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ORIGINAL INVESTIGATION

Overnight Transcutaneous Carbon Dioxide Monitoring in Eucapnic Patients with Obstructive Sleep Apnea Syndrome

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Abstract

OBJECTIVES: We monitored increases in CO_2 levels during sleep by measuring transcutaneous pCO_2 ($PtcCO_2$) to determine its relationship with polysomnographic data in normocapnic patients with obstructive sleep apnea syndrome (OSAS).

MATERIAL AND METHODS: Between October 2011 and December 2012, 139 patients underwent $PtcCO_2$ monitoring with polysomnography. All patients were evaluated with arterial blood gas (ABG) measurements and pulmonary function tests (PFTs). We excluded 13 patients with COPD and/or daytime hypercapnia and 29 patients whose $PtcCO_2$ records could not be evaluated.

RESULTS: The patients' mean age was 46.8±10.3 years. Fifty-nine patients (60.8%) were male, and 38 (39.2%) patients were female. The mean overnight $PtcCO_2$ was ≤45 mm Hg in 84 (86.6%) patients and >45 mm Hg in 13 (13.4%) patients. In the group with $PtcCO_2$>45 mm Hg, 10 patients had an apnea-hypopnea index (AHI) >15, and 3 patients had an AHI<15, without a statistically significant difference (p=0.078). The mean apnea and apnea/interapnea periods were similar. The mean $PtcCO_2$ values correlated with time spent when the SpO_2 was <90% (r=0.220, p<0.031). When we grouped the patients by AHI, 60 (61.8%) patients had an AHI>15 (moderate to severe OSAS), and 37 (37.2%) had an AHI<15 (mild OSAS). Of the former group, 16.7% had a mean $PtcCO_2$ >45 mm Hg, whereas this ratio was 8.1% in the latter group. The difference was not statistically significant (p=0.359). In the group with an AHI>15, the highest $PtcCO_2$ levels were significantly higher (p<0.05).

CONCLUSION: We conclude that seemingly eucapnic OSAS patients may experience hypercapnia when sleeping, and $PtcCO_2$ monitoring may be useful in the early diagnosis of hypercapnia.

KEY WORDS: Obstructive sleep apnea syndrome, transcutaneous PCO_2, nocturnal hypercapnia

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INTRODUCTION

In healthy adults, the hypercapnic ventilatory response is depressed during sleep. This ventilatory response is lower in NREM sleep than in wakefulness and is lowest in REM sleep. Generally, arousal develops before the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) rises more than 10 mm Hg over the $PaCO_2$ values of wakefulness to prevent further increases in $PaCO_2$ [1]. Berthon-Jones and Sullivan defined the threshold of increase in $PaCO_2$ that causes arousal as 6 mm Hg in healthy adults [2].

Mechanisms that prevent hypercapnia during sleep may be damaged in patients with sleep breathing disorders. Chronic hypercapnia in association with obesity has been termed 'obesity hypoventilation syndrome.' Patients suffering from this syndrome can exhibit nocturnal hypoventilation unrelated to upper airway obstruction [3]. On the other hand, obstructive sleep apnea syndrome (OSAS) is characterized by intermittent closure of the pharyngeal airway during sleep, resulting in episodic hypoxemia and sleep disruption. Maintenance of eucapnia during sleep in OSAS requires a balance between CO_2 loading during apnea and CO_2 elimination. However, some patients with OSAS may exhibit daytime hypercapnia. The prevalence of daytime hypercapnia in these patients varies from 11%-43%, according to previous reports [4-11]. In these studies, lower forced expiratory volume in 1 second (FEV_1), vital capacity (VC), total lung capacity (TLC), minimum overnight saturation level of oxygen by pulse oximetry (SpO_2), higher body mass index (BMI), and apnea-hypopnea index (AHI) have been found to be related to hypercapnia. On the other hand, some studies have reported an association between AHI and daytime hypercapnia in patients with OSAS, even after excluding chronic obstructive pulmonary disease (COPD) patients [9,10]. Labaan's study detected daytime hypercapnia in OSAS patients without COPD or obesity [10]. These results point out that there might be other mechanisms causing chronic daytime hypercapnia in patients with OSAS. Berger et al. [12] found that acute hypercapnia during periodic breathing while

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sleeping may occur when ventilation/perfusion (V/Q) is mismatched. They also found that compensation for CO_2 accumulation during 'apnoea/hypopnoea may be limited by the duration of the inter-event interval, as well as by the magnitude of the inter-event ventilation.'

With these findings in mind, we investigated whether PCO_2 monitoring should be practiced routinely in patients with OSAS during a polysomnography. Further, we investigated which method should be used for monitoring. Routine transcutaneous PCO_2 ($PtcCO_2$) monitoring has minimal clinical use in adult polysomnographies; its slow response time makes it unsuitable for monitoring blood gas pressures during sleep, in which rapid and short-lasting changes can occur. $PtcCO_2$ monitoring may be of some use in adults with waking hypercapnia or suspected sleep-related alveolar hypoventilation [13,14]; however, many studies have shown that continuous $PtcCO_2$ monitoring is useful in monitoring and diagnosing sleep-related breathing disorders, especially in children, intensive care patients, patients with non-invasive mechanical ventilation support, and perioperative patients [15-21]. The American Academy of Sleep Medicine (AASM) manual for scoring sleep mentioned both end-tidal PCO_2 and $PtcCO_2$ measurements as being optional for hypoventilation scoring [22].

Regarding these findings, we aimed to examine $PtcCO_2$ increases and the relation between increased $PtcCO_2$ and polysomnographic findings prospectively by monitoring $PtcCO_2$ during polysomnographies in eucapnic OSAS patients, as only a few studies have been done with such patients.

MATERIAL AND METHODS

We performed polysomnographies and $PtcCO_2$ monitoring on 139 patients admitted to our clinic between October 2011 and December 2012 who complained of witnessed sleep apnea, snoring, and daytime sleepiness. All patients signed an informed consent form before entering the study. Before the polysomnography, we measured arterial blood gases (ABGs) while patients were in the supine position during wakefulness. The day after the polysomnography, we performed pulmonary function tests (PFTs). Twenty-nine patients were excluded, because their $PtcCO_2$ records were unreliable. Out of the remaining 110 patients with reliable records, we excluded 9, because they had COPD, and we excluded 4 because they had daytime hypercapnia without COPD, according to the PFT and ABG procedures we performed. We diagnosed COPD according to GOLD criteria in patients with a post-bronchodilator $FEV_1/FVC<0.7$ [23].

The standard overnight polysomnography (PSG) included electroencephalography (EEG) recordings, electrooculography (EOG) recordings, submental and bilateral leg electromyographs, and an electrocardiography (ECG). We measured air flow with a nasal pressure transducer and an oro-nasal thermistor; respiratory effort via respiratory inductance plethysmography; and arterial oxyhemoglobin saturation via a finger pulse oximeter (SpO_2). All signals were collected and digitalized by computerized PSG systems (Comet Grass, Astro-Med, Inc., West Warwick, RI, USA and Viasys Cephalo Pro,SomnoStar, VIASYS Healthcare, Hoechberg, Germany) by experienced technicians. We scored sleep stages in 30-second epochs using the Rechtachaffen-Kales and 2007 AASM scoring systems [22,24]. We analyzed each epoch for the number of episodes of apnea and hypopnea. We defined apnea as a cessation of air flow for more than 10 seconds and hypopnea as a reduction of air flow >50% for >10 seconds plus oxygen desaturation of >3% or arousal [22,25]. We calculated the apnea/interapnea duration ratio using the average apnea and interapnea times. Certified specialists who were experienced in sleep medicine conducted this scoring. We determined the disease classifications according to the AASM's 2005 guide [26]. We graded patients according to the AASM's 1999 criteria as follows: an AHI<5 as normal, an AHI of ≥5 and ≤15 as mild, an AHI of >15 and ≤30 as moderate, and an AHI above 30 as severe [25].

We monitored $PtcCO_2$ with a V-Sign Sensor attached to the patients' earlobes using the SenTec digital monitoring system and VSTATS PC-based software (Switzerland), which previous sleep studies have proven to be reliable [13-15]. We identified the average, maximum, and minimum $PtcCO_2$ values by downloading the overnight records. We excluded unreliable records (20) (inexplicable, abrupt, and excessive increases in $PtcCO_2$ or sustained $PtcCO_2$<30 mm Hg). We classified mean $PtcCO_2$ levels of more than 45 mm Hg as overnight hypercapnia.

Statistical Analysis

We entered all of the data into the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 17.0 package program. We analyzed the categorical variables using chi-square and Fisher's exact tests. We presented the results as the mean±SD. We assessed group differences with the Mann-Whitney U-test and the student's t-test. We determined correlations between $PtcCO_2$ and anthropometric, respiratory, and polysomnographic variables using Pearson's correlation coefficient.

RESULTS

The mean age of all 97 patients included in the study was 46.8±10.3. Fifty-nine (60.8%) patients were male, and 38 (39.2%) were female. Eighty-six (86.6%) patients had a $PtcCO_2$<45 mm Hg, and 13 (13.4%) patients had a $PtcCO_2$>45 mm Hg. All of the patients in the second group had an AHI>5. Even though AHI scores were higher in the second group, the difference was not statistically significant (p=0.078). There was no significant difference between the two groups in terms of mean apnea duration, the apnea/interapnea duration ratio, or sleep SpO_2 measurements. When we made comparisons according to sleep architecture, there was a significant increase (p=0.018) in the N2 ratio in the second group; the N3 ratio was lower, but the difference was not statistically significant (p=0.066). The demographic properties and PFT, ABG, and polysomnography findings are illustrated in Table 1.

In 14 (14.5%) patients, the percentage of total sleep time (TST%) with SpO_2 <90% was above 30%. The mean $PtcCO_2$ value during sleep correlated with the percentage of TST with SpO_2 <90% (Figure 1) and ABG measurement results. There was no correlation in terms of other polysomnography findings (Table 2).

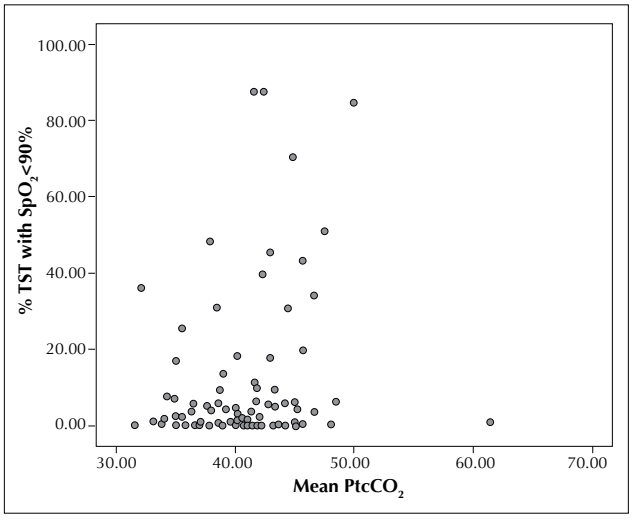

Figure 1. The correlation between mean $PtcCO_2$ and %TST with SpO_2<90%

$PtcCO_2$: transcutaneous PCO_2; SpO_2: pulse oxygen saturation; TST%: the percentage of total sleep time

When we categorized the patients according to their AHI scores, 60 (61.8%) had an AHI>15 (moderate to severe OSAS), and 37 (38.2%) had an AHI <15 (mild OSAS or normal). Eleven patients in the second group had an AHI<5 (normal), and all of these patients had a $PtcCO_2$ <45 mm Hg. Ten (16.7%) patients from the first group had a $PtcCO_2$ >45 mm Hg, and 3 (8.1%) patients from the second group had a $PtcCO_2$ >45 mm Hg, but the difference was not statistically significant (p=0.359). On the other hand, the maximum $PtcCO_2$ was significantly higher in the AHI >15 group (p<0.05). Also, the mean age, BMI, apnea index (AI), oxygen desaturation index (ODI), apnea duration, and N2% were significantly higher, whereas the N3%, the mean SpO_2%, and the minimum SpO_2% were significantly lower (p<0.05 for all). All of these measurements can be seen in Table 3.

DISCUSSION

In our study, 13 (13.4%) patients had a $PtcCO_2$ >45 mm Hg during the night of the polysomnography. Even though the difference was not statistically significant, AHI levels were higher in this group, suggesting a possible relationship between OSAS severity and hypercapnia during sleep. In 14.5% of all patients, %TST with SpO_2 <90% was above 30%. Average $PtcCO_2$ during sleep and %TST with SpO_2 <90% showed a correlation, which was not a surprising finding, considering the close relation between SpO_2 and $PtcCO_2$. When patients were divided according to their AHI levels, the maximum $PtcCO_2$ values were significantly higher in the AHI >15 group. This finding further supports the previous claim that OSAS severity and hypercapnia during sleep are related. The most important point is that these patients' wakefulness ABG parameters were within normal limits.

The prevalence of daytime hypercapnia in OSAS patients varies between 11%-43%, according to previous reports [4-11]. These patients are at a higher risk of developing serious cardiovascular disease, leading to early mortality [9,27]. Keeping this risk in mind, our findings may point to a similar risk increase in patients who do not have daytime hypercapnia but who do have sleep hypercapnia.

Previous studies have found that chronic airway obstruction, obesity, gender, nocturnal respiratory abnormalities, abnor-

Table 1. Demographic properties, PFT, ABG and polysomnography findings of the cases with $PtcCO_2$>45 mm Hg and <45 mm Hg

	$PtcCO_2$ ≤45 (n=84) Mean and SD	$PtcCO_2$ >45 (n=13) Mean and SD	p value
Age (year)	46.3±10.4	49.6±9.7	0.385
Gender (%) M/F	63/37	46.1/53.9	0.244
BMI (kg/m²)	30.9±5.7	33.1±5.2	0.176
PaO_2 (mm Hg)	92±16	85.7±12.3	0.369
$PaCO_2$ (mm Hg)	37±4.1	39.3±2.8	0.082
SaO_2 (%)	96.2±3.9	96.4±1.5	0.665
FEV_1 (%)	97.4±12.3	95±23.3	0.848
FVC (%)	100.7±13.4	97.5±25.7	0.689
FEV_1/FVC	80.5±5.6	81±7.5	0.921
AHI	30.6±28.1	44.7±30.8	0.078
AI	17.8±25.9	25.8±31.1	0.307
ODI	22.9±24.4	37±34.6	0.131
Minimum SpO_2 (%)	80.8±10.1	76.1±12.1	0.162
Mean SpO_2 (%)	93.6±3.1	92.8±2.7	0.223
TST% with SpO_2< 90%	9.7±18.3	19±26.5	0.197
NREM apnea time (sec)	19.8±8.6	21.8±6.7	0.287
NREM hypopnea time (sec)	25.6±6.6	25.7±4.3	0.767
REM apnea time (sec)	21.3±14.9	22.7±9.6	0.520
REM hypopnea time (sec)	26.8±16.1	24.7±12.4	0.577
Mean apnea time (sec)	21.6±10.2	23±5.6	0.282
Apnea time/ interapnea time	0.54±1.31	0.47±0.75	0.298
Sleep efficiency (%)	82.1±9.4	77.8±14.1	0.327
REM (%)	15.4±5.2	14±5	0.322
N1 (%)	7.6 ±4.6	7.4±4	0.781
N2 (%)	62.1±9.3	67±6.2	0.018
N3 (%)	14.7±7.4	11.4±6.1	0.066
Basal $PtcCO_2$ (mm Hg)	38.3±3.3	39.9±2.6	0.074
Max $PtcCO_2$ (mm Hg)	44.6±4	50.9±3.7	<0.001
Min $PtcCO_2$ (mm Hg)	35.4±2.9	39.9±2.2	<0.001
Mean $PtcCO_2$ (mm Hg)	39.4±3.2	47.8±4.3	<0.001
Mean heart rate	68±9.2	71.5±12.3	0.174

$PtcCO_2$: transcutaneous PCO_2; M: male; F: female; BMI: body mass index; PaO_2: partial oxygen pressure; $PaCO_2$: partial carbon dioxide pressure; SaO_2: arterial oxygen saturation; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; AHI: apnea-hypopnea index; AI: apnea index; ODI: oxygen desaturation index; SpO_2: pulse oxygen saturation; TST%: the percentage of total sleep time; NREM: non-rapid eye movement; REM: rapid eye movement; Max: maximum; Min: minimum

Table 2. The correlation between mean $PtcCO_2$ with the other parameters

	Correlation (r)	p value
Age	0.058	0.574
BMI (kg/m^2)	0.133	0.205
PaO_2 (mm Hg)	-0.261	0.037
$PaCO_2$ (mm Hg)	0.332	0.007
SaO_2 (%)	0.058	0.644
FEV_1 (%)	-0.124	0.241
FVC (%)	-0.151	0.152
FEV_1/FVC	0.095	0.369
AHI	0.125	0.224
AI	0.087	0.397
ODI	0.163	0.113
Minimum SpO_2 (%)	-0.199	0.052
Mean SpO_2 (%)	-0.164	0.110
TST% with SpO_2<90%	0.220	0.031
NREM apnea time	0.122	0.236
NREM hypopnea time	-0.016	0.879
REM apnea time	0.059	0.567
REM hypopnea time	-0.090	0.383
Mean apnea time	0.133	0.195
Apnea time/interapnea time	0.025	0.805
Sleep efficiency (%)	-0.056	0.590
REM (%)	0.006	0.955
N1 (%)	0.064	0.534
N2 (%)	0.035	0.737
N3 (%)	-0.085	0.408
Basal $PtcCO_2$ (mm Hg)	0.437	0.000
max $PtcCO_2$ (mm Hg)	0.687	0.000
min $PtcCO_2$ (mm Hg)	0.778	0.000
Mean heart rate	0.097	0.347

$PtcCO_2$: transcutaneous PCO_2; BMI: body mass index; PaO_2: partial oxygen pressure; $PaCO_2$: partial carbon dioxide pressure; SaO_2: arterial oxygen saturation; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; AHI: apnea-hypopnea index; AI: apnea index; ODI: oxygen desaturation index; SpO_2: pulse oxygen saturation; TST%: the percentage of total sleep time; NREM: non-rapid eye movement; REM: rapid eye movement; Max: maximum; Min: minimum

Table 3. Demographic properties and PFT, ABG, and polysomnography findings of the cases with AHI>15 and AHI<15

	AHI>15 (n=60)	AHI<15 (n=37)	p value
Age (year)	50±9.3	41.5±9.7	<0.001
Gender (%) M/F	63.3/36.7	56.8/43.2	0.519
BMI (kg/m^2)	32.5±5.8	29.2±4.7	0.007
PaO_2 (mm Hg)	92.3±16.5	88.9±13.7	0.424
$PaCO_2$ (mm Hg)	37.3±3.8	37.3±4.6	0.976
SaO_2 (%)	96.4±3.7	95.8±3.6	0.529
FEV_1 (%)	97.3±15.5	96.6±11.8	0.816
FVC (%)	100.6±17.6	99.8±11.5	0.823
FEV_1/FVC	80.3±6.4	80.9±4.7	0.656
AHI	47.5±27	8.1±4.5	<0.001
AI	29.5±29.2	1.6±1.8	<0.001
ODI	37.2±26.5	4.6±3.3	<0.001
Minimum SpO_2 (%)	75.3±10.3	88±4	<0.001
Mean SpO_2 (%)	92.4±3.3	95.2±1.2	<0.001
%TST with SpO_2< 90 (%)	16.2±22.4	2.3±9.4	0.001
NREM apnea time	23.3±7.1	14.8±7.7	<0.001
NREM hypopnea time	25.6±5.4	25.5±7.7	0.961
REM apnea time	27.4±12.9	11.9±11	0.000
REM hypopnea time	27±17	25.6±13.2	0.658
Mean apnea time	25.8±8.8	15.2±7.2	<0.001
Apnea time/interapnea time	0.86±1.50	0.01±0.01	0.001
Sleep efficiency (%)	80.7±9.5	83±11.3	0.289
REM (%)	15.6±5.4	14.7±4.7	0.415
N1 (%)	8.2 ±5.2	6.5±2.7	0.079
N2 (%)	64.5±10.2	59.7±5.5	0.010
N3 (%)	11.4±7.2	18.9±4.9	<0.001
Basal $PtcCO_2$ (mm Hg)	38.9±3.5	37.9±2.8	0.168
Max $PtcCO_2$ (mm Hg)	46.4±4.7	43.8±3.7	0.007
Min $PtcCO_2$ (mm Hg)	36.3±3.2	35.4±3.2	0.169
Mean $PtcCO_2$ (mm Hg)	40.9±4	40±4.9	0.359
Mean heart rate	69±10.2	67.5±8.7	0.466

$PtcCO_2$: transcutaneous PCO_2; BMI: body mass index; PaO_2: partial oxygen pressure; $PaCO_2$: partial carbon dioxide pressure; SaO_2: arterial oxygen saturation; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; AHI: apnea-hypopnea index; AI: apnea index; ODI: oxygen desaturation index; SpO_2: pulse oxygen saturation; TST%: the percentage of total sleep time; NREM: non-rapid eye movement; REM: rapid eye movement; Max: maximum; Min: minimum

mal ventilator responses, and alcohol intake contribute to daytime hypercapnia in patients with OSAS [4-11,28]. Many studies specified AHI as an independent risk factor for daytime hypercapnia [9,11,29,30]. Our findings suggest that AHI might also be an independent risk factor for sleep hypercapnia.

A study based on male Japanese OSAS patients found that 38% of OSAS patients had daytime hypercapnia; it also found that the average SpO_2% during sleep was significantly lower for hypercapnic patients [29]. Other studies found that %TST with SpO_2<90% was significantly higher in patients with daytime hypercapnia [28,30]. Our finding regarding the correlation between %TST with SpO_2 <90% and hypercapnia during sleep is consistent with those studies, which highlight the presence of nighttime hypercapnia in seemingly eucapnic patients during the daytime.

There was no difference in mean age, gender, BMI, ODI, mean and minimum SpO_2 %, or % TST with SpO_2 <90% between the $PtCO_2$ groups. In patients with a $PtCO_2$ >45 mm Hg, N3% was lower and N2% was higher than in the $PtCO_2$

<45 mm Hg group. We believe that the occurrence of higher N3% and lower N2% is associated with increased AHI scores and not directly related to CO_2 levels.

Berger's studies detected a lower post-event minute ventilation and a higher apnea/interapnea duration ratio in hypercapnic patients compared to eucapnic patients by evaluating post-event minute ventilation and interapnea time following every apnea [31,32]. Even though we did not use breath-by-breath analysis in our study, by calculating average apnea and interapnea times, we could not detect a relation between the apnea/interapnea duration ratio and average $PtcCO_2$ or hypercapnia during sleep.

Although some studies suggest that $PtcCO_2$ monitoring during sleep is not reliable because of the occurrence of sharp changes caused by the patients' movements during sleep [13,14], other studies comparing $PtcCO_2$ monitoring to ABG measurements in children during polysomnographies, in intensive care patients, in patients with non-invasive mechanical ventilation support, and in perioperative patients have proven this method's reliability [15-21]. The AASM recommends $PtcCO_2$ monitoring for patients suspected to have obesity hypoventilation syndrome. Taking these facts into consideration, although not taking ABG measurements during sleep might be a limitation of our study, we think that our results are reliable, because we used a method that has been proven to be reliable by previous studies. We also discarded any unreliable records.

In conclusion, hypercapnia develops during sleep in seemingly eucapnic OSAS patients. We believe $PtcCO_2$ monitoring to be useful in the early diagnosis of hypercapnia, taking into account the relation of hypercapnia with increased morbidity and mortality in OSAS patients. Further studies with higher patient numbers are needed on this topic.

Ethics Committee Approval: Because $PtcCO_2$ monitoring during polysomnography is recommended by AASM, ethic committee approval was not considered necessary.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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