Clinical Predictors of Obesity Hypoventilation Syndrome in Obese Subjects With Obstructive Sleep Apnea

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BACKGROUND: Arterial blood gas (ABG) analysis is not a routine test in sleep laboratories due to its invasive nature. Therefore, the diagnosis of obesity hypoventilation syndrome (OHS) is underestimated. We aimed to evaluate the differences in subjects with OHS and pure obstructive sleep apnea (OSA) and to determine clinical predictors of OHS in obese subjects. METHODS: Demographics, body mass index (BMI), Epworth Sleepiness Scale score, polysomnographic data, ABG, spirometric measurements, and serum bicarbonate levels were recorded. RESULTS: Of 152 obese subjects with OSA (79 females/73 males, mean age of 50.3 ± 10.6 y, BMI of 40.1 ± 5.6 kg/m^2, 51.9% with severe OSA), 42.1% (n = 64) had OHS. Subjects with OHS had higher BMI (P = .02), neck circumference (P < .001), waist circumference (P < .001), waist/hip ratio (P = .02), Epworth Sleepiness Scale scores (P = .036), ABG and serum bicarbonate levels (P < .001), apnea-hypopnea index (P = .01), oxygen desaturation index (P < .001), and total sleep time with S_{pO_2} < 90% (P < .001) compared with subjects with pure OSA (n = 88). They also had lower daytime P_{aO_2} (P < .001), sleep efficiency (P = .032), mean S_{pO_2} (P < .001), and nadir S_{pO_2} (P < .001) . Serum bicarbonate levels and nadir S_{pO_2} were the only independent predictive factors for OHS. A serum bicarbonate level of ≥ 27 mmol/L as the cutoff gives a satisfactory discrimination for the diagnosis of OHS (sensitivity of 76.6%, specificity of 74.6%, positive predictive value of 54.5%, negative predictive value of 88.9%). A nadir S_{pO_2} of < 80% as the cutoff gives a satisfactory discrimination for the diagnosis of OHS (sensitivity of 82.8%, specificity of 54.5%, positive predictive value of 56.9%, negative predictive value of 81.4%). When we used a serum bicarbonate level of ≥ 27 mmol/L and/or a nadir S_{pO_2} of < 80% as a screening measure, only 3 of 64 subjects with OHS were missed. CONCLUSIONS: Serum bicarbonate level and nadir saturation were independent predictive factors for the diagnosis of OHS. *Key words: hypercapnia; nadir saturation; obesity; obesity hypoventilation syndrome; obstructive sleep apnea; serum bicarbonate.* [Respir Care 2015;60(5):666–672. © 2015 Daedalus Enterprises]

Introduction

Obesity hypoventilation syndrome (OHS) is characterized by alveolar hypoventilation, severe sleep-disordered breathing, abnormal pulmonary mechanics, hypersomnolence, and multiple comorbidities.[1,2] Patients with OHS have higher morbidity, lower quality of life, more healthcare expenses, greater risk of pulmonary hypertension, and higher mortality compared with eucapnic obese patients with or without obstructive sleep apnea (OSA).[3-6] Diagnosis of OHS requires arterial blood gas (ABG) analysis, but ABG analysis is not routinely performed in sleep laboratories due to its invasive nature. Therefore, OHS is

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often unrecognized. Daytime hypercapnia in patients with OSA has been reported at 10–38%, and prevalence increases with rising body mass index (BMI).[2,7-14] Most patients with OHS have coexisting OSA.[15] As patients with OHS have a worse prognosis than patients with pure OSA and use more health-care resources, understanding the clinical characteristics of OHS is important. In this study, we therefore aimed to determine the predictors of OHS in class II and III obese (BMI $\geq$ 35 kg/m^2) subjects with OSA.

Methods

This prospective study was conducted in the Istanbul Faculty of Medicine of Istanbul University from January 2013 to January 2014. The subjects voluntarily gave their informed written consent. The study was carried out according to the principles of the Helsinki Declaration and was approved by the Istanbul Faculty of Medicine institutional board (2013/381).

We studied all consecutive subjects with class II and III obesity (BMI $\geq$ 35 kg/m^2) who were admitted to the sleep laboratory because of a clinical suspicion of OSA from January 2013 to January 2014. The exclusion criteria were a diagnosis of neuromuscular disease, chest wall disease, kyphoscoliosis, diaphragmatic paralysis, obstructive or restrictive pulmonary diseases, severe hypothyroidism, congestive heart failure, or renal failure; receiving diuretic treatment; total sleep time of $<$ 4 h on polysomnography; drug use affecting sleep architecture (benzodiazepine, narcotic drugs); and failure to perform spirometry.

The demographics, characteristic symptoms of OSA (snoring, witnessed apnea, excessive daytime sleepiness), anthropometric measurements, BMI, and comorbidities were recorded. BMI was calculated using the formula of Khosla and Lowe[16]: weight (kg)/height^2 (m^2). Neck circumference was measured at the level of the cricothyroid membrane. Waist circumference was measured from the midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the midaxillary line. Hip circumference was measured around the widest portion of the buttocks. The Epworth Sleepiness Scale (ESS) was used to measure daytime sleepiness. An ESS score of $\geq$ 10 was considered to be excessive daytime sleepiness. All subjects underwent spirometry, daytime ABG analysis, and all-night polysomnography. Spirometry (ZAN 74N, nSpire Health, Sydney, Australia) was performed according to approved standards.[17] FEV_1 and FVC were recorded as percent of predicted. ABG analysis was performed on room air after 15 min of rest using an ABL 5 blood gas analyzer (Radiometer, Brønshøj, Denmark) in the morning before polysomnography. Serum bicarbonate levels were measured (Cobas 6000, Roche Diagnostics, Ibaraki, Japan) in the morning on the same day of polysomnography.

QUICK LOOK

Current knowledge

Obesity hypoventilation syndrome (OHS) is characterized by alveolar hypoventilation, severe sleep-disordered breathing, hypersomnolence, and multiple comorbidities. Subjects with OHS have higher morbidity, lower quality of life, greater health-care expenses, and a higher risk of pulmonary hypertension and mortality compared with eucapnic obese subjects. The diagnosis of OHS requires blood gas analysis, a procedure not always available in a sleep lab.

What this paper contributes to our knowledge

OHS subjects had higher body mass index, waist circumference, waist/hip ratio, and bicarbonate levels and lower daytime oxygenation. Sleep efficiency and nadir oxygen saturation were also lower with OHS compared with sleep apnea alone. Serum bicarbonate levels $\geq$ 27 mmol/L and nadir oxygen saturation of $<$ 80% provided a satisfactory discrimination for the diagnosis of OHS.

Assessment of Polysomnographic Findings

All-night polysomnography was performed on all subjects. Polysomnography included recording of electroencephalogram (central and occipital), electrooculogram, submental and pretibial electromyography, oronasal flow (thermistor and nasal pressure transducer), thoracoabdominal movements (abdominal and thoracic strain gauges), and S_{pO_2}.[18] Sleep stages and respiratory events were scored according to the American Academy of Sleep Medicine 2007 guidelines.[19] Obstructive apnea was defined as a cessation of air flow of $\geq$ 90% compared with baseline for $\geq$ 10 s while there was evidence of persistent respiratory effort. Hypopnea was defined as an amplitude reduction of $\geq$ 30% in air flow for $\geq$ 10 s that was associated with an oxygen desaturation of $\geq$ 3% and arousal.[19] Polysomnographic records were scored by a trained technician and interpreted by a sleep specialist. OSA was diagnosed if the apnea-hypopnea index (AHI) was $\geq$ 5/h with the presence of clinical symptoms or if AHI was $\geq$ 15/h without any symptoms. OSA severity was graded as mild (AHI = 5–14/h), moderate (AHI = 15–29/h), or severe (AHI $\geq$ 30/h).[19,20] OHS was defined as a combination of obesity (BMI $\geq$ 30 kg/m^2), daytime hypercapnia ($P_{aCO_2} > 45$ mm Hg), and sleep-disordered breathing in the absence of other known causes of hypercapnia.[21] OSA subjects without daytime hypercapnia are referred to as pure OSA.

Statistical Analysis

Statistical analysis was done using the SPSS 17.0 pocket program (SPSS, Chicago, Illinois). Descriptive values were given as mean ± SD. Categorical variables were expressed as the number of cases and percentages. The Kolmogorov-Smirnov test was used to identify normal distribution of the data. For comparison of normally distributed variables, the Student *t* test was used, whereas the Mann-Whitney *U* test was used for comparison of variables without normal distributions. Comparison of categorical variables was performed using the chi-square test. All data are presented as mean ± SD. $P \leq .05$ was considered to be statistically significant. The Pearson correlation coefficient was used to examine the relationship between the polysomnographic data, ABG, spirometric measurements, and serum bicarbonate levels. Logistic regression analysis was performed to determine the related factors of OHS (AHI, BMI, oxygen desaturation index [ODI], serum bicarbonate levels, sleep time with $S_{pO_2} < 90\%$, nadir S_{pO_2}). The area under the receiver operating characteristic curve for serum bicarbonate levels was analyzed to determine a cutoff level of bicarbonate for identifying OHS. To assess the predictive performance of serum bicarbonate levels, multiple 2×2 contingency tables were used to calculate sensitivity, specificity, and positive and negative predictive values.

Results

A total of 165 class II and III obese subjects were enrolled in the study. Thirteen subjects with AHI < 5/h were excluded from the study. The remaining 152 subjects (79 females, 73 males, mean age of 50.3 ± 10.6 y, BMI of 40.1 ± 5.6 kg/m^2) with OSA (51.9% severe, 28.9% moderate, 19% mild) were evaluated. For 152 subjects, the mean total sleep time was 432.4 ± 64 min, the sleep efficiency percentage was 84 ± 10%, stage I–II sleep was 69.8 ± 15.3%, stage III sleep was 20.9 ± 12.7%, and rapid eye movement sleep was 9.4 ± 6.8%. The mean arousal index was 23.2 ± 16.0/h; the arousal index was > 10 in 80.2% ($n = 122$) of the subjects. The AHI of all subjects was 40.2 ± 27.1/h (range of 5.2–118/h). The ODI was 43.3 ± 30.3/h (range of 2–125/h). The mean S_{pO_2} was 92.6 ± 5.7%, and the nadir S_{pO_2} was 73.2 ± 15.6%. The percentage of total sleep time with $S_{pO_2} < 90\%$ was 19.5 ± 25.9%.

Of 152 subjects with OSA, 88 had a diagnosis of pure OSA without hypercapnia, and 64 had a diagnosis of OHS (42.1%). For the pure OSA group, 45.4% had severe, 35.2% had moderate, and 19.3% had mild OSA. For the OHS group, 60.9% had severe, 20.3% had moderate, and 18.7% had mild OSA. Demographics, spirometric measurements, ABG analysis results, ESS scores, and serum bicarbonate levels of the OHS and pure OSA groups are given in Table 1. BMI ($P = .02$), neck circumference ($P < .001$), waist circumference ($P < .001$), waist/hip ratio ($P = .02$), ESS scores ($P = .036$), daytime ABG bicarbonate levels ($P < .001$), and serum bicarbonate levels ($P < .001$) were significantly higher, whereas daytime P_{aO_2} was significantly lower ($P < .001$) in subjects with OHS.

Nearly all subjects (148/152) had current echocardiography, but systolic pulmonary arterial pressures could be measured in 107 of them. Pulmonary arterial pressures was similar in the OHS and pure OSA groups (30.8 ± 5.7 vs 29.6 ± 5.4 mm Hg, $P = .29$). Of 107 subjects, 23.4% ($n = 25$) had pulmonary arterial pressures ≥ 35 mm Hg (range of 35–52 mm Hg). The frequency of subjects with pulmonary arterial pressures ≥ 35 mm Hg was also similar in both groups (21.3% vs 19.7%, $P = .63$). The right ventricle diameter was significantly higher in the OHS group than in the pure OSA group (2.86 ± 0.33 cm vs 2.71 ± 0.26 cm, $P = .003$).

Polysomnographic data for the OHS and pure OSA groups are given in Table 2. The AHI ($P = .01$), ODI ($P < .001$), and total sleep time with $S_{pO_2} < 90\%$ ($P < .001$) were significantly higher in subjects with OHS. Sleep efficiency ($P = .032$), mean S_{pO_2} ($P < .001$), and nadir S_{pO_2} ($P < .001$) were significantly decreased in subjects with OHS.

The variables that were associated with the presence of OHS (serum bicarbonate, BMI, AHI, ODI, nadir S_{pO_2}, time spent with $S_{pO_2} < 90\%$) were examined by logistic regression analysis. Multiple logistic regression analysis showed that serum bicarbonate levels and nocturnal nadir S_{pO_2} were the independent predictive factors for OHS. There was a collinearity between AHI, ODI, lowest S_{pO_2}, and sleep time spent with $S_{pO_2} < 90\%$. When we removed AHI from the analysis, the result did not change. The area under the receiver operating characteristic curve for serum bicarbonate levels was 0.77. In the receiver operating characteristic analysis, using a serum bicarbonate level of ≥ 27 mmol/L as the cutoff gives a satisfactory discrimination in class II and III obese subjects for OHS diagnosis (sensitivity of 76.6%, specificity of 74.6%, positive predictive value of 54.5%, negative predictive value of 88.9%). Table 3 gives the predictive parameters of different serum bicarbonate levels for identifying subjects with OHS.

For all 152 subjects, serum bicarbonate levels correlated with age ($r = .23$, $P = .003$), BMI ($r = .19$, $P = .02$), neck circumference ($r = .19$, $P = .02$), waist circumference ($r = .24$, $P = .003$), hip circumference ($r = .19$, $P = .02$), daytime P_{aO_2} ($r = -0.19$, $P = .02$), P_{aCO_2} ($r = .52$, $P < .001$), S_{aO_2} ($r = -0.32$, $P < .001$), ABG bicarbonate levels ($r = .43$, $P < .001$), ODI ($r = .22$, $P = .007$), mean S_{pO_2} ($r = -0.17$, $P = .033$), nadir S_{pO_2} ($r = -0.30$, $P < .001$), and time spent with $S_{pO_2} < 90\%$ ($r = .27$, $P = .001$). No correlation was found between AHI and serum bicarbon-

Table 1. Demographics, Spirometric Measurements, ESS Scores, and ABG of Study Groups

	Subjects With OHS ($n = 64$)	Subjects With Pure OSA ($n = 88$)	P
Age, y	51.4 ± 10.3	49.7 ± 10.9	.27
Males/females, *n*	28/36	50/37	.059
Smoking history, %	54.6	44.3	.20
BMI (mean ± SD), kg/m^2	41.3 ± 6.2	39.2 ± 5.0	.02
Neck circumference (mean ± SD), cm	42.2 ± 4.1	40 ± 3.7	< .001
Waist circumference (mean ± SD), cm	123.0 ± 12.9	116.1 ± 10.4	< .001
Hip circumference (mean ± SD), cm	126.7 ± 12.7	124.2 ± 11.3	.20
Waist/hip ratio (mean ± SD)	0.974 ± 0.1	0.938 ± 0.9	.02
Comorbidity, %	85.9	82.9	.40
Hypertension	50	47.7	.46
Hyperlipidemia	54.6	48.8	.29
Diabetes mellitus	31.2	29.5	.46
Ischemic heart disease	7.8	7.9	.61
Cerebrovascular disease	0	2.2	.34
FVC (mean ± SD), % predicted	97.6 ± 17.7	101.1 ± 17.8	.25
FEV_1 (mean ± SD), % predicted	97.4 ± 18.5	99 ± 18.6	.59
FEV_1/FVC (mean ± SD)	0.83 ± 0.05	0.82 ± 0.04	.27
ESS score (mean ± SD)	8.5 ± 5.6	6.6 ± 5.9	.036
Daytime P_{aO_2} (mean ± SD), mm Hg	73.9 ± 10.9	82.1 ± 8.5	< .001
Daytime P_{aCO_2} (mean ± SD), mm Hg	49 ± 4.1	41.4 ± 2.6	< .001
Daytime ABG bicarbonate (mean ± SD), mmol/L	25.7 ± 2	24.4 ± 1.3	< .001
Serum bicarbonate (mean ± SD), mmol/L	27.3 ± 2.5	24.8 ± 2.2	< .001

ESS = Epworth Sleepiness Scale
ABG = arterial blood gas
OHS = obesity hypoventilation syndrome
OSA = obstructive sleep apnea
BMI = body mass index

ate levels. No difference was observed in serum bicarbonate levels at different OSA stages.

For subjects with only OHS, serum bicarbonate levels correlated with age (r = .38, $P = .002$), BMI (r = .28, $P = .03$), hip circumference (r = .32, $P = .01$), daytime P_{aCO_2} (r = .34, $P = .005$), daytime S_{aO_2} (r = −0.26, $P = .041$), and ABG bicarbonate levels (r = .42, $P = .001$).

Most of the subjects with OHS (82.8%) had a nadir S_{pO_2} of < 80%. A nadir S_{pO_2} of < 80% as the cutoff gives a satisfactory discrimination in class II and III obese subjects for the diagnosis of OHS (sensitivity of 82.8%, specificity of 54.5%, positive predictive value of 56.9%, negative predictive value of 81.4%). When we use a serum bicarbonate level of ≥ 27 mmol/L and/or a nadir S_{pO_2} of < 80% as a screening measure, we missed only 3 of 64 subjects with OHS.

For all 152 subjects, the nadir S_{pO_2} correlated with neck circumference (r = −0.28, $P < .001$), waist circumference (r = −0.30, $P < .001$), waist/hip ratio (r = −0.18, $P = .02$), ESS scores (r = −0.23, $P = .005$), daytime P_{aO_2} (r = .21, $P = .01$), daytime P_{aCO_2} (r = −0.48, $P < .001$), S_{aO_2} (r = .27, $P = .001$), ABG bicarbonate levels (r = −0.21, $P = .01$), AHI (r = −0.59, $P < .001$), ODI (r = −0.69, $P < .001$), mean S_{pO_2} (r = .55, $P < .001$), and time spent with $S_{pO_2} < 90\%$ (r = −0.69, $P < .001$). For only subjects with OHS, the nadir S_{pO_2} correlated with daytime P_{aCO_2} (r = −0.32, $P = .009$), AHI (r = −0.59, $P < .001$), ODI (r = −0.66, $P < .001$), mean S_{pO_2} (r = .47, $P < .001$), and time spent with $S_{pO_2} < 90\%$ (r = −0.65, $P < .001$).

Discussion

In this study, we prospectively investigated the clinical predictors of OHS in obese subjects with OSA. OHS prevalence in patients with OSA varies from 11 to 38%.[2,7-14,22-25] The prevalence increases with obesity severity. In our study, OHS prevalence was 42.1% in OSA subjects with class II and III obesity, which is higher than in previous studies.[2,8-14,22-25] The mean BMI of our subjects was higher than in most previous studies.[9-12,14,23-25] This might be the reason for our higher rate. However, the frequency of OHS in our study was also higher than in previous studies with a mean BMI of > 40 kg/m^2.[2,8,13,22] The largest OHS study in the literature was retrospective, and the prevalence of OHS was 11%.[12] In that study, the prevalence was 24% in

Table 2. Polysomnographic Data of Study Groups

	Subjects With OHS ($n = 64$)	Subjects With Pure OSA ($n = 88$)	P
Sleep efficiency (mean ± SD), %	86.0 ± 8.8	82.5 ± 10.6	.03
Total sleep time (mean ± SD), min	438.8 ± 58.1	427.8 ± 67.8	.29
Stages I and II (mean ± SD), %	71.8 ± 15.3	68.4 ± 15.2	.18
Stage III (mean ± SD), %	19.4 ± 12.3	21.9 ± 12.9	.24
REM (mean ± SD), %	8.9 ± 6.5	9.8 ± 6.9	.42
AHI/h (mean ± SD)	47.0 ± 29.6	35.3 ± 24.1	.01
NREM AHI/h (mean ± SD)	46.6 ± 31.1	34.8 ± 25.1	.01
REM AHI/h (mean ± SD)	44.5 ± 26.8	35.9 ± 24.2	.06
AI/h (mean ± SD)	31.6 ± 31.6	21 ± 22.5	.004
HI/h (mean ± SD)	11.4 ± 12.1	14.0 ± 10.6	.19
Mild OSA, %	18.7	19.3	> .99
Moderate OSA, %	20.3	35.2	.07
Severe OSA, %	60.9	45.4	
Arousal index (mean ± SD)	23.8 ± 16.8	22.8 ± 15.5	.69
Mean S_{pO_2} (mean ± SD), %	90.2 ± 7.7	94.4 ± 2.3	< .001
Nadir S_{pO_2} (mean ± SD), %	64.2 ± 18.1	78.1 ± 10.2	< .001
ODI/h (mean ± SD)	55.4 ± 31.2	34.3 ± 26.3	< .001
NREM ODI/h (mean ± SD)	55.4 ± 32.0	34.1 ± 27.2	< .001
REM ODI/h (mean ± SD)	52.8 ± 27.5	36.1 ± 24.6	.001
Sleep time spent with $S_{pO_2} < 90\%$ (mean ± SD), %	32.5 ± 30.8	10 ± 16.1	< .001

OHS = obesity hypoventilation syndrome
OSA = obstructive sleep apnea
REM = rapid eye movement
AHI = apnea-hypopnea index
NREM = non-rapid eye movement
AI = apnea index
HI = hypopnea index
ODI = oxygen desaturation index

Table 3. Predictive Parameters for Serum Bicarbonate Levels in Obesity Hypoventilation Syndrome

	Serum bicarbonate		
	≥ 26 mmol/L	≥ 27 mmol/L	≥ 28 mmol/L
Sensitivity, %	60.5 (48.6–71.5)	76.6 (62–87.7)	81.2 (63.5–92.7)
Specificity, %	77.5 (67.4–85.7)	74.6 (65.7–82.1)	69.9 (61.4–77.6)
Positive predictive value, %	69.7 (57.1–80.4)	54.5 (41.8–66.8)	39.4 (27.6–52.2)
Negative predictive value, %	69.7 (69.6–78.5)	88.9 (81–94.3)	93.9 (87.3–97.7)
Odds ratio	5.3 (2.7–10.4)	9.6 (4.3–21.2)	10.1 (3.8–26.4)

subjects with a BMI above 40 kg/m^2.[12] There are few prospective studies, and OHS prevalence in these studies is between 13% and 37%.[2,8,13,23]

Patients with OHS have higher mortality than pure OSA patients with a similar degree of obesity.[26,27] Hospitalization rates and use of health-care service requirements are also high for these patients.[5,6] Therefore, identifying patients with OHS is important. However, there are few studies that evaluated the clinical differences between OHS and OSA.[8,14,24] According to one of these studies, subjects with OHS were significantly younger and heavier and had lower P_{aO_2} and higher P_{aCO_2} than subjects with OSA and had more severe restrictive defects on spirometry.[8] On the other hand, Trakada et al[14] reported that subjects with OHS were older and did not differ in terms of pulmonary function compared with non-subjects with OHS. They also reported that subjects with OHS were more obese and more somnolent; had higher neck, waist, and hip circumferences and waist/hip ratios; had lower P_{aO_2}, P_{aCO_2}, and mean and nadir S_{pO_2} during sleep; and spent more time with $S_{pO_2} < 90\%$ during sleep.[14] Macavei et al[25] compared the data of subjects with OHS and normocapnic obese subjects. They reported that subjects with OHS were older and heavier and had higher anthropometric measurements, lower spirometric values, and worse ABG and nocturnal oxygenation parameters (ODI, mean and nadir S_{pO_2}, time spent with $S_{pO_2} < 90\%$). In a recent study, Basoglu and Tasbakan[24] showed that subjects with OHS had higher rates of daytime sleepiness; decreased FVC, FEV_1, and P_{aO_2}; and increased ABG P_{aCO_2} and bicarbonate levels. Mean and nadir S_{pO_2} during sleep were decreased, and sleep time spent with $S_{pO_2} < 90\%$ was increased in subjects with OHS. Our findings are consistent with the previous studies. Our subjects with OHS had higher BMI, neck circumference, waist circumference, waist/hip ratio, ESS scores, daytime ABG bicarbonate levels, AHI, ODI, and total sleep time with $S_{pO_2} < 90\%$ compared with subjects with pure OSA. Mean and nadir S_{pO_2} were significantly decreased in subjects with OHS.

The most common comorbidities in OHS are hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, and gastroesophageal reflux disease.[14,24,25] Similarly, the most common comorbidities were hyperlipidemia, hypertension, and diabetes mellitus in our subjects with OHS (54.6%, 50%, and 31.2%, respectively). However, there was no significant difference in comorbidities between subjects with OHS and pure OSA.

In terms of the invasive nature of ABG analysis, identification of simple and noninvasive predictors of OHS is important. Studies evaluating the clinical predictors of OHS reported that higher BMI and AHI and lower FEV_1, FVC, daytime P_{aO_2}, mean and nadir nocturnal S_{pO_2}, sleep time spent with $S_{pO_2} < 90\%$, and ABG and serum bicarbonate levels are predictors of hypercapnia.[2,8-10,12,13,24,25,28] Most of these studies did not provide particular thresholds that may be useful in clinical practice to predict OHS. In a few of these studies, bicarbonate levels were found to be related to OHS diagnosis.[2,24,25]

In OSA, recurrent upper airway obstruction can lead to acute intermittent hypercapnia during sleep.[29-33] When obstructive events are too long and repetitive, compensation

failure occurs and leads to excessive hypercapnia. Nocturnal intermittent hypercapnia in OSA leads to renal bicarbonate retention to compensate for acute respiratory acidosis.[33,34]

As we know, patients with OHS have both obstructive events and severe hypoventilation during sleep, which lead to daytime hypercapnia. In the light of these data, patients with OHS should have high serum bicarbonate levels. Additionally, we do not expect high serum bicarbonate levels in patients with OSA. We speculated that serum bicarbonate levels should differentiate subjects with OHS from subjects with pure OSA. Three studies showed that increased bicarbonate levels are a sensitive screening measure for daytime hypercapnia, but 2 of these studies used ABG bicarbonate, not serum bicarbonate.[2,24,25]

In the literature, there is only one study that evaluated serum bicarbonate.[2] This study revealed that serum bicarbonate levels ($P < .001$), AHI ($P = .006$), and nocturnal nadir S_{pO_2} ($P < .001$) were independent predictive factors of OHS.[2] That study selected a threshold of 27 mmol/L for serum bicarbonate and found a sensitivity of 92% and a specificity of 50%. When combining serum bicarbonate levels of > 27 mmol/L and AHI > 100 as screening measures, only 3% of subjects with OHS were missed.[2] Our findings for bicarbonate were consistent with that study, but AHI was not a predictor of OHS in our study. We found that serum bicarbonate levels and nocturnal nadir saturation were the predictive factors related to OHS.

The mean BMI and AHI of subjects in the study of Mokhlesi and Tulaimat[2] were higher than those of our subjects. This might be the reason that we did not find AHI to a predictor in our study. However, Mokhlesi and Tulaimat[2] used only BMI, AHI, nadir S_{pO_2}, and serum bicarbonate levels as potential variables for OHS prediction. In contrast, we used BMI, AHI, ODI, nadir S_{pO_2}, and sleep time spent with $S_{pO_2} < 90\%$. This might explain why we did not find AHI to be a predictor of OHS in our study. There was a collinearity between AHI, ODI, nadir S_{pO_2}, and sleep time spent with $S_{pO_2} < 90\%$, but when we removed AHI from the analysis, the result did not change. In our study, serum bicarbonate levels ≥ 27 mmol/L had a sensitivity of 76.6%, a specificity of 74.6%, a positive predictive value of 54.5%, and a negative predictive value of 88.9%. Additionally, a nadir S_{pO_2} of $< 80\%$ had a sensitivity of 82.8%, a specificity of 54.5%, a positive predictive value of 56.9%, and a negative predictive value of 81.4%. When we use serum bicarbonate levels ≥ 27 mmol/L and/or a nadir S_{pO_2} of $< 80\%$ as a screening measure, 3 of 64 subjects with OHS were missed.

In the study of Basoglu and Tasbakan,[24] hypercapnia was found to be associated independently with ABG bicarbonate levels and S_{aO_2}. Bicarbonate levels ≥ 27 mmol/L had a sensitivity of 88.1% and a specificity of 73.1%, and an S_{aO_2} of $\leq 95\%$ had a sensitivity of 64.4% and a specificity of 73.9% for identifying OHS.[24] Macavei et al[25] reported that P_{aO_2} and ABG bicarbonate levels were independent predictors of OHS and that bicarbonate > 27 mmol/L had an 85.7% sensitivity and an 89.5% specificity for diagnosis of OHS, with a 68.1% positive predictive value and a 95.9% negative predictive value.

Our study showed that serum bicarbonate levels were significantly higher in subjects with OHS compared with subjects with pure OSA. However, no correlation was found between AHI and serum bicarbonate levels. No difference was observed between bicarbonate levels at different OSA stages. Additionally, we found a moderate correlation between serum bicarbonate and daytime ABG bicarbonate levels, P_{aCO_2}, and S_{aO_2}. According to these findings, elevated serum bicarbonate levels can be helpful in identifying patients with OHS.

OHS can be diagnosed only after other causes of hypercapnia have been excluded. In some previous studies, respiratory comorbidities causing hypercapnia were not exclusion criteria.[8,12] Excluding respiratory diseases that might cause hypercapnia and a study sample with a definite diagnosis of OHS are strong points of our study. The presence of COPD is a confusing factor for OHS prevalence.[35] The prevalence of daytime hypercapnia in patients with OSA is higher when associated with COPD.[12] Similar results were reported by Chaouat et al.[36] The prevalence of daytime hypercapnia was 27% in subjects with OSA and COPD and 8% in subjects with OSA only. In our study, all subjects had spirometric and ABG results, and we excluded subjects with COPD. Excluding OHS subjects without OSA and using a homogenous group are additional strong points of our study.

Nevertheless, there are some limitations of our study. Our study group did not include class I obese subjects. We aimed to find more OHS subjects, so we selected class II and III obese subjects. We could not use end-tidal CO_2 measurements or capnography. However, we think that the OHS prevalence in our study would be greater whether we performed end-tidal CO_2 measurements or capnography.

Conclusions

OHS is common in class II and III obese patients with OSA. Serum bicarbonate levels ≥ 27 mmol/L and a nadir S_{pO_2} of $< 80\%$ in OSA patients with class II and III obesity should prompt clinicians to measure ABG to confirm the presence of hypercapnia. Serum bicarbonate is a reasonable screening measure for hypercapnia, especially because it is less invasive than an arterial puncture. More studies should be done to determine the place of serum bicarbonate and nocturnal nadir S_{pO_2} in the diagnosis of OHS and threshold levels.

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