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Increased load on the respiratory muscles in obstructive sleep apnea

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ABSTRACT

We wished to quantify, in patients with obstructive sleep apnoea (OSA), the activity of the respiratory muscles in relation to upper airway occlusion and patency in sleep. We hypothesized that particular levels of neuromuscular activation are directly associated with upper airway patency. 21 patients with previously diagnosed OSA and 21 healthy control subjects underwent respiratory muscle testing and polysomnography. Neural respiratory drive, as measured by the electromyogram of the diaphragm (EMG_{di}) was elevated in the obese OSA patients, awake and supine (13.1(5.6)%max), compared to normal subjects (mean (SD) 8.1(2.3)%max, $p < 0.01$). During unobstructed breathing in sleep (stage N2) normal subjects had an EMG_{di} of 7.7(3.9) compared to 22.8(19.2)%max in the OSA group ($p < 0.001$). Prior to airway occlusion, $EMG_{submandibular}$ and EMG_{di} dropped markedly, and then, following occlusion, increased progressively to their highest levels at airflow onset. Patients with OSA require specific and increased levels of neural respiratory drive to sustain ventilation in sleep.

1. Introduction

Sleep-disordered breathing (SDB) is common, reduces quality of life and is an important public health problem (Stradling and Davies, 2004). However, the pathophysiology of obstructive sleep apnea (OSA) (Remmers et al., 1978), the most common form of SDB (Stradling and Davies, 2004), is complex (Henke et al., 1992; Younes, 2003; Stradling and Davies, 2004). There is an ongoing debate whether and to what extent generalized neuromuscular alterations in addition to anatomical disposition contribute to upper airway occlusion (Schwab and Strohl, 2003). Neuromuscular tone of the upper airway plays a key role in the pathogenesis of OSA (Remmers et al., 1978), as previously shown by alterations of the critical occlusion pressure during neuromuscular anaesthesia (Eastwood et al., 2002) and in patients during normal sleep (Fogel et al., 2001; Patil et al., 2007). Temporary desynchronization between the activation of the upper airway muscles and the inspiratory muscles might further complicate matters (Remmers et al., 1978). Results of earlier studies measuring both upper airway and respiratory muscle electromyograms suggest that occlusive and mixed apneas result from an instability of ventilatory control during sleep (Önal et al., 1982; Önal and Lopata, 1982).

The electromyogram of the diaphragm (EMG_{di}) provides useful information on neural respiratory drive during wakefulness (Sinderby et al., 1998) and sleep (Luo et al., 2008; Steier et al., 2008). EMG_{di} during spontaneous breathing compared to maximum maneuvers reflects the load-to-capacity ratio of the ventilatory system, and allows comparisons between subjects (Sinderby et al., 1998; Steier et al., 2008), but has not been described in OSA. Measuring activity of accessory respiratory muscles adds to the assessment of neural respiratory drive (Henke et al., 1992).

Gleeson et al. (1990) described that arousal from sleep is associated with particular inspiratory intrathoracic pressures, as measured with an esophageal balloon catheter, independent of the cause of the rise in drive (hypoxemia, hypercapnia, resistance). Our group recently described the usefulness of measuring neural respiratory drive during upper airway obstruction in sleep (Luo et

Abbreviations: AHI, Apnea–hypopnea-index; AOC, Airway occlusion; AOP, Airway opening; CI, Confidence interval; CPAP, Continuous positive airway pressure; EEG, Electroencephalogram; EOG, Electrooculogram; EMG, Electromyogram; $EMG_{abdomen}$, Electromyogram of the abdominal muscles (surface recording); EMG_{di}, Electromyogram of the diaphragm (transesophageal multipair electrode); EMG_{neck}, Electromyogram of the neck muscles (surface recording); EMG_{para}, Electromyogram of the parasternal intercostals (surface recording); $EMG_{submandibular}$, Electromyogram of the submandibular area (surface recording); MVV, Maximal voluntary ventilation; P_{di}, Transdiaphragmatic pressure; P_{es}, Esophageal pressure; P_{gas}, Gastric pressure; OSA, Obstructive sleep apnea; SD, Standard deviation; SEM, Standard error of the mean; SDB, Sleep-disordered breathing; TLC, Total lung capacity.

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al., 2008). We therefore wished to precisely quantify neural respiratory drive, as measured with the diaphragm electromyogram, and further investigate the role of the respiratory muscles in relation to upper airway occlusion and patency in sleep, hypothesizing that particular levels of neuromuscular activation are associated with arousal and airway reopening. Specific levels of neural respiratory would indicate a threshold associated with arousal from sleep.

2. Patients, methods and materials

We studied OSA patients over a range of severity. In addition, we investigated normal subjects without SDB or other significant comorbidities to establish values of neural respiratory drive in normal sleep. OSA was defined as more than 5 apneas/h, longer than 10 s, in symptomatic patients, although the mean apnea–hypopnea-index (AHI) greatly exceeded this threshold (Kryger et al., 1989). Patients with a high pretest probability for sleep-disordered breathing and naïve to treatment with continuous positive airway pressure (CPAP) were recruited from the Chest Unit, King's College Hospital after screening using overnight pulse oximetry. Subjects with airways obstruction or obesity hypoventilation syndrome were excluded. Suitable patients were then invited for polysomnography in the physiology laboratory. In 21 of 25 subjects OSA was confirmed and they are the subjects included in this study. Normal subjects were recruited from King's College Hospital staff, friends of staff and families by advertising on the hospital based intranet. Groups were matched for gender and age. The study was approved by King's College Hospital local research ethics committee and informed consent was obtained from each subject.

We measured inspiratory, diaphragm specific, and expiratory muscle strength according to the ATS/ERS joint statement on respiratory muscle testing (2002). A multipair electrode catheter (Yinghui Medical Tech Ltd.®, Guangzhou, China) was inserted via one nostril to record the transesophageal EMGdi, as previously described (Polkey et al., 2000; Luo et al., 2008), connected to RA-8® amplifiers (Yinghui Medical Tech Ltd.®, Guangzhou, China) that further transmitted the signal to an analog-to-digital converter, Powerlab® 16/30 (ADInstruments®, Colorado Springs, CO, USA), and to a computer running Chart® 5.4 software (ADInstruments®, Colorado Springs, CO, USA). The catheter consisted of 10 electrode coils, each 10 mm in length and 2.2 mm in diameter, with a gap between adjacent recording coils of 0.5 mm. Positioning of the catheter at the electrically active region of the diaphragm (EAR_{di}) was achieved by observing spontaneous EMG_{di} and compound muscle action potential (CMAP) amplitude after magnetic stimulation of the phrenic nerves (anterolateral approach) (Polkey et al., 2000; Luo et al., 2008). The EMG of the neck muscles, parasternal intercostals, and abdominal muscles was recorded using surface electrodes (Kendall Arbo®, Tyco Healthcare®, Neustadt, Germany) from standard positions (Maarsingh et al., 2000; Duivermann et al., 2004; Lasserson et al., 2006). The surface electrodes were positioned on the right sternocleidomastoid (neck) muscle 2 cm above the clavicle and 3 cm beneath the mastoid process (EMG_{neck}; Maarsingh et al., 2000). For recording the EMG of the parasternal intercostals (EMG_{para}) electrodes were placed on each side of the sternum 3 cm from the midline in the second intercostal space (Maarsingh et al., 2000; Duivermann et al., 2004). The EMG of the abdominal muscles ($EMG_{abdomen}$) was recorded from surface electrodes over the external oblique. For this purpose, 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. A second electrode was placed approximately 4–5 cm anterior to that location (Lasserson et al., 2006). A reference electrode was placed on the skin 6 cm lateral to the midline below the clavicle. Although standard positions were used, surface EMG recordings are not specific for muscles.

2.1. Recordings and maximization maneuvers

After positioning, EMG and pressures were recorded during resting breathing and during maneuvers which have been shown to produce maximal or near maximal diaphragm activation, at least 5 times for each, until consistent results were achieved (Sinderby et al., 1998):

(1) whilst breathing in as much as possible (total lung capacity maneuver, TLC);
(2) whilst breathing in as hard as possible against a closed shutter ($P_{l,max}$ maneuver);
(3) maximal sniffs (Sniff maneuver);
(4) maximal voluntary ventilation for 15 s ("sprint" MVV maneuver).

In addition, maximal coughs were measured at least 5 times to assess expiratory muscle strength. After these initial maneuvers, EMG and pressures were continuously recorded during spontaneous breathing over the whole night. The data analyzed reflects measurements recorded in the supine posture.

2.2. Overnight surveillance and submandibular electromyogram ($EMG_{submandibular}$)

Full polysomnography was performed using Alice 4® and Alice 5® equipment (Respironics®, Murrysville, PA, USA). Sleep and respiratory events were scored according to standard terminology (Iber et al., 2007). The electroencephalogram (EEG) was measured with golden-surface electrodes according to the international 10–20 system (C_3-M_2, C_4-M_1, O_2-M_1). Following skin preparation with Nuprep® abrasive gel (D.O. Weaver & Co.®, Aurora, CO, USA) and alcohol wipes three surface electrodes (Ambu® Neuroline 720, Ballerup, Denmark) were attached to the submental area to measure $EMG_{submandibular}$, one in the midline 1 cm above the inferior edge of the mandible, one 2 cm below the inferior edge of the mandible and 2 cm to the right of the midline and one 2 cm to the left of the midline (Iber et al., 2007). An apnea episode was defined as absence of airflow for longer than 10 s, whilst abdominal and chest wall movements could be observed. Electrooculogram (EOG) was measured using golden-surface electrodes to detect eye movements (E_1-M_2; E_2-M_2). Airflow was measured via a combined oronasal thermistor. Abdominal and chest wall movements were detected via uncalibrated inductance plethysmography bands around the chest and abdomen, as well as by recording intrathoracic and intra-abdominal pressures (P_{es}, P_{gas}). Patients did not drink alcohol prior to the sleep study and no pre-medication was given to promote sleep.

2.3. Analysis of EMG activity

All EMG and pressure recordings during spontaneous breathing were sampled at 2 kHz, except for the submandibular EMG which was sampled at 200 Hz; CMAPs were recorded at 10 kHz. EMG data were amplified and filtered with a high-pass 30 Hz filter and an additional low-pass filter of 1 kHz. The rectified signals of the EMG (root-mean-square (RMS) of the raw data) were quantified off line (time constant 100 ms, moving average) and expressed as percentage of maximum EMG activity derived from the maneuver (TLC, $P_{l,max}$, Sniff, MVV) that produced the highest value. We analyzed two sequences of seven consecutive breaths, the first sequence including the breaths prior to and following onset of airway occlusion (AOC), and the second sequence described the breaths