Upsala J Med Sci 97: 141–148

Airway Obstruction, Obesity and CO_2 Ventilatory Responsiveness in the Sleep Apnea Syndrome

Thorarinn Gislason[1] and Ritva Tammivaara[2]

From the Departments of [1]Pulmonary Medicine and [2]Clinical Physiology, Akademiska Sjukhuset, University of Uppsala, Uppsala, Sweden

ABSTRACT

In 32 patients with sleep apnea syndrome (SAS), pulmonary function, blood gases and the ventilatory response to CO_2 (CO_2 VR) were studied before and 6 months after uvulopalato-pharyngoplasty. Nine of the SAS patients had airway obstruction (AO-SAS), defined as $FEV_{1.0} \leq$ 72 % of the predicted value. They had a significantly higher $PaCO_2$, lower PaO_2 and a lower CO_2 VR than the remaining SAS patients. Preoperatively 4 SAS patients were hypercapnic ($PaCO_2$ >5.8 kPa) and compared with the normocapnic ones they were more obese; in 3 of them $FEV_{1.0}$ was ≤ 72%. The hypercapnic SAS patients had a significantly lower CO_2 VR. The CO_2 VR was significantly correlated to AO and the degree of oxygen desaturation during sleep, but not to the number of episodes of apnea and hypopnea nor their length. The VR to CO_2 did not predict the postoperative outcome.

Postoperatively 2 hypercapnic obese AO-SAS patients showed a large decrease in episodes of apnea and hypopnea and an increase in CO_2 VR, and became normocapnic. Other patients showed no consistent changes in CO_2 VR postoperatively.

INTRODUCTION

The sleep apnea syndrome (SAS) is a frequently diagnosed disorder which is characterized by loud snoring and repeated upper airway obstructions during sleep (1,2). Many aspects of the inter-relationship between SAS, pulmonary function, obesity, hypercapnea and the ventilatory response to CO_2 (CO_2 VR) are still unclear. Aubert-Tulken and coworkers found a shift to the left in the curve of the CO_2 VR after tracheostomy in a 41-year-old male patient who was hypercapnic and had pulmonary airway obstruction (3). Guilleminault and Cumminskey reported that among 5 eucapnic, nonobese men with SAS the CO_2 VR was doubled after tracheostomy (4). Among 8 hypercapnic SAS patients 4 became eucapnic after treatment (5). In 19 closely followed SAS patients there was no change in the slope of the CO_2 VR during successful treatment with continuous positive airway pressure (CPAP) (6). However, in 10 of the patients, who were initially hypercapnic, there was an increase in the CO_2 VR measured as the position on the CO_2 VR

curve (6). We have so far found no reports on the possible results of uvulopalatopharyngoplasty (UPPP) on hypercapnea and the CO_2 VR.

The aim of this prospective study was to evaluate the CO_2 VR among SAS patients in relation to airway obstruction, obesity, the severity of the SAS, and arterial blood gases, before and after UPPP.

METHODS

Patients: This study comprised all SAS patients who underwent UPPP for SAS between September 1984 and April 1986 at Akademiska Sjukhuset, Uppsala, Sweden. In all there were 31 men and 3 women, with a mean age of 49 years (range 30-68). Fourteen were current smokers and one had stopped smoking less than one year previously. The study protocol had been approved by the Ethics Committee of the Medical Faculty of Uppsala University.

The clinical characteristics of the SAS patients and the operative procedure have been described in detail elsewhere (7). Five had a history of chronic obstructive pulmonary disease and 1 had bronchial asthma. Two were treated with beta-2 agonists, and 2 with theophylline preparations. All but 1 were habitual snorers, and all-night polysomnographic studies had confirmed the SAS diagnosis. An apnea was defined as a 10 second or longer complete cessation of both nasal and oral air flow and a hypopnea was defined as a marked decrease in oro-nasal air flow for at least 10 seconds, followed by a fall in baseline oxygen saturation by at least 4% or arousal. An index of apneas (A) and hypopneas (H), was calculated as the total number of such events per hour of sleep (1). Preoperatively these 34 SAS patients had a mean (A+H) index of 44 (median 30, range 9-101). Six months postoperatively all 34 patients came for follow-up studies and 22 patients (65%) showed a decrease in the (A+H) index by more than 50% and were therefore classed as responders to UPPP (7). Sixteen patients had an (A+H) index below 10 postoperatively. All but 4 SAS patients were overweight, with a body mass index (BMI) of ≥ 29 kg/m^2 and the mean BMI for all patients was 32.7 (SD 5.7) kg/m^2 (Table 1).

Lung function tests and blood gases: Lung volumes and maximal flow volume curves were determined by standard spirometry and body plethysmography. Arterial pH, PO_2, and PCO_2 were measured with a Corning 168 pH, PO_2 and PCO_2 blood gas analyzer (Corning Medical, Halstead, England). Oxygen saturation was measured continuously during sleep with a BIOX III Pulse oximeter. The number of apneas and hypopneas per hour of sleep that caused a fall in SaO_2 below 85% were especially recorded.

Testing of ventilatory regulation: All tests of the VR to hyperoxic hypercapnea were performed at the same time of day by a modification of the rebreathing method described by Read (8), while the patients were awake and at rest. We have previously described the CO_2 rebreathing test in detail (9). The VR slope was calculated as the change in ventilation (ΔV l/min) caused by a rise in end-tidal PCO_2 by 1 kPa (=7.5 mmHg). The position of the VR line (l/min) was expressed as the

minute ventilation at a PCO_2 of 8 kPa (6).

Table 1. SAS patients with airway obstruction (AO-SAS) compared with the other SAS patients. BMI: body mass index; $FEV_{1.0}$: forced expiratory volume in one second; VC: vital capacity; RV: residual volume; TLC: total lung capacity; FRC: functional residual capacity. A: apneas; H: hypopneas; EVF: erythrocyte volume fraction.

	AO-SAS (n=9)		**Other SAS patients** (n=23)		
	Mean	(S.D.)	Mean	(S.D.)	p-value
Age (yrs)	54	(10)	47	(10)	=0.1
BMI (kg/m^2)	37.0	(6.4)	31.4	(4.9)	<0.01
EVF (%)	46	(5)	44	(3)	=0.2
Pulmonary function tests					
$FEV_{1.0}$ (% pred.)	65	(7)	97	(12)	
RV (% pred)	129	(37)	102	(30)	<0.05
TLC (% pred)	84	(14)	100	(10)	<0.001
$FEV_{1.0}/VC$ (%)	71	(9)	77	(6)	<0.05
Blood gases					
PaO_2 (kPa)	9.1	(1.0)	10.7	(1.2)	<0.002
$PaCO_2$ (kPa)	5.8	(1.0)	5.0	(0.5)	<0.01
$\Delta V/\Delta PCO_2$ (l/min/kPa)	13.1	(6.2)	24.8	(10.1)	<0.01
Sleep data					
(A+H) index (No. per hour)	58	(30)	39	(26)	=0.09
Mean length of A+H (sec)	21	(5)	24	(7)	=0.4
A+H with $SaO_2 < 85\%$ (No. per hour)	32	(25)	9	(15)	<0.005
Postoperative reduction in (A+H) index (%)	58	(37)	58	(38)	=0.97

Statistics: Statistical probability was tested by a Student's **t** test on unpaired values, except in comparisons of changes in VR, when paired values were used. The correlations between different parameters were assessed by least square linear regression.

RESULTS

Among the 34 patients treated by UPPP, all but 2 underwent representative lung function tests. Flow parameters revealed airway obstruction (AO), defined as an $FEV_{1.0}$ of $\leq 72\%$ of the

predicted value, among 9 SAS. These patients will be referred to as AO-SAS. Compared with the remainder they were more overweight ($p<0.01$) and had lower PaO_2 and higher $PaCO_2$ at rest ($p<0.01$) (Table 1). The AO-SAS patients had a somewhat, but not significantly higher (A+H) index, but their mean length of A+H was the same. The AO-SAS patients desaturated more often during sleep than the other SAS patients. There was no difference regarding the postoperative results between the AO-SAS patients and the others, as both groups showed a 58% decrease in the (A+H) index postoperatively. $FEV_{1.0}$ was not predictive of the UPPP results and 5 of the AO-SAS patients were later classed as responders to UPPP, while four were non-responders (7). The pulmonary function tests 6 months postoperativly revealed only minor individual changes in $FEV_{1.0}$, and all those classed preoperatively as AO-SAS patients still had an $FEV_{1.0}$ of $\leq 72\%$ of the predicted value. After UPPP they continued to be more hypoxemic (PaO_2: 8.6 (1.3) kPa) than the remainder (PaO_2: 11.0 (1.6) kPa, $p<0.01$) and their medication was similar. This was true both for responders to UPPP and non-responders.

$PaCO_2$: Preoperatively 4 SAS patients were hypercapnic, with $PaCO_2$ >5.8 kPa (Cases No 1,2,17 and 31 in ref. 7). Compared with the normocapnic patients they were more obese and showed a tendency to a higher (A+H) index, but the length of A+H was the same in these 2 groups (Table 2). Three of the hypercapnic patients also had an $FEV_{1.0}$ value $\leq 72\%$, but the fourth had a high $FEV_{1.0}$, so the difference was not significant for this small sample ($p=0.1$).

Table 2. Hypercapnic (n=4) and normocapnic (n=28) SAS patients. (Abbreviations see Table 1).

	Hypercapnic	**Normocapnic**	p-value
BMI (kg/m^2)	41.2 (7.6)	31.9 (4.8)	<0.003
EVF (%)	48 (4)	44 (3)	=0.06
PaO_2 (kPa)	9.1 (1.6)	10.4 (1.2)	=0.06
$FEV_{1.0}$ (% pred)	76 (13)	91 (21)	=0.2
$FEV_{1.0}$/VC(%)	77(11)	75(7)	=0.6
RV (% pred)	156 (43)	100 (27)	<0.001
$\Delta V/\Delta PCO_2$ (l/min/kPa)	11 (7)	23 (10)	<0.02
(A+H) index (No. per hour)	65 (28)	40 (26)	=0.09
A+H with $SaO_2 < 85\%$ (No. per hour)	43 (15)	10 (7))	<0.002

Ventilatory response to CO_2: Altogether 32 SAS patients underwent a test of the CO_2 VR before UPPP and all but two were tested again 6 months postoperatively (Table 3). The mean slope of the CO_2 VR curve was 21 (10) l/min/kPa and the mean ventilation at 8 kPa was 47 (23)

l/min (Table 3). There was a significant negative correlation between the number of A+H causing an SaO_2 desaturation < 85% and the CO_2 VR (VR = 35.3 +(-0.95 x No. of desaturations), $p<0.02$). The CO_2 VR was also significantly correlated to obesity (VR = 37.6 +(0.21 x BMI) $p<0.05$) and also to the degree of AO (VR = 71.6 + 0.81 x FEV1, $p<0.05$). The 9 AO-SAS patients displayed a significantly lower CO_2 VR than the others ($p<0.005$), estimated both as the slope and as minute ventilation at 8 kPa (Table 3). The 4 hypercapnic SAS patients also exhibited a very low CO_2 VR (1.8, 18.0, 13.0 and 9.6 l/min/kPa), and this was significantly lower than in the rest of the patients with SAS (Table 2). The CO_2 VR was not significantly correlated to (A+H) index or the mean length of apneas and hypopneas.

Table 3. The ventilatory response to CO_2 in l/min, pre- and postoperatively. No statistical difference was observed.

	Preoperatively		**Postoperatively**	
	Slope (ΔV/kPa) Mean (SD)	Vent. at 8 kPa Mean(SD)	Slope (ΔV/kPa) Mean (SD)	Vent. at 8 kPa Mean (SD)
All patients (n=30)	21 (10)	47 (23)	24 (14)	45 (22)
AO-SAS patients (n=8)	13 (6)	31 (18)	13 (7)	33 (20)
Other SAS patients (n=22)	24 (10)	53 (22)	28 (15)	49 (22)
Responders to UPPP (n=20)	23 (11)	53 (22)	26 (16)	49 (23)
Nonresponders to UPPP (n=10)	18 (8)	37 (22)	19 (8)	36 (16)

Postoperative findings: There was no consistent change postoperatively in the CO_2 VR, either among responders or nonresponders to UPPP, or among AO-SAS patients (Table 3). Postoperatively one hypercapnic patient had no apneas or hypopneas and the slope of his CO_2 VR increased from 1.8 to 7.3 l/min/kPa, and $PaCO_2$ decreased from 7.5 to 5.8 kPa. Another patient showed a 35% reduction in (A+H) index postoperatively and his $PaCO_2$ fell from 5.9 to 5.4 kPa; the slope of the CO_2 VR curve increased from 18 to 25 l/min/kPa and ventilation at 8 kPa from 36 to 45 l/min. The remaining 2 patients showed only a minor decrease in the (A+H) index postoperatively and were still hypercapnic.

Smokers vs. nonsmokers: Among the SAS patients the smokers were more hypoxic (PaO_2 = 9.7 (1.4) kPa vs.10.6 (1.1) kPa, $p< 0.05$) than the nonsmokers and they also had higher $PaCO_2$ values (5.5 (0.9) kPa vs. 5.0 (0.4) kPa, $p< 0.05$). Their $FEV_{1.0}$ was also somewhat lower ($FEV_{1.0}$ = 83 (18) vs. 95 (19) % pred, p=0.08). There was no difference between the smokers and nonsmokers as to sleep data, the CO_2 VR or the erythrocyte volume fraction.

DISCUSSION

The findings in our study group of SAS patients clearly illustrate the great subject variability in the severity of this disorder and their heterogeneous ventilatory and pulmonary status. The CO_2 VR varied considerably among SAS patients, but was significantly related to AO and obesity. We used ventilation as a parameter of chemosensitivity, but in patients with obstructive lung disease ventil-ation may be limited by expiratory airflow and not actual drive to breathe (10). However, as the airway obstruction in our patients was not so great (7), we consider that the low CO_2 VR among the AO-SAS patients, can only partly be explained by mechanical limitation imposed by lower airway dysfunction. This connection between airway obstruction, a low CO_2 VR and hypercapnea has been pointed out in a previous case report (4) and also by Bradley and coworkers (11). They found that among 50 consecutive SAS patients the presence of diffuse airway obstruction was an important predisposing factor to the development of CO_2 retention and all of their seven hypercapnic patients had AO (11). One of our hypercapnic patients had no signs of AO ($FEV_{1.0}$=95 % (of pred), but he suffered from extreme obesity (BMI=40.9 kg/m^2) (7). In a group of 28 SAS patients with airway obstruction hypercapnea was much more common among SAS patients with high lifetime alcohol comsumption (12). Our data on alcohol consumption are only based on information from our standard interview and we know that among our 4 hypercapnic SAS patients, 2 reported heavy alcohol intake, 1 never drinker, and no information was available from the fourth.

Patients with low CO_2 VR more frequently desaturated below 85%, but other data from sleep studies were not related to the CO_2 VR. These results are similar to the results from Kunitomo et al, but they reported that the awake hypercapnic ventilatory drive was significantly inversely correlated with maximal desaturation during REM sleep but showed no correlation with any other sleep desaturation parameters (13). In our study this is at least partly because these patients had greater pulmonary obstruction and their baseline awake SaO_2 position is closer to the steep portion of the oxyhemoglobin dissociation curve.

There was no consistent change in the CO_2 VR after UPPP, either in the group of SAS patients as a whole or in the different subgroups (Table 3). This is contrary to a previous finding of a shift in the VR curve to the left and an increase in the slope of the VR curve after tracheostomy (3) and also to a report on 5 initially normocapnic men, for whom an increase in the slope was observed 3 months after tracheostomy (4). In the largest study in this field hitterto it was found that among 19 SAS patients treated with CPAP, only those 10 patients with elevated daytime CO_2 showed a progressive increase in ventilation at 8 kPa, but there was no change in the slope of the CO_2 VR (6). One possible explanation for the lack of increase in the mean CO_2 VR in our study might be that so few of our patients were hypercapnic. Another reason may be that compared to CPAP and tracheostomy, UPPP does not eliminate all apneas and hypopneas as effectively. The patients in references 3 and 4 were all tracheostomized and this might possibly have influenced the VR

independently of the relief of apneas and hypopneas. After tracheostomy there is a decrease in dead space ventilation, which increases the alveolar ventilation and might lead to lower $PaCO_2$, at least during sleep. Although 16 of our SAS patients had an (A+H) index below 10 postoperatively (7) they might still be suffering from partial upper airway obstruction (14). The mechanisms that cause a decrease in the CO_2 VR might therefore still be operative.

A small subgroup among our SAS patients with airways obstruction and extreme obesity also had hypercapnea and a low CO_2 VR. Two of them who showed postoperatively the greatest improvement in the (A+H) index, became normocapnic and in their cases the low CO_2 VR was partly reversible. A possible explanation for this is that increased endogenous opioid activity might occur as an adaptive reaction (15).

ACKNOWLEDGEMENTS

Supported by grants from the Swedish National Association against Heart and Chest Diseases, Stockholm, The King Oscar II Jubilee Foundation, Stockholm and the Thuring Foundation, Stockholm.

REFERENCES

1. Guilleminault, C., Cumminsky, J., & Dement, W.C.: Sleep Apnea Syndromes: Recent Advances. Adv Intern Med 26:347-74, 1980.
2. Krieger, J.: Sleep apnea syndromes in adults. Bull Eur Physiopath Respir 22:147-89, 1986.
3. Aubert-Tulkens, G., Willems, B., Veriter, Cl., Coche, E. & Stanescu, D.C.: Increase in ventilatory response to CO2 following tracheostomy in obstructive sleep apnea. Bull Eur Physiopath Respir 16:587-93, 1980.
4. Guilleminault, C., & Cumminsky, J.: Progressive improvement of apnea index and ventilatory response to CO2 after tracheostomy in obstructive sleep apnea syndrome. Am Rev Respir Dis 126:14-20, 1982.
5. Rapoport, D.M., Stuart, M.G., Epstein, H., & Goldring, R.M.: Hypercapnea in obstructive sleep apnea syndrome. Chest 89:627-35, 1986.
6. Berthon-Jones, M. & Sullivan, C.E.: Time course of change in the ventilatory response to CO2 with long-term CPAP therapy for obstructive sleep apnea. Am Rev Respir Dis 135:144-7, 1987.
7. Gislason, T., Lindholm, C-E., Almqvist, M., Birring, E., Boman, G., Eriksson, G., Larsson, S.G., Lidell, C., & Svanholm, H.: Uvulopalatopharyngoplasty in the sleep apnea syndrome - predictors of results. Arch Otolaryngol 144:45-51, 1988.
8. Read, D.J.C.: A clinical method for assessing the ventilatory response to carbon dioxide. Aust Ann Med 16:20-32, 1967.
9. Gislason, T., Sandhagen, B., & Boman, G.: Transcutaneous CO2 monitoring in adults with sleep-related breathing disorders. Upsala J Med Sci 94:171-81, 1989.
10. Plotkowski, L.M., Hannhart, B, Elfassi, R., Sautegeau, A., Peslin, R., & Sadoul, P.: Role

of the mechanical impairment on the ventilatory response to CO2 in chronic airway obstruction. Clin Respir Physiol 23:51-6, 1987.

11. Bradley, T.D., Rutherford, R., Lue, F., Moldofsky, H., Grossman, R.F., Zamel, N., & Phillipson, E.A.: Role of diffuse airway obstruction in the hypercapnia of obstructive sleep apnea. Am Rev Respir Dis 134:920-4, 1986.
12. Chan, S.C., Gurnstein, R.R., Bye, P.T.P., Woolcock, A.J., & Sullivan, C.E.: Obstructive sleep apnea with severe chronic airflow limitation. Am Rev Respir Dis 140:1274-8, 1989.
13. Kuniotomo, F., Kimura, H., Tatsumi, K., Kuriyama, T., Watanabe, S., & Honda, Y.: Abnormal breathing during sleep and chemical control of breathing during wakefulness in patients with sleep apnea syndrome. Am Rev Respir Dis 139:164-9, 1989.
14. Polo, O., Brissaud, L., Fraga, J., Déjean, Y., & Billiard, M.: Partial upper airway obstruction in sleep after uvulopalatopharyngoplasty. Arch Otolaryngol Head Neck Surg 115:1350-54, 1989.
15. Gislason, T., Almqvist, M., Boman, G., Lindholm, C-E., & Terenius, L.: Increased CSF odioid activity in sleep apnea syndrome-regress after successful treatment. Chest 96:250-54, 1989.

Correspondence and request for reprints:

Thorarinn Gislason, M.D
Dept. of Pulmonary Medicine
Vífilsstadir,
210 Gardabær, Iceland