Eur Respir J 2008; 32: 1479–1487
DOI: 10.1183/09031936.00018808

Sleep-disordered breathing in unilateral diaphragm paralysis or severe weakness

J. Steier*, C.J. Jolley*, J. Seymour*, S. Kaul*, Y.M. Luo#, G.F. Rafferty*, N. Hart¶, M.I. Polkey+ and J. Moxham*

ABSTRACT: **Few data exist concerning sleep in patients with hemidiaphragm paralysis or weakness. Traditionally, such patients are considered to sustain normal ventilation in sleep.**

In the present study, diaphragm strength was measured in order to identify patients with unilateral paralysis or severe weakness. Patients underwent polysomnography with additional recordings of the transoesophageal electromyogram (EMG) of the diaphragm and surface EMG of extra-diaphragmatic respiratory muscles. These data were compared with 11 normal, healthy subjects matched for sex, age and body mass index (BMI).

In total, 11 patients (six males, mean±SD age 56.5±10.0 yrs, BMI 28.7±2.8 kg·m^{-2}) with hemidiaphragm paralysis or severe weakness (unilateral twitch transdiaphragmatic pressure 3.3±1.7 cmH_2O (0.33±0.17 kPa) were studied. They had a mean±SD respiratory disturbance index of 8.1±10.1 events·h^{-1} during non-rapid eye movement (NREM) sleep and 26.0±17.8 events·h^{-1} during rapid eye movement (REM) sleep (control groups 0.4±0.4 and 0.7±0.9 events·h^{-1}, respectively). The diaphragm EMG, as a percentage of maximum, was double that of the control group in NREM sleep (15.3±5.3 *versus* 8.9±4.9% max, respectively) and increased in REM sleep (20.0±6.9% max), while normal subjects sustained the same level of activation (6.2±3.1% max).

Patients with unilateral diaphragm dysfunction are at risk of developing sleep-disordered breathing during rapid eye movement sleep. The diaphragm electromyogram, reflecting neural respiratory drive, is doubled in patients compared with normal subjects, and increases further in rapid eye movement sleep.

KEYWORDS: **Electromyogram, rapid eye movement sleep, respiratory muscles**

Patients with diaphragm paralysis may develop breathlessness as a consequence of the reduced capacity of the respiratory system [1, 2]. During sleep in normal subjects, ventilation depends particularly on diaphragm function [3]. In patients with diaphragm dysfunction, during both rapid eye movement (REM) sleep and wakefulness, electromyographic activity of the extradiaphragmatic respiratory muscles [4–7] is higher than normal as a compensation for diaphragm weakness.

The results of studies looking at breathing patterns in unilateral or bilateral diaphragm paralysis (UDP and BDP, respectively) have been inconsistent [8–13]. Some studies have reported disturbed sleep, inadequate ventilation during sleep and daytime sleepiness caused by diaphragm dysfunction [8, 11], while others have found little impact on the normal sleep pattern unless there is additional load on the ventilatory system [9, 10, 14]. Previous studies either did not focus on UDP (had mixed populations of BDP and UDP [8, 9] or exclusively BDP [5, 11] patients), did not distinguish between REM and non-REM (NREM) sleep-associated sleep-disordered breathing (SDB) [10], did not characterise the subjects other than with noninvasive measurements [15] or studied animal models. Therefore, the studies that did not perform invasive respiratory muscle tests did not test a homogenous population of UDP patients and it is likely that the different results reflect the heterogeneity of the patients studied, in terms of weakness and ventilatory load.

Clinically it is often assumed that patients with UDP have no problems during sleep unless other comorbidities are present [9, 10]. It has previously been noted that some patients with

AFFILIATIONS
*King's College London School of Medicine, King's College Hospital,
¶St Thomas' Hospital,
+Royal Brompton Hospital, London, UK.
#Guangzhou Medical College, The State Key Laboratory of Respiratory Disease, Guangzhou, China.

CORRESPONDENCE
J. Steier
King's College London School of Medicine
King's College Hospital
Chest Unit
2nd floor Cheyne Wing
Denmark Hill
London SE5 9PJ
UK
Fax: 44 2032993589
E-mail: joerg.steier@kcl.ac.uk

Received:
February 07 2008
Accepted after revision:
July 20 2008

SUPPORT STATEMENT
J. Steier is a recipient of a Long-Term Research Fellowship from the European Respiratory Society (No. 18).

STATEMENT OF INTEREST
Statements of interest for C.J. Jolley, Y.M. Luo and J. Moxham can be found at www.erj.ersjournals.com/misc/statements.shtml

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

This article has supplementary material accessible from www.erj.ersjournals.com

clinically diagnosed UDP present with daytime symptoms, including breathlessness and sleepiness [14]. In these patients, SDB and, in particular during phases of REM sleep, hypoventilation could occur [8].

Hypothesis

The current authors hypothesised that patients with unilateral diaphragm paralysis or severe weakness and no other respiratory abnormalities could develop SDB during REM sleep. Therefore, a group of UDP patients was investigated during sleep. To the authors' knowledge, this is the first study looking at REM sleep-related SDB in an accurately diagnosed population with UDP.

METHODS, MATERIALS AND PATIENTS

Study subjects

In total, 39 patients referred with a clinical diagnosis of hemidiaphragm paralysis had comprehensive respiratory muscle function assessment. These tests demonstrated that 14 of them had BDP, 17 had UDP or severe weakness and eight had normal diaphragm function. Of the patients with UDP or severe weakness, 11 consented to polysomnography. All had a unilateral twitch transdiaphragmatic pressure (P_{di}) of <6 cmH_2O (0.6 kPa) with normal twitch pressures on the contralateral side.

Additionally, 11 normal subjects served as a control group. All participants gave written consent. The study was approved by King's College Hospital Research Ethics Committee (London, UK).

Methods

The following assessments were made. Additional detail on the methods for making these measurements is provided in the online supplementary material.

Questionnaires

The Medical Research Council (MRC) dyspnoea scale, the Chronic Respiratory Diseases Questionnaire (CRDQ), the St George's Respiratory Questionnaire (SGRQ) and the Epworth Sleepiness Scale (ESS) were used. The history of changes in sleep, problems with posture and breathlessness was also noted.

Lung function tests and arterialised earlobe blood gases

The patients underwent spirometry according to the British Thoracic Society guidelines [16]. Vital capacity (VC) was measured in sitting and supine positions. Arterialised earlobe blood was collected into a capillary tube and analysed (Bayer Rapidlab 248®; Diamond Diagnostics®, Holliston, MA, USA).

Respiratory muscle tests

Inspiratory, diaphragm-specific and expiratory muscle strengths were measured according to the American Thoracic Society/European Respiratory Society statement on respiratory muscle testing [17].

Electromyogram of the diaphragm

A multipair electrode catheter (developed by Y.M. Luo; Yinghui Medical Tech Ltd®, Guangzhou, China) was inserted *via* one nostril to record the transoesophageal electromyogram (EMG) of the diaphragm (EMG_{di}), as previously described [18, 19], connected to RA-8® amplifiers (Yinghui Medical Tech Ltd®) that further transmitted the signal to an analogue-to-digital converter, Powerlab® 16/30 (ADInstruments®, Colorado Springs, CO, USA), running Chart® 5.4 (ADInstruments®).

Compound muscle action potential (CMAP) amplitude and latency after magnetic stimulation of the phrenic nerves were measured. Reference values for the right phrenic nerve are CMAP mean$\pm$SD 1.45$\pm$0.35 mV and latency 6.9$\pm$0.9 ms, and for the left phrenic nerve CMAP 1.68$\pm$0.47 mV and latency 7.6$\pm$0.7 ms [20].

EMG of extradiaphragmatic respiratory muscles

The EMG of the neck muscles (EMG_{neck}), parasternal intercostals and abdominal muscles was recorded using surface electrodes (Kendall Arbo®; Tyco Healthcare®, Neustadt, Germany) from standard positions [21–24].

The EMG was recorded during the following manoeuvres, which have previously been shown to achieve maximum activation of the diaphragm [25, 26]: 1) while breathing in as much as possible (total lung capacity manoeuvre); 2) while breathing in as hard as possible against a closed airway (maximal inspiratory pressure ($P_{I,max}$) manoeuvre); 3) during maximal sniffs; 4) during maximum voluntary ventilation (MVV) over 15 s (''sprint MVV''); and 5) during maximal coughs and expiration against an occluded valve (maximal expiratory pressure ($P_{E,max}$) manoeuvre). At least five attempts were performed for each, until consistent results were achieved.

Overnight surveillance

Full polysomnography was performed using Alice 4® equipment (Respironics®, Murrysville, PA, USA). Sleep and respiratory events were scored with standard terminology [27].

Analysis

The overnight EMG data were normalised to maximum EMG activity during a maximal effort and expressed as a percentage of maximum (% max) EMG activity. The researcher analysing the EMG data was blinded to the results of the polysomnography analysis. A 10-min period of a deep sleep cycle was compared with 10 min of a REM sleep cycle. In order to select these periods, the first occurrences of such periods during the night were chosen. If a single sleep stage did not last 10 min, the remaining time was analysed from the next sleep cycle. There was a significant impact of posture and arousal on the EMG_{di} signal. Therefore, only REM and NREM data that were obtained in the supine position were compared and arousal events were excluded. Only sleep stages 2 and 3 were included in the analysis, due to the unstable nature of sleep stage 1. Results were expressed as mean$\pm$SD following testing for normalities. A p-value <0.05 was considered significant. The independent variables t-test was used for group comparisons. In addition, a repeated-measure one-way ANOVA was used for the analysis of REM and NREM sleep parameters within and between the groups, with *post hoc* analysis using Bonferroni's correction for multiple comparisons. A multiple linear regression analysis to find independent predictors of REM-related SDB was not possible due to the low sample size (n=22); therefore, the r-values for the best fit between potential

TABLE 1 Clinical features of patients

Patient	Sex	Age yrs	BMI kg·m^{-2}	UDP	MRC	ESS	Paradox	Sleeping side	Comorbidities
1	M	53	26.8	Right	1	18	Yes	Left	None
2	F	64	28.8	Right	2	10	Yes	None	Ulcerative colitis
3	M	58	28.7	Right	2	16	Yes	Left	None
4	M	76	28.4	Right	4	13	Yes	Left	Gastro-oesophageal reflux, chronic anaemia
5	M	59	29.6	Right	2	6	Yes	Left	Coronary artery disease
6	F	62	29.6	Right	2	3	No	Left	None
7	F	47	32.5	Right	3	14	No	Left	Depression
8	F	44	22.9	Right	4	17	No	None	Depression
9	F	57	30.9	Left	4	21	Yes	Right	Diabetes mellitus
10	M	41	31.8	Right	2	9	Yes	Left	None
11	M	61	25.8	Right	3	7	Yes	Left	None

BMI: body mass index; UDP: unilateral diaphragm paralysis or severe weakness; MRC: Medical Research Council dyspnoea scale; ESS: Epworth Sleepiness Scale; paradox: thoracoabdominal paradox by inspection and analysis of traces of oesophageal and gastric pressure swings; sleeping side: preferred sleeping position; M: male; F: female.

predictors (sex, age, body mass index (BMI) and diaphragm weakness) and REM-related SDB are reported [28].

RESULTS

The characteristics of the patients are given in table 1. Nine out of 11 patients preferred to sleep with the normal hemidiaphragm downwards, two had no preference and none preferred sleeping with the abnormal hemidiaphragm downwards (for the normal subjects, all 11 had no preferred sleeping side; p=0.035). Thoracoabdominal paradox was observed in eight patients (numbers 1–5 and 9–11) and was associated with a weaker hemidiaphragm (unilateral twitch Pdi 2.6±1.3 *versus* 4.9±1.5 cmH_2O (0.26±0.13 *versus* 0.49±0.15 kPa) in patients and controls, respectively; p=0.029). Although there was a trend for patients to be older and have a slightly higher BMI, the patient group was not significantly different from the control group in terms of age (56.5±10.0 *versus* 44.5±21.4 yrs, respectively; p=0.106), sex (both groups six males and five females) and BMI (28.7±2.8 *versus* 26.3±2.6 kg·m^{-2}, respectively; p=0.051; table 1).

All but one patient (number 8) performed the volitional respiratory muscle tests satisfactorily. Twitch Pdi and sniff Pdi were reduced in the patients. $P_{I,max}$, sniff oesophageal pressure and sniff nasal pressure were also reduced, whereas $P_{E,max}$, cough gastric pressure (Pgas) and twitch Pgas following magnetic stimulation at the level of the 10th thoracic segment were normal (table 2 and online supplementary material).

Phrenic nerve latency was prolonged in nine out of 11 patients on the weak side and in five out of 11 patients on the strong side. The CMAP was markedly reduced on the weaker side, with 10 out of 11 patients having a CMAP less than the lower limit of normal [20]. On the strong side the CMAP was markedly reduced in four patients (table 3).

The forced expiratory volume in one second (FEV1) was low in the patient group and, compared with the control group, the FEV1/VC ratio indicated a mild obstructive defect. VC was reduced in the patient group and showed a further fall when supine; patient no. 8 was excluded from the analysis of these data because of inability to perform the VC manoeuvre while supine. Although none of the patients was hypercapnic, the arterial oxygen tension was mildly reduced (table 4).

During polysomnography, frequent hypopnoeas and apnoeas were observed in REM sleep (fig. 1). Only two patients (numbers 7 and 8) had no SDB and these had the highest twitch Pdi on their weak side (5–6 cmH_2O (0.5–0.6 kPa)). Baseline oxygenation in the patient group was normal during NREM sleep but dropped during hypopnoeas in REM sleep.

TABLE 2 Results of respiratory muscle function tests for patient and control groups

	UDP	Control	p-value
Tw Pdi, bilateral	17.3±5.0	26.2±5.5	0.001
Tw Pdi, weak side	3.3±1.7	10.4±1.9$^{\#}$	<0.001
Tw Pdi, strong side	11.2±2.2	13.4±3.3¶	0.083
Sniff Pdi	71.0±40.2	136.7±39.9	0.001
Sniff Poes	63.6±34.5	112.7±39.5	0.006
Sniff Pnasal	56.2±31.3	99.6±43.6	0.014
$P_{I,max}$	49.4±29.8	110.0±43.7	0.001
$P_{E,max}$	96.8±33.7	118.4±50.9	0.253
Cough Pgas	186.1±50.8	202.7±63.2	0.504
Tw T10	43.7±33.5^{+}	35.3±11.0	0.444

Data are presented as mean± SD cmH_2O, unless otherwise stated. UDP: unilateral diaphragm paralysis or severe weakness; Tw: twitch; Pdi: transdiaphragmatic pressure; Poes: oesophageal pressure; Pnasal: nasal pressure; $P_{I,max}$: maximal inspiratory pressure; $P_{E,max}$: maximal expiratory pressure; Pgas: gastric pressure; T10: Pgas following magnetic stimulation at the level of the 10th thoracic segment. All twitches were elicited with magnetic stimulation. $^{\#}$: normal subjects with normal hemidiaphragm strength measured on the less strong side; ¶: normal subjects with normal hemidiaphragm strength measured on the stronger side; $^{+}$: not available in four patients. 1 cmH_2O=0.1 kPa.

TABLE 3 Phrenic nerve conduction studies

	UDP	Control	p-value
Latency ms			
Weak side	11.3±3.0	6.7±0.8#	<0.001
Strong side	9.3±2.2	6.9±1.0¶	0.004
CMAP mV			
Weak side	0.370±0.254	1.405±0.430#	<0.001
Strong side	0.891±0.299	1.359±0.370¶	0.004
Weaker side R:L n	10:1		

Data are presented as mean±SD, unless otherwise stated. UDP: unilateral diaphragm paralysis or severe weakness; CMAP: compound muscle action potential; R: right; L: left. #: normal subjects with normal hemidiaphragm strength measured on the less strong side; ¶: normal subjects with normal hemidiaphragm strength measured on the stronger side.

TABLE 4 Pulmonary function test results

	UDP	Control	p-value
FEV_1 % pred	62.5±16.6	99.0±13.1	<0.001
VC % pred	74.4±18.4	102.3±22.8	0.005
FEV_1/VC ratio %	71.3±10.5	80.8±5.2	0.014
VC drop# %	20.7±5.7¶	6.4±4.7	<0.001
P_{a,O_2} kPa	10.08±1.19	12.10±1.42	0.002
P_{a,CO_2} kPa	4.92±0.33	5.07±0.45	0.389

Data are presented as mean±SD, unless otherwise stated. UDP: unilateral diaphragm paralysis or severe weakness; FEV_1: forced expiratory volume in one second; % pred: % predicted; VC: vital capacity; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension. #: fall in VC when changing from sitting to supine position; ¶: patient no. eight was excluded due to inability to perform the manoeuvre.

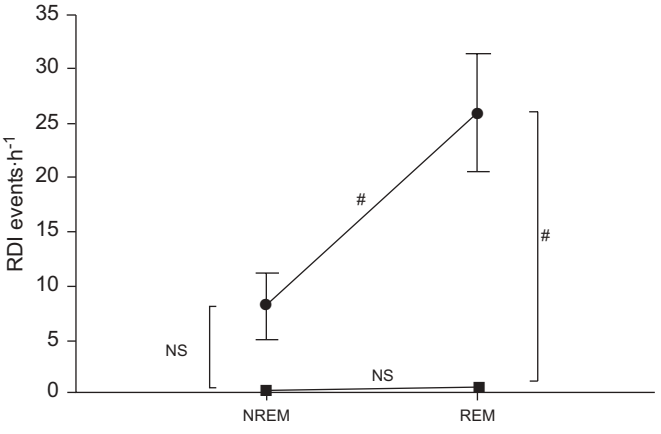

FIGURE 1. Mean±SEM respiratory disturbance index (RDI) for patient (●) and control groups (■). There was a significant increase in RDI in rapid eye movement (REM) sleep compared with non-REM (NREM) sleep in patients with unilateral diaphragm paralysis. The intergroup difference was significant for REM sleep. NS: nonsignificant. #: p<0.0001.

TABLE 5 Results of polysomnography

	UDP	Control	p-value
TST min	260.4±108.2	298.5±77.7	0.353
REM time min	36.5±21.0	53.7±22.3	0.078
RDI events·h^{-1}			
REM	26.0±17.8	0.7±0.9	<0.001
NREM	8.1±10.1	0.4±0.4	0.080
Sa,O_2 %			
REM	92.9±2.3	95.9±1.6	0.002
NREM	93.6±1.9	95.5±1.6	0.024
Nadir	85.9±4.6	92.0±2.1	0.001

Data are presented as mean±SD, unless otherwise stated. UDP: unilateral diaphragm paralysis or severe weakness; TST: total sleep time; REM: rapid eye movement sleep; RDI: respiratory disturbance index; NREM: non-REM sleep; Sa,O_2: arterial oxygen saturation.

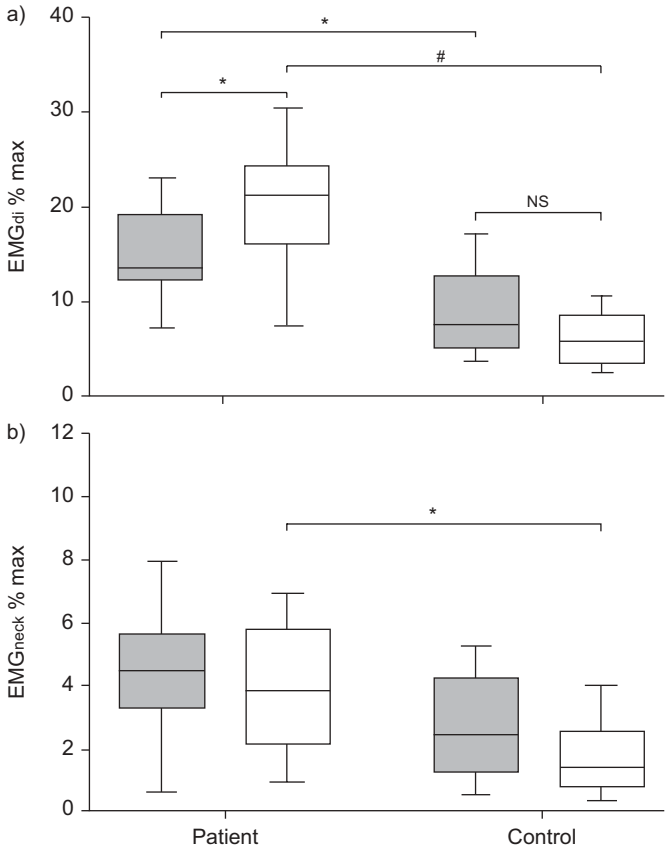

FIGURE 2. a) Electromyogram of the diaphragm (EMG_{di}). Box-and-whisker plot showing the median, quartiles and extreme values. The box represents the interquartile range, which contains 50% of the values, and the whiskers extend from the box to the highest and lowest values. Neural respiratory drive of patients with unilateral diaphragm paralysis, as measured by the EMG_{di} (percentage of maximum (% max)), was double that of the control subjects during nonrapid eye movement (NREM) sleep (■). It increased in the patient group during rapid eye movement (REM) sleep (□), while for control subjects activation remained the same. b) Electromyogram of the neck muscles (EMG_{neck}). The neck muscles in patients remained active in REM sleep. NS: nonsignificant. *: p<0.05; #: p<0.0001.

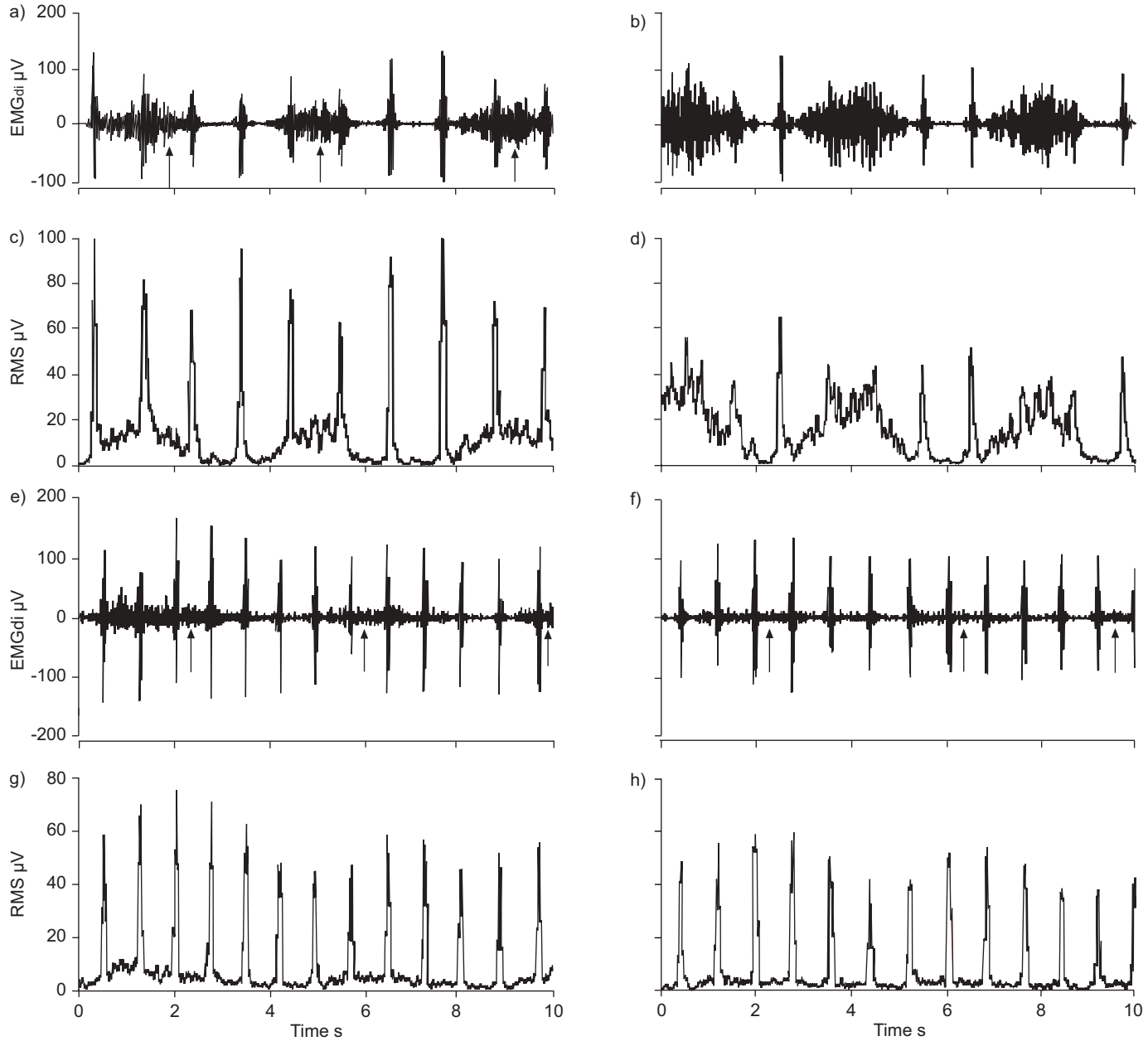

FIGURE 3. Samples of 10 s of electromyogram signals of the diaphragm (EMGdi; a, b, e and f) and the root mean square (RMS; 50-ms time constant, moving average; c, d, g and h) during nonrapid eye movement (NREM; a, c, e and g) and rapid eye movement (REM; b, d, f and h) sleep in a patient with unilateral diaphragm paralysis (a–d) and in a control subject (e–h). Inspiratory activity of the diaphragm is marked with arrows. Note the increase of neural respiratory drive in the patient during REM sleep, while the control subject exhibited a lower level of activation.

The respiratory disturbance index (RDI) in NREM sleep was more variable in the UDP patients but not significantly higher than in the normal subjects (table 5). The RDI was, in NREM sleep, elevated in the subgroup of patients who had a thoracoabdominal paradox ($p=0.002$).

Quality of life was significantly reduced in patients compared with the control group (for further details see online supplementary material). All domains of the SGRQ and the CRDQ were statistically different in the patient group compared with control subjects, reaching more than the minimal clinically important difference. The largest differences were observed in the CRDQ ''dyspnoea'' domain and SGRQ ''activity'' and ''symptoms'' scores. The MRC dyspnoea scale and the ESS were significantly increased in patients compared with controls (MRC: 2.4 ± 1.0 *versus* 1.2 ± 0.4 points, respectively; $p=0.002$; ESS: 11.9 ± 5.7 *versus* 3.7 ± 2.8 points, respectively; $p<0.001$; table 1).

The EMGdi was elevated in patients with UDP in sleep, compared with control subjects (15.3 ± 5.3 *versus* 8.9 ± 4.9% max in NREM, respectively; $p<0.05$; figs 2a and 3). While levels of EMGdi were sustained during NREM and REM sleep phases in the control group (8.9 ± 4.9 and 6.2 ± 3.1% max, respectively;

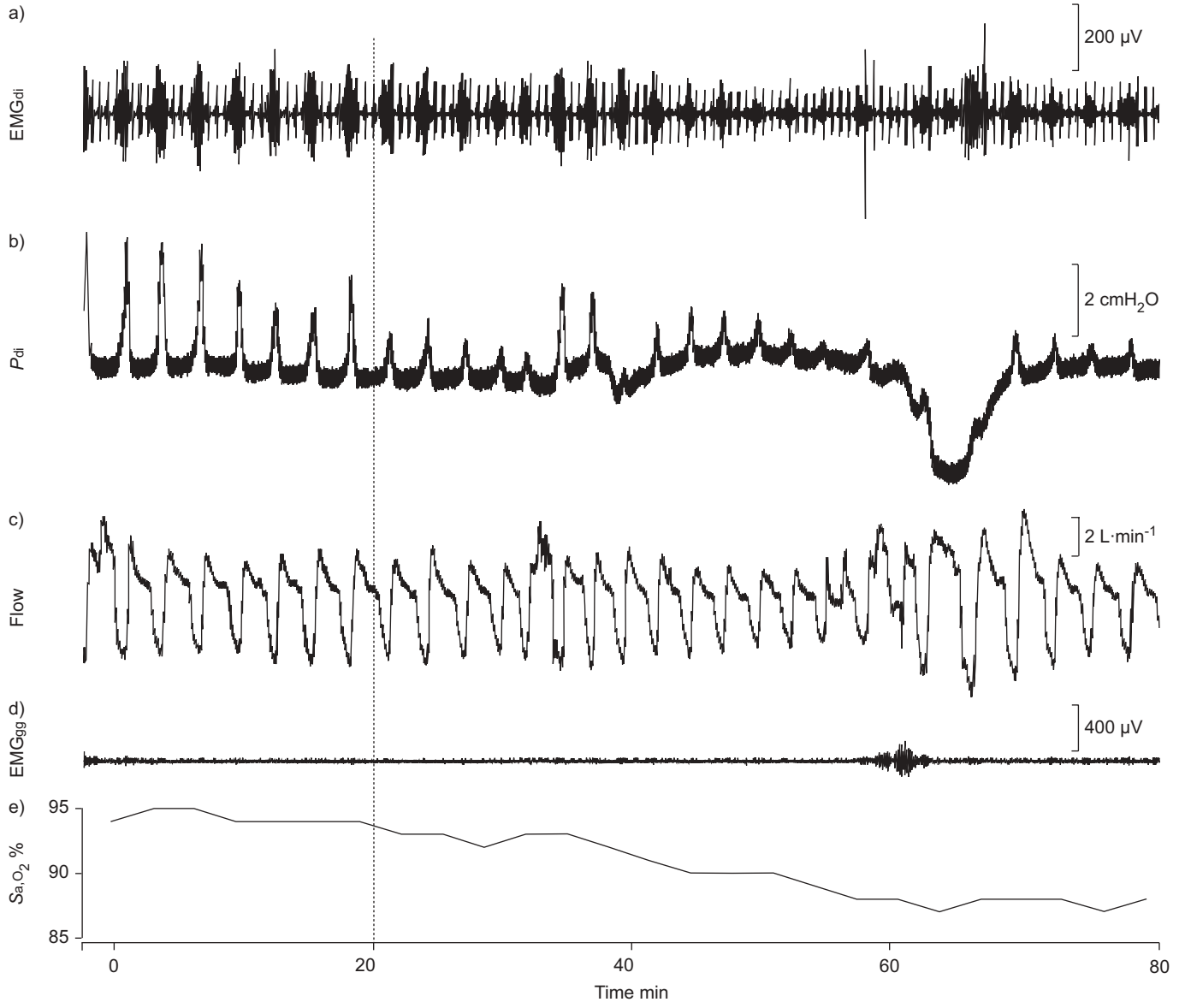

FIGURE 4. a) Neural respiratory drive, as measured by electromyogram (EMG) of the diaphragm (EMG_{di}), b) transdiaphragmatic pressure (P_{di}), c) flow, measured by pneumotachograph, d) genioglossus EMG (EMG_{gg}) and e) arterial oxygen saturation (S_{a,O_2}) during rapid eye movement (REM) sleep in a patient with unilateral diaphragm paralysis. Following a loss of initially high central drive, inspiratory effort was reduced and the patient developed a hypopnoea that was eventually overcome by an arousal reaction. ·····: first occurrence of phasic REM.

p=nonsignificant (NS)), they were increased in the patients during REM sleep compared with NREM sleep (20.0±6.8 *versus* 15.3±5.3% max, respectively; $p<0.05$; figs 2a, 3 and 4). There was no difference in the activation of the neck muscles between patients and control subjects in NREM sleep (fig. 2b). In REM sleep, activation of the neck muscles decreased from the NREM value only in the normal subjects ($p=0.032$; fig. 2b).

The parasternal intercostals were equally activated in NREM and REM sleep in patients and control subjects (p=NS). There was also no significant difference between patients and control subjects in the activation of the abdominal muscles, although additional activation was observed in some patients during REM sleep.

The variability of EMG_{di} during sleep, as measured by the SD of the mean of the EMG_{di} (% max) of every breath for a 10-min period, was higher in patients with UDP than in normal subjects in both REM and NREM sleep ($p<0.01$). In UDP patients, it was 6.9 and 5.4% max EMG_{di} in REM and NREM sleep, respectively, while in healthy subjects it was 2.1 and 2.4% max EMG_{di} in REM and NREM sleep, respectively. Only one patient with UDP, who had no SDB, had a SD <4% max EMG_{di} (patient no. 7; 2.9%), while the only normal subject who reached a SD >3% max EMG_{di} was a snorer. The variability of the EMG_{neck} over a 10-min period, measured in the same manner, was similar in both groups in NREM sleep (3.2 *versus* 4.0% max EMG_{neck}; p=NS) and lower in the normal subjects in REM sleep (2.6 *versus* 4.4% max EMG_{neck}; $p<0.05$).

The only variable significantly correlated with the REM RDI was diaphragm weakness ($r=0.784$, $p<0.001$). Age ($r=0.332$,

p=0.132), sex (r= -0.118, p=0.60) and BMI (r=0.381, p=0.08) were not significantly correlated with REM sleep-related SDB.

DISCUSSION

In patients with hemidiaphragm paralysis or severe weakness who present with related respiratory symptoms, neural respiratory drive to the diaphragm in NREM sleep is significantly increased compared with that of healthy individuals. While there is a decrease in the activation of peripheral skeletal muscle in the healthy population during REM sleep [29], and levels of neural respiratory drive remain the same, the response of UDP patients is different. They activate the diaphragm more during REM sleep. In addition, like BDP patients [5], they also activate their accessory respiratory muscles (neck muscles) during REM sleep to attenuate hypoventilation, although the use of these muscles for posture, as well as movement artefacts, probably contributed to the wide spread of the current data. During inspiration, in REM sleep, the abdominal muscles were active in some patients. While this is likely to be a compensatory response, its function is not completely understood and requires further exploration.

The present study showed a significant increase in respiratory-related events during REM sleep, which caused SDB. This is consistent with the previous finding that patients with BDP have only REM sleep-related SDB [11, 12]. Most of the events were hypopnoeas, although there was some obstruction in two patients that became worse during REM sleep. All patients with a twitch P_{di} <5 cmH_2O (0.5 kPa) on the weaker side had REM-related SDB. Two patients with a twitch P_{di} >5 cmH_2O had no SDB, suggesting a threshold level of diaphragm dysfunction below which SDB is more likely.

The predominant mechanism of respiratory events during REM sleep in the present patient population was of central origin, according to the criteria of the American Academy of Sleep Medicine Task Force (point 4.2.2.1; definition of central apnoea/hypopnoea events) [30].

In contrast, neural respiratory drive, while relatively low during the onset of an obstructive apnoea or hypopnoea, rises parallel to inspiratory pressures during the time of upper airway occlusion, reflecting the respiratory effort against a high resistance [31]. In the UDP patients there was a different pattern: mean drive was relatively high during REM sleep, falling only slightly during phasic REM; the flow indicated that the upper airway was open; and there was no snoring. In three UDP patients in whom P_{di} was measured overnight, it was observed that the respiratory events during REM sleep were not associated with increased inspiratory pressures.

The current authors conclude that, in the population studied, the main mechanism leading to REM-related SDB was central hypopnoea that occurred despite an elevated overall mean neural drive, because the respiratory muscle pump was not able to sustain sufficient alveolar ventilation (fig. 4).

The observed changes in sleep pattern and habits indicate that compensatory mechanisms are active even in patients without overt SDB. In some of the patients with UDP thoracoabdominal paradox was observed, and these patients had weaker diaphragms and more severe SDB. In addition, the self-reported changes of sleeping-side preference make it likely that subjects have a more improved respiratory function when lying with the stronger hemidiaphragm downwards. Changes in sleep habits or postures should be inquired after when UDP is suspected.

The level of neural drive, in terms of EMG_{di} % max, is a measure of the load-to-capacity balance of the ventilatory system. Measuring neural respiratory drive in terms of transoesophageal EMG_{di} may offer a way of detecting SDB and assessing the response to therapy, and may be a sensitive tool for recording changes that occur in response to increased resistance in the pharynx, as in obstructive sleep apnoea [31]. The measurement of EMG_{neck} in REM sleep may also be useful. The present study showed that healthy subjects, provided they do not snore, have little variation in EMG_{di}. Variability of the signal, normalised to maximum manoeuvres, may thus be a marker for the extent of sleep disturbance. The same is true for the EMG_{neck} during REM sleep.

The quality of life measures showed that patients with UDP or severe weakness were more symptomatic than normal subjects. UDP can cause breathlessness and sleepiness, as indicated by changes in the CRDQ dyspnoea score, the MRC dyspnoea scale and the ESS. It is noteworthy that thoraco-abdominal paradox only occurred in patients with a unilateral twitch P_{di} <5 cmH_2O (0.5 kPa), and all such patients had SDB. This physical sign may serve to identify patients at risk of SDB.

Whereas BDP is considered a potential health risk [13], UDP is usually considered to be benign. The current data show that UDP can lead to SDB and reduced quality of life. The weaker the hemidiaphragm, the more likely SDB is to develop.

It is important to consider factors that could increase the risk of SDB in UDP. Obesity would be expected to be important. It imposes an additional load on the reduced capacity of the respiratory system, thereby predisposing to hypoventilation [6]. However, over the range of BMI of the patient population studied, diaphragm weakness, as measured by unilateral twitch P_{di}, was the only factor correlated with REM-related SDB.

HART *et al.* [7] showed an unexpectedly large reduction in exercise capacity in patients with UDP. LAROCHE *et al.* [32] found UDP patients to be more breathless than expected. An early study by DOUGLAS and CLAGETT [33] found 10–24% of patients with hemidiaphragm paralysis to be breathless. PATAKAS *et al.* [15] described 12 patients with nocturnal hypoxia and presumed UDP, but characterised the patients insufficiently for accurate diagnosis of unilateral phrenic nerve dysfunction. As shown in the present study, only 17 out of 39 patients who were clinically suspected to have UDP actually had unilateral involvement when assessed with electrophysiological tests of the phrenic nerves. Nevertheless, the findings from previous studies lend support to the hypothesis that patients with UDP may be significantly symptomatic.

Limitations to the present study

The clinical diagnosis of hemidiaphragm paralysis or weakness is not accurate, and definitive assessment requires measurement of transdiaphragmatic pressures [34]. Clinically, patients suspected as having hemidiaphragm paralysis can have either bilateral involvement or no weakness

at all, despite the chest radiograph showing an elevated hemidiaphragm [34]. This causes problems when recruiting patients to clinical studies. Patients with severe symptoms and weakness are more likely to be referred and subsequently participate in clinical studies. Thus, the results of the present study may not be generalisable to all patients with hemidiaphragm paralysis. However, the data clearly show that UDP can be symptomatic and reduce quality of life.

In the present study, arterial carbon dioxide tension was not measured overnight and, therefore, the degree of REM sleep-related hypoventilation cannot be defined. However, the observed pathophysiology seems to be similar to that of patients with BDP in whom carbon dioxide retention has been measured and REM sleep hypoventilation confirmed [12, 13]. Therefore, it is likely that the REM-related frequent hypopnoeas and apnoeas in UDP patients cause hypoventilation.

The current authors acknowledge that the RDI for the total sleep time was relatively low in the UDP patients. This was because the sleep disturbance was largely confined to the REM-sleep period with only mild or no SDB in NREM sleep. However, the relatively severe disturbance during REM sleep caused clinically relevant symptoms, as shown by the reported symptom scores and the quality of life data. These patients showed compensatory patterns of respiratory muscle recruitment, indicating a response of the nervous system to compensate for weakness, particularly during REM sleep. In agreement with the total sleep time RDI, the periods of oxygen desaturation were also relatively short in these patients.

Another potential limitation in the present study is that the patient group tended to be more obese than controls. However, in the patients studied, REM-related SDB was independent of BMI.

In the current study, arousals occurred more often in both patients and control subjects than in a normal healthy population. This is likely to be due to the complexity and invasiveness of the study (polysomnography, transoesophageal catheter, surface EMGs). However, the arousals in the normal subjects were not caused by respiratory effort. These minor disturbances in sleep patterns were the same in patient and control groups. Therefore, the REM-related hypopnoeas in the patient group cannot be attributed to the study set-up.

The surface EMG provides a relatively nonspecific way to measure the activity of a particular muscle. Positioning the electrodes on the surface of the sternocleidomastoid and the rectus abdominis may have resulted in the recording of EMG signals of other neck or abdominal muscles (hence the labelling of traces as EMG_{neck} or $EMG_{abdomen}$). In addition, it is acknowledged that the maximisation manoeuvres for expiratory abdominal muscle activation have not been standardised in previous studies. However, two standard manoeuvres ($P_{E,max}$ and cough P_{gas}) showed good reproducibility of EMG data, and expiratory muscle strength was similar between the two groups.

It might be of concern that the inspiratory activation of the abdominal muscles observed in some patients could have been diaphragm activity detected by the surface EMG electrodes. No inspiratory surface EMG activity was detected in REM sleep in normal subjects. The current authors' in-house data from patients with BDP and, therefore, no spontaneous diaphragm EMG activity, show the same inspiratory activity of the abdominal muscles during sleep. This provides confidence that activation of the abdominal muscles was measured without contamination from the diaphragm. The abdominal EMG activity referred to was observed during inspiration. It is not completely understood how inspiratory activity of otherwise expiratory muscles can help to compensate for diaphragmatic muscle weakness. However, the present authors hereby clarify that this inspiratory activity was also observed in BDP patients in whom no spontaneous diaphragmatic EMG could be recorded. The observed surface EMG signals in such patients have to originate in the abdominal muscles. Abdominal muscle activation in patients with a thoracoabdominal paradox might result in a stabilisation of the anterior abdominal wall, avoiding inspiratory inward movement of the abdomen. This would also help to stabilise the weaker hemidiaphragm, which otherwise would be pulled upwards by the intrathoracic negative pressure.

Conclusion

Patients with hemidiaphragm paralysis or severe weakness can develop rapid eye movement sleep-related sleep-disordered breathing, independent of body mass, sex and age. In such patients, frequent hypopnoeas during rapid eye movement sleep with compensatory activation of the accessory respiratory muscles is observed. There seems to be a threshold of unilateral twitch transdiaphragmatic pressure (5 cmH_2O) above which patients with unilateral diaphragm weakness do not develop sleep-disordered breathing. It is sensible to screen for and address the long-term risks of sleep-disordered breathing in symptomatic patients with unilateral diaphragm paralysis. Once the diagnosis is confirmed, treatment, including noninvasive ventilation, should then be considered in order to improve health status.

REFERENCES

1 Schoenhofer B, Koehler D, Polkey MI. Influence of immersion in water on muscle function and breathing pattern in patients with severe diaphragm weakness. *Chest* 2004; 125: 2069–2074.

2 Moxham J. Respiratory muscles. *In*: Hughes JMB, Pride NB, eds. Lung Function Tests: Physiological Principles and Clinical Applications. London, W.B. Saunders, 2001; pp. 58–68.

3 Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003; 168: 10–48.

4 Teitelbaum J, Borel CO, Magder S, Traystman RJ, Hussain SN. Effect of selective diaphragmatic paralysis on the inspiratory motor drive. *J Appl Physiol* 1993; 74: 2261–2268.

5 Bennett JR, Dunroy HM, Corfield DR, *et al.* Respiratory muscle activity during REM sleep in patients with diaphragm paralysis. *Neurology* 2004; 62: 134–137.

6 Arnulf I, Similowski T, Salachas F, *et al.* Sleep disorders and diaphragmatic function in patients with amyotrophic lateral sclerosis. *Am J Respir Crit Care Med* 2000; 161: 849–856.

7 Hart N, Nickol AH, Cramer D, *et al.* Effect of severe isolated unilateral and bilateral diaphragm weakness on

exercise performance. *Am J Respir Crit Care Med* 2002; 165: 1265–1270.
8 White JE, Drinnan MJ, Smithson AJ, Griffiths CJ, Gibson GJ. Respiratory muscle activity and oxygenation during sleep in patients with muscle weakness. *Eur Respir J* 1995; 8: 807–814.
9 Mulvey DA, Aquilina RJ, Elliott MW, Moxham J, Green M. Diaphragmatic dysfunction in neuralgic amyotrophy: an electrophysiologic evaluation of 16 patients presenting with dyspnea. *Am Rev Respir Dis* 1993; 147: 66–71.
10 Laroche CM, Carroll N, Moxham J, Green M. Clinical significance of severe isolated diaphragm weakness. *Am Rev Respir Dis* 1988; 138: 862–866.
11 Skatrud J, Iber C, McHugh W, Rasmussen H, Nichols D. Determinants of hypoventilation during wakefulness and sleep in diaphragmatic paralysis. *Am Rev Respir Dis* 1980; 121: 587–593.
12 Stradling JR, Warley AR. Bilateral diaphragm paralysis and sleep apnoea without diurnal respiratory failure. *Thorax* 1988; 43: 75–77.
13 Davis J, Goldman M, Loh L, Casson M. Diaphragm function and alveolar hypoventilation. *Q J Med* 1976; 45: 87–100.
14 Hughes PD, Polkey MI, Moxham J, Green M. Long-term recovery of diaphragm strength in neuralgic amyotrophy. *Eur Respir J* 1999; 13: 379–384.
15 Patakas D, Tsara V, Zoglopitis F, Daskalopoulou E, Argyropoulou P, Maniki E. Nocturnal hypoxia in unilateral diaphragmatic paralysis. *Respiration* 1991; 58: 95–99.
16 Guidelines for the measurement of respiratory function. Recommendations of the British Thoracic Society and the Association of Respiratory Technicians and Physiologists. *Respir Med* 1994; 88: 165–194.
17 American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; 166: 518–624.
18 Polkey MI, Duguet A, Luo Y, *et al.* Anterior magnetic phrenic nerve stimulation: laboratory and clinical evaluation. *Intensive Care Med* 2000; 26: 1065–1075.
19 Luo YM, Harris ML, Lyall RA, Watson A, Polkey MI, Moxham J. Assessment of diaphragm paralysis with oesophageal electromyography and unilateral magnetic phrenic nerve stimulation. *Eur Respir J* 2000; 15: 596–599.
20 Luo YM, Lyall RA, Harris ML, Rafferty GF, Polkey MI, Moxham J. Quantification of the esophageal diaphragm electromyogram with magnetic phrenic nerve stimulation. *Am J Respir Crit Care Med* 1999; 160: 1629–1634.
21 Maarsingh EJ, van Eykern LA, Sprikkelman AB, Hoekstra MO, van Aalderen WM. Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility. *J Appl Physiol* 2000; 88: 1955–1961.
22 Duiverman ML, van Eykern LA, Vennik PW, Koëter GH, Maarsingh EJ, Wijkstra PJ. Reproducibility and responsiveness of a noninvasive EMG technique of the respiratory muscles in COPD patients and in healthy subjects. *J Appl Physiol* 2004; 96: 1723–1729.
23 White JE, Drinnan MJ, Smithson AJ, Griffiths CJ, Gibson GJ. Respiratory muscle activity during rapid eye movement (REM) sleep in patients with chronic obstructive pulmonary disease. *Thorax* 1995; 50: 376–382.
24 Konrad P, Schmitz K, Denner A. Neuromuscular evaluation of trunk-training exercises. *J Athl Train* 2001; 36: 109–118.
25 Sinderby C, Beck J, Spahija J, Weinberg J, Grassino A. Voluntary activation of the human diaphragm in health and disease. *J Appl Physiol* 1998; 85: 2146–2158.
26 Luo YM, Moxham J. Measurement of neural respiratory drive in patients with COPD. *Respir Physiol Neurobiol* 2005; 146: 165–174.
27 Rechtschaffen A, Kales A. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington DC, US Government Printing Office; 1968. NIH Publication No. 204.
28 Petrie A, Sabin C. Medical Statistics at a Glance. 2nd Edn. Oxford, Blackwell Publishing Ltd, 2005; pp. 16, 18, 49–55, 72–79.
29 Rechtschaffen A, Siegel J. Sleep and dreaming. *In*: Rechtschaffen A, Siegel J, eds. Principles of Neuroscience. 4th Edn. New York, McGraw-Hill, 2000; pp. 936–947.
30 Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; 22: 667–689.
31 Luo YM, Wu HD, Tang J, *et al.* Neural respiratory drive during apnoeic events in obstructive sleep apnoea. *Eur Respir J* 2008; 31: 650–657.
32 Laroche CM, Mier AK, Moxham J, Green M. Diaphragm strength in patients with recent hemidiaphragm paralysis. *Thorax* 1988; 43: 170–174.
33 Douglass BE, Clagett OT. The prognosis in idiopathic diaphragmatic paralysis. *Dis Chest* 1960; 37: 294–297.
34 Chetta A, Rehman AK, Moxham J, Carr DH, Polkey MI. Chest radiography cannot predict diaphragm function. *Respir Med* 2005; 99: 39–44.