattern was adopted. The last minute of EMG data at each level was analyzed and averaged to reduce contributions of volitional respiratory variations. Particularly the recruitment of expiratory muscle activity could have influenced the sensation of discomfort. However, any impact of volitional variation of the breathing pattern is likely to be higher in incremental exercise protocols than at rest and EMG signals during exercise protocols are recorded with acceptable reproducibility at "pseudo-steady state."[30]

Inspiratory and Expiratory EMG Signals to Define CPAP-awake

The absolute EMG signal was significantly higher for the EMGpara (inspiratory) than for the EMGabdomen (expiratory) muscles due to a closer contact, less filtering due to adipose tissue and higher EMG activity. The EMGpara was therefore leading in the decision to define what was the nadir of NRD at CPAP-*awake* and in all patients the recording of the parasternal and the abdominal EMG agreed in defining CPAP-*awake*. However, CPAP levels at which there is more marked EMGabdomen activity are an important indication for when the respiratory system begins to recruit additional muscle function and they define a point at which subjects/patients often start to feel more breathless.

Variability of EMG Response

Despite the variability of the EMG response, seven patients (7/15 = 46.7%) reported a higher modified Borg score at CPAP-*sleep* than at CPAP-*awake*, reflecting a change in the level of discomfort. The minimally clinically important difference for the Borg score has been reported as one point ("1").[31] Considering the relatively high rate of noncompliant patients on CPAP,[32] it is reasonable to postulate that even a modest increase in the degree of breathlessness can disturb nighttime rest and sleep quality.

CONCLUSIONS

The measurement of NRD is helpful to determine optimal respiratory support using CPAP therapy in awake and obese patients. However, the discrepancy between awake pressures and those required for effective CPAP control while asleep raises the question whether patients on CPAP experience breathlessness and whether this affects their long-term compliance. Further work needs to be undertaken to understand whether non-obese subjects respond in a similar way to obese patients and if the adjustment of CPAP to optimize chest inflation and reduce levels of NRD can improve long-term compliance.

REFERENCES

1. Remmers JE, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. J Appl Physiol Respir Environ Exerc Physiol 1978;44:931–8.
2. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013;177:1006–14.
3. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnea by continuous positive airway pressure applied through the nares. Lancet 1981;1:862–5.
4. Collard P, Pieters T, Aubert G, Delguste P, Rodenstein DO. Compliance with nasal CPAP in obstructive sleep apnea patients. Sleep Med Rev 1997;1:33–44.
5. Chai-Coetzer CL, Luo YM, Antic NA, et al. Predictors of long-term adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea and cardiovascular disease in the SAVE study. Sleep 2013;36:1929–37.
6. Steier J, Lunt A, Hart N, Polkey MI, Moxham J. Observational study of the effect of obesity on lung volumes. Thorax 2014;69:752–9.
7. Steier J, Jolley CJ, Seymour J, Roughton M, Polkey MI, Moxham J. Neural respiratory drive in obesity. Thorax 2009;64:719–25.
8. Reilly C, Ward K, Jolley CJ, et al. Neural respiratory drive, pulmonary mechanics and breathlessness in patients with cystic fibrosis. Thorax 2011;66:240–6.
9. Jolley CJ, Luo YM, Steier J, Rafferty GF, Polkey MI, Moxham J. Neural respiratory drive and breathlessness in chronic obstructive pulmonary disease. Eur Respir J 2015;45:355–64.
10. Jolley CJ, Luo YM, Steier J, et al. Neural respiratory drive in healthy subjects and in COPD. Eur Respir J 2009;33:289–97.
11. Positive Airway Pressure Titration Task Force of the American Academy of Sleep Medicine: Kushida CA, Chediak A, Berry RB, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med 2008;4:157–71.
12. Steier J, Jolley CJ, Polkey MI, Moxham J. Nocturnal asthma monitoring by chest wall electromyography. Thorax 2011;66:609–14.
13. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–81.
14. National Institute of Clinical Excellence (NICE) technology appraisal guidance (TA139). CPAP for OSA costing template and report. 2008. www.nice.org.uk/guidance/ta139.
15. Randerath WJ, Verbraecken J, Andreas S, et al. Non-CPAP therapies in obstructive sleep apnoea. Eur Respir J 2011;37:1000–28.
16. Smith I, Nadig V, Lasserson TJ. Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines for adults with obstructive sleep apnoea. Cochrane Database Syst Rev 2009;15:CD007736.
17. Pankow W, Podszus T, Gutheil T, Penzel T, Peter J, Von Wichert P. Expiratory flow limitation and intrinsic positive end-expiratory pressure in obesity. J Appl Physiol 1998;85:1236–43.
18. Colrain IM, Trinder J, Fraser G, Wilson GV. Ventilation during sleep onset. J Appl Physiol 1987;63:2067–74.
19. Steier J, Jolley CJ, Seymour J, et al. Sleep-disordered breathing in unilateral diaphragm paralysis or severe weakness. Eur Respir J 2008;32:1479–87.
20. Johnson MW, Remmers JE. Accessory muscle activity during sleep in chronic obstructive pulmonary disease. J Appl Physiol 1984;57:1011–7.
21. Jeffery S, Butler JE, McKenzie DK, Wang L, Gandevia SC. Brief airway occlusion produces prolonged reflex inhibition of inspiratory muscles in obstructive sleep apnea. Sleep 2006;29:321–8.
22. Steier J, Jolley CJ, Seymour J, et al. Increased load on the respiratory muscles in obstructive sleep apnea. Respir Physiol Neurobiol 2010;171:54–60.
23. Davis JN, Sears TA. The proprioceptive reflex control of the intercostal muscles during their voluntary activation. J Physiol 1970;209:711–38.
24. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 2012;185:435–52.
25. Banzett RB, O'Donnell CR, Guilfoyle TE, et al. Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. Eur Respir J 2015;45:1681–91.
26. Banzett RB, Schwartzstein RM. Dyspnea: don't just look, ask! Am J Respir Crit Care Med 2015;192:1404–6.
27. Faisal A, Alghamdi BJ, Ciavaglia CE, et al. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. Am J Respir Crit Care Med 2016;193:299–309.
28. Jolley CJ, Moxham J. Dyspnea intensity: a patient-reported measure of respiratory drive and disease severity. Am J Respir Crit Care Med 2016;193:236–8.
29. Luo J, Xiao S, Qiu Z, Song NS, Luo YM. Comparison of manual versus automatic continuous positive airway pressure titration and the development of a predictive equation for therapeutic continuous positive airway pressure in Chinese patients with obstructive sleep apnoea. Respirology 2013;18:528–33.
30. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167:1451–2.
31. Oxberry SG, Bland JM, Clark AL, Cleland JG, Johnson MJ. Minimally clinically important difference in chronic breathlessness: every little helps. Am Heart J 2012;164:229–35.
32. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. Sleep Med Rev 2011;15:343–56.

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