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Control of breathing in obstructive sleep apnoea and in patients with the overlap syndrome

L. Radwan*, Z. Maszczyk*, A. Koziorowski*, M. Koziej**, J. Cieslicki**, P. Sliwinski**, J. Zielinski**

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ABSTRACT: In some patients obstructive sleep apnoea (OSA) may co-exist with chronic obstructive pulmonary disease (COPD) and respiratory failure; the so-called "overlap syndrome". Obstructive, hypercapnic patients have both blunted ventilatory and mouth occlusion pressure responses during CO_2 stimulation. The purpose of this study was to compare the pattern of breathing and CO_2 response between OSA patients and those with the overlap syndrome.

Twenty obese men with OSA and normal lung function (Group A), 11 obese men with overlap syndrome (Group B) and 13 healthy nonobese subjects (Group C) were examined. Lung function tests, breathing pattern, mouth occlusion pressure ($P_{0.2}$) at rest, and respiratory responses during CO_2 rebreathing were investigated. Diagnosis of OSA was established by standard polysomnography.

There were no statistical differences between Groups A and B in apnoea+hypopnoea index (62 *vs* 54), mean arterial oxygen saturation (Sa_{O_2}) during sleep (85 *vs* 84%) and in body mass index (BMI) 34.3 *vs* 36.3 kg·m^{-2}. Minute ventilation, mean inspiratory flow and $P_{0.2}$ at rest were increased in both groups of patients in comparison to controls. During CO_2 rebreathing, group A had normal ventilatory and $P_{0.2}$ responses, similar to controls, (2.7±1.1 *vs* 2.1±0.4 *l*·min^{-1}·mmHg^{-1} and 0.7±0.3 *vs* 0.71±0.25 cmH_2O·mmHg^{-1}, respectively). However, Group B had significantly decreased ventilatory and $P_{0.2}$ responses to CO_2 (0.71±0.23 *l*·min^{-1}·mmHg^{-1} and 0.34±0.17 cmH_2O·mmHg^{-1}, respectively).

This comparison showed that patients with OSA had normal CO_2 response when awake, whereas those with overlap syndrome had diminished CO_2 response when awake. It seems that co-existence of COPD with hypercapnic respiratory failure is the main cause of decreased CO_2 response in the overlap syndrome.

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*Lung Function Laboratory and **Dept of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warszawa, Poland.

Correspondence: L. Radwan
Lung Function Lab.
Institute of Tuberculosis and Lung Diseases
Plocka 26
01-138 Warszawa
Poland

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Control of breathing in awake patients with obstructive sleep apnoea (OSA) has been evaluated by many authors with conflicting results. In some studies [1–4], sleep fragmentation due to apnoea was associated with blunted chemoreflexes; hypercapnic ventilatory and mouth occlusion pressure responses were decreased. Other studies [5–8] and our own [9], demonstrate normal respiratory responses during CO_2 stimulation in normacapnic OSA patients. However, some authors [6, 10], found that, ventilatory CO_2 response was depressed in OSA patients with chronic hypercapnia.

During recent years, we have studied patients with OSA and also a group of patients with OSA and coexisting chronic obstructive pulmonary disease (COPD) and respiratory failure, so-called "overlap syndrome", as proposed by FLENLEY [11, 12]. The purpose of this study was to compare the breathing pattern and CO_2 response in patients with OSA and normal lung function with that in patients with overlap syndrome and hypercapnic respiratory failure.

Material and methods

Two groups of patients and a control group were investigated. Group A consisted of 20 obese men with OSA, without respiratory symptoms and with almost normal lung function results. Their mean age was 45±6 yrs, and body mass index (BMI) 34.4±6.3 kg·m^{-2}. Group B consisted of 11 obese men with OSA and hypercapnic respiratory failure due to COPD (overlap syndrome). Their mean age was 53±8 yrs, and BMI 36.3±5.8 kg·m^{-2}.

Group C consisted of 13 healthy, nonobese subjects with no sleep complaints and no sleep symptoms typical of OSA. Their mean age was 34±7 yrs, and BMl was 22.3±3.0 kg·m^{-2}.

In all Group A and B patients, lung function tests, including volumes, maximal expiratory flows and airway resistance were performed with the use of body plethysmograph (Masterlab, Jaeger). Predicted values were those of the European Coal and Steel Community (ECSC) [13]. Blood gases were measured in arterialized capillary blood using a Corning 168 analyser.

The pattern of breathing, minute ventilation ($\dot{V}_E$) and mouth occlusion pressure ($P_{0.2}$) were measured with the use of a pneumotachograph, electromanometer and occlusion pressure valve, with the subject in the sitting position, awake and at rest. Ventilatory and mouth occlusion pressure responses during CO_2 rebreathing test, according to Read, were measured with the same set of equipment. CO_2 concentration before and during rebreathing was measured with the use of a mass spectrometer (Centronix). Inspired volume, and end-tidal CO_2 were recorded continuously on a six-channel recorder (Watanabe). The respiratory response was evaluated from minute ventilation and mouth occlusion pressure slopes ($\Delta\dot{V}_E/\Delta P_{CO_2}$) and $\Delta P_{0.2}/\Delta P_{CO_2}$ and from absolute values of ventilation and $P_{0.2}$ at an end-tidal carbon dioxide tension (P_{ET,CO_2}) 60 mmHg. The strength of respiratory muscles, maximal inspiratory (MIP) and expiratory (MEP) pressures, were measured at the mouth with the use of a manometer.

The diagnosis of OSA was established by standard polysomnography, and was performed using a computerized system (Somnostar 4100; Sensormedics). Sleep staging was carried out according to standard criteria [14]. Sleep efficiency was defined as percentage ratio of total sleep time to sleep period. Breathing disorders were classified as obstructive, central or mixed. Apnoea was defined as cessation of nasal or oral airflow for at least 10 s [15]. Hypopnoea was defined as a 50% decrease of thoracic and abdominal respiratory signal for 10 s or more [16)]. Significant desaturation was defined as a fall in Sa_{O_2} of 4% or more from the preceding stable Sa_{O_2} when asleep [17]. Sleep and respiration were scored visually on a high resolution screen. The apnoea +hypopnoea index (AHI) was calculated from hand-scoring of polygraphic data as a mean number of disordered breathing episodes for one hour of sleep. AHI was considered diagnostic for OSA when ≥10.

Statistical significance of differences between data were tested with the unpaired t-test.

Results

Polysomnography confirmed the diagnosis of OSA in both groups of patients. There were no statistical differences between Groups A and B in BMI, AHI and mean Sa_{O_2} during sleep (table 1). Lung function values were within normal limits in Group A, with the exception of a decreased mean value of maximal expiratory flow at 25% forced vital capacity (MEF_{25}). Mean arterial oxygen tension (Pa_{O_2}) was 8.9 kPa (66.7 mmHg). All patients were normocapnic (table 2), with the exception of one having an arterial carbon dioxide tension (Pa_{CO_2}) 6.4 kPa (48 mmHg).

All patients in Group B had symptoms of bronchial obstruction, lung hyperinflation, moderate hypoxaemia, slight hypercapnia and increased serum bicarbonate concentration. They also had lower values of maximal inspiratory and expiratory pressures, probably due to lung hyperinflation (table 2).

In both groups, we found increased resting ventilation. In Group A it was due mainly to increased tidal volume (V_T), and in Group B it was predominantly due to higher frequency of breathing. Patients in Group B had lower V_T, higher frequency of breathing and higher mouth occlusion pressure compared with Group A. Mean inspiratory flow (V_T/T_I) and mouth occlusion pressure ($P_{0.2}$) were increased in both groups in comparison to controls (table 3).

During CO_2 rebreathing, Group A patients had ventilatory and $P_{0.2}$ responses similar to those of the control group. However, Group B patients had significantly decreased ventilatory and $P_{0.2}$ responses during rebreathing (table 4) in comparison to controls. Also, absolute values of ventilation and $P_{0.2}$ at P_{ET,CO_2} of 60 mmHg were decreased in Group B patients. The differences in respiratory response between Group A and B patients were also statistically significant ($p<0.001$).

Table 1. – Results of polysomnography in patients with OSA (Group A) and overlap syndrome (Group B)

	Group A (n=20)	Group B (n=11)	p-value
Age yrs	45±6	53±8	<0.01
BMI $kg \cdot m^{-2}$	34.3±6.3	36.3±5.8	NS
Sleep efficiency %	67±10	83±14	<0.01
AHI	62±19	54±22	NS
Mean Sa_{O_2} during sleep %	85±5	84±3	NS

BMI: body mass index; AHI: apnoea/hypopnoea index; Sa_{O_2}: arterial oxygen saturation; NS: nonsignificant; OSA: obstructive sleep apnoea.

Table 2. – Mean results of lung function tests in patients with OSA (Group A) and overlap syndrome (Group B)

	Group A (n=20)	Group B (n=11)	p-value
FVC % pred	107±16	64±19.1	<0.001
FEV_1 % pred	98±15	43±15	<0.001
FEV_1/FVC %	76±5	53±11.8	<0.001
Raw $kPa \cdot l^{-1} \cdot s$	0.22±0.06	0.73±0.38	<0.001
TGV % pred	104±20	140±42	<0.01
TLC % pred	105±10	102±16	NS
Pa_{O_2} kPa	8.9±0.8	6.8±0.6	<0.001
mmHg	66.7±6.1	50.8±4.7	
Pa_{CO_2} kPa	5.3±0.5	6.8±1.0	<0.001
mmHg	40.0±3.6	50.7±7.7	
HCO_3 $mmol \cdot l^{-1}$	23.3±3.6	29.7±6.2	<0.001
MIP cmH_2O	120±37	77±33	<0.05
MEP cmH_2O	198±47	131±32	<0.001

Data are presented as mean±SD. FVC: forced vital capacity; % pred: percentage of predicted value; FEV_1: forced expiratory volume in one second; Raw: airways resistance; TGV: thoracic gas volume; TLC: total lung capacity; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; OSA: obstructive sleep apnoea; NS: nonsignificant.

Discussion

The pattern of breathing was abnormal in both groups of patients with OSA in comparison to control, nonobese

Table 3. – Pattern of breathing during resting ventilation in patients with OSA (Group A), overlap syndrome (Group B) and in control subjects (Group C)

	Group A (n=20)	Group B (n=11)	Group C (n=13)
$\dot{V}_E$ $l \cdot min^{-1}$	15.3±3.1***	12.8±3.5**	9.2±2.5
V_T l	0.95±0.19***	0.59±0.17	0.62±0.18
T_I s	1.6±0.5	1.07±0.21	1.8±0.82
Ttot s	3.8±0.55	2.78±0.55**	4.3±1.5
V_T/T_I $l \cdot s^{-1}$	0.62±0.13***	0.56±0.14***	0.37±0.10
$P_{0.2}$ cmH_2O	3.6±1.6**	6.4±3.6***	2.2±0.4

$\dot{V}_E$: minute ventilation; V_T: tidal volume; T_I: inspiratory time; Ttot: total breath duration; V_T/T_I: mean inspiratory flow; $P_{0.2}$: mouth occlusion pressure; OSA: obstructive sleep apnoea. In statistical analysis, Group A and B were compared with Group C. ***: p<0.001; **: p<0.01.

Table 4. – Ventilatory and mouth occlusion pressure responses during CO_2 rebreathing test in patients with OSA (Group A), overlap syndrome (Group B) and in control subjects (Group C)

	Group A (n=20)	Group B (n=11)	Group C (n=13)
$\Delta\dot{V}_E/\Delta P_{CO_2}$ $l \cdot min^{-1} \cdot mmHg^{-1}$	2.7±1.1	0.71±0.23***	2.1±0.4
$\Delta P_{0.2}/\Delta P_{CO_2}$ $cmH_2O \cdot mmHg^{-1}$	0.7±0.3	0.34±0.17***	0.71±0.25
$\dot{V}_E$ at P_{ET,CO_2} 60 mmHg $l \cdot min^{-1}$	66.7±21.4	26.7±10.9***	58.8±15.7
$P_{0.2}$ at P_{ET,CO_2} 60 mmHg cmH_2O	15.1±5.9	8.8±4.7***	18.9±8.0

$\dot{V}_E$: minute ventilation; P_{CO_2}: carbon dioxide tension; $P_{0.2}$: mouth occlusion pressure; P_{ET,CO_2}: end-tidal carbon dioxide tension; OSA: obstructive sleep apnoea. In statistical analysis, Group A and B were compared with Group C. ***: p<0.001; **: p<0.01.

subjects. Patients with the overlap syndrome had a higher frequency of breathing and lower tidal volume than patients with OSA. Mean inspiratory flow and mouth occlusion pressure were increased in both groups, indicating higher neuromuscular output.

The mechanism of increased neuromuscular output in OSA patients is not yet established, but obesity and changed thoracic mechanics may play a role. It is documented that chest wall compliance is reduced in obese patients, due to deposition of adipose tissue [18, 19]. This change in thoracic elasticity may enhance so-called "load compensation reflex" similar to healthy subjects with an added elastic [20] or mass load [21].

Another factor causing higher neuromuscular output in awake OSA patients might be increased hypoxic drive due to slight hypoxaemia. In patients with overlap syndrome, the change in breathing pattern was additionally affected by disturbed mechanics of breathing and gas exchange.

In our study, CO_2 sensitivity in awake OSA patients was in the normal range, similar to the values of the control group. This is in accordance with our earlier data [9], and that of others [5–7]. However, in patients with the overlap syndrome and hypercapnia, ventilatory and mouth occlusion pressure responses were decreased. There are few studies of CO_2 sensitivity in patients with OSA and co-existing hypercapnia. GARAY *et al.* [6] demonstrated an inverse relationship between waking P_{CO_2} and hypercapnic ventilatory response. BERTHON-JONES and SULLIVAN [22] and, more recently, VERBRAECKEN *et al.* [10] also found decreased ventilatory response in OSA patients with hypercapnia. In addition, hypercapnic patients with COPD and without sleep disorders had decreased CO_2 sensitivity [23–25].

In obstructive patients with the overlap syndrome, a low ventilatory response to CO_2 is caused mainly by disturbed lung mechanics and gas exchange. Mouth occlusion pressure response to CO_2 in patients with the overlap syndrome may have been affected in several ways. In these patients with chronic hypercapnia, we found increased blood bicarbonate concentration. This factor inhibits CO_2 sensitivity and decreases mouth occlusion pressure response [23–25]. Some authors [26] have postulated that hyperinflation of the lung may also decrease mouth occlusion pressure response. As hyperinflation was also found in patients with overlap syndrome, this factor has to be taken into account. In addition, lower respiratory muscle strength and constitutional or genetic factors may be responsible for lowered ventilatory and mouth occlusion pressure responses in patients with overlap syndrome (Group B), as has been suggested in hypercapnic COPD patients [27].

Comparison of the two groups of patients showed that those with OSA had normal CO_2 response, whereas those with the overlap syndrome had diminished CO_2 response like hypercapnic patients with COPD alone. It seems that co-existence of COPD with hypercapnic respiratory failure is the main cause of decreased CO_2 response in overlap syndrome. However, breathing pattern was abnormal in both groups of patients with OSA, probably as a consequence of obesity and changed thoracic mechanics.

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