Original Article

# Frequency and predictors of obesity hypoventilation in hospitalized patients at a tertiary health care institution

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Submission: 17-09-2013
Accepted: 09-12-2013

**Abstract:**

**OBJECTIVES:** Patients with obesity hypoventilation syndrome (OHS) have significant morbidity and mortality. Early diagnosis and treatment is important and there are limited data on its prevalence and predictive factors. The objective of this observational study was to determine the frequency and predictors of OHS in hospitalized patients at a tertiary health care institution.

**MATERIALS AND METHODS:** All blood gas analyses of hospitalized adult (age over 18 years) patients were prospectively recruited from the biochemistry laboratory at a tertiary health care center between August 2009 and July 2010. Patients who had hypercapnia ($PaCO_2 \geq 45$ mmHg) while breathing room air were included and clinical and laboratory data were obtained from hospital records. A standard questionnaire was also filled by face-to-face interview with patients and/or relatives.

**RESULTS:** A total of 9480 patients' arterial blood gases were evaluated and 330 patients (3.4%) who met the selection criteria were included in the analysis during the study period. Hypoventilation was associated with acute diseases in 64.2% and chronic diseases in 35.8% of the patients. Of the chronic hypoventilation patients, 24.4% had OHS. Univariate logistic regression analysis showed that, female gender, body mass index (BMI), smoking, $PaO_2$, $SaO_2$ and a $PaCO_2$/BMI <1.5 were significantly related to OHS. In multivariate logistic regression analysis, BMI >35 kg/m$^2$, $SaO_2$ <91.4% and $PaCO_2$/BMI <1.5 were significantly related to OHS. A $PaCO_2$/BMI <1.5 was an independent variable strongly predictive of OHS (odds ratio: 36.9, 95% of the confidence interval: 2.75-492.95, $P = 0.007$).

**CONCLUSIONS:** OHS is a common cause of chronic alveolar hypoventilation. A careful examination $PaCO_2$/BMI ratio may prevent misdiagnoses among hypercapnic patients.

**Key words:**

Hypercapnia, hypoventilation, obesity hypoventilation syndrome, respiratory failure

**Access this article online**

Quick Response Code:

**Website:** www.thoracicmedicine.org

**DOI:** 10.4103/1817-1737.128851

Alveolar hypoventilation exists when the partial arterial carbon dioxide pressure ($PaCO_2$) is 45 mmHg or higher. The pathophysiology underlying hypoventilation can range from abnormal central respiratory drive, increased workload, mechanical failure, to abnormal mechanics or a combination of these conditions.[1] Obesity hypoventilation syndrome (OHS) is defined as the combined presence of obesity (body mass index [BMI] >30 kg/m$^2$) and daytime arterial hypercapnia ($PaCO_2$ >45 mmHg), in the absence of other causes of hypoventilation.[2,3] Patients with OHS have a poor quality of life, more healthcare expenses, a greater risk of pulmonary hypertension and a higher mortality rate. It is often unrecognized and treatment is frequently delayed.[4] As the patients have significant morbidity and mortality, early diagnosis and treatment is important. In clinical practice, chronic obstructive pulmonary disease (COPD) is the most common cause of chronic hypoventilation. However, no studies are carried out on the following diseases and their prevalence.[5] The objective of this observational study was to determine the frequency and predictors of OHS in hospitalized patients at a tertiary health care institution.

## Materials and Methods

This prospective and observational study was conducted at a tertiary care hospital and was approved by the hospital's ethics committee. All arterial blood gas analyses of hospitalized adult (age >18 years) patients were prospectively recruited from the biochemistry laboratory, each day from August 2009 to July 2010. Patients who had respiratory hypercapnia ($PaCO_2 \geq 45$ mmHg) were asked to volunteer for the study. Abnormal blood gas results ($PaCO_2 \geq 45$ mmHg) were re-tested during day-time while patients were awake at clinically stable condition. Arterial blood samples were drawn after a 10 min rest in a sitting position. Out-patients, patients with

metabolic acidosis and those who did not give informed consent were excluded.

A standard questionnaire (including demographic data, patient history, previous diagnoses and drug use, etc.,) was filled by face-to-face interview with patients and/or relatives. Other clinical and laboratory data (physical exam findings and routine laboratory evaluations, pulmonary function tests, blood gases, prior and current diagnoses) were obtained from hospital records. Hypoventilation was defined as an arterial partial pressure of $PaCO_2$ ≥45 mmHg. Patients who have hypercapnia ($PaCO_2$ ≥45), a pH within normal range (pH = 7.36-7.44) and elevated $HCO_3^-$ level following at least 3 weeks of stable disease were categorized as chronic hypoventilation. Causes of hypoventilation were determined according to the guideline by Subramanian and Strohl [Figure 1].[6] OHS was defined as obesity (BMI >30 kg/m$^2$) with awake hypoventilation in the absence of other known causes of hypoventilation (obstructive or restrictive parenchymal lung diseases, kyphoscoliosis, neuromuscular disorders and hypothyroidism).[2,3] Diagnosis of asthma and COPD was determined according to the GOLD and GINA criteria.[7,8]

## Statistical analysis

The Kolmogorov-Smirnov test was used to test for a normal distribution of continuous variables. Data characterized by a normal distribution were expressed as mean ± standard deviation. Parameters without such a distribution were expressed as a median with range. ANOVA and student's *t*-tests were used for the comparison of data which had a normal

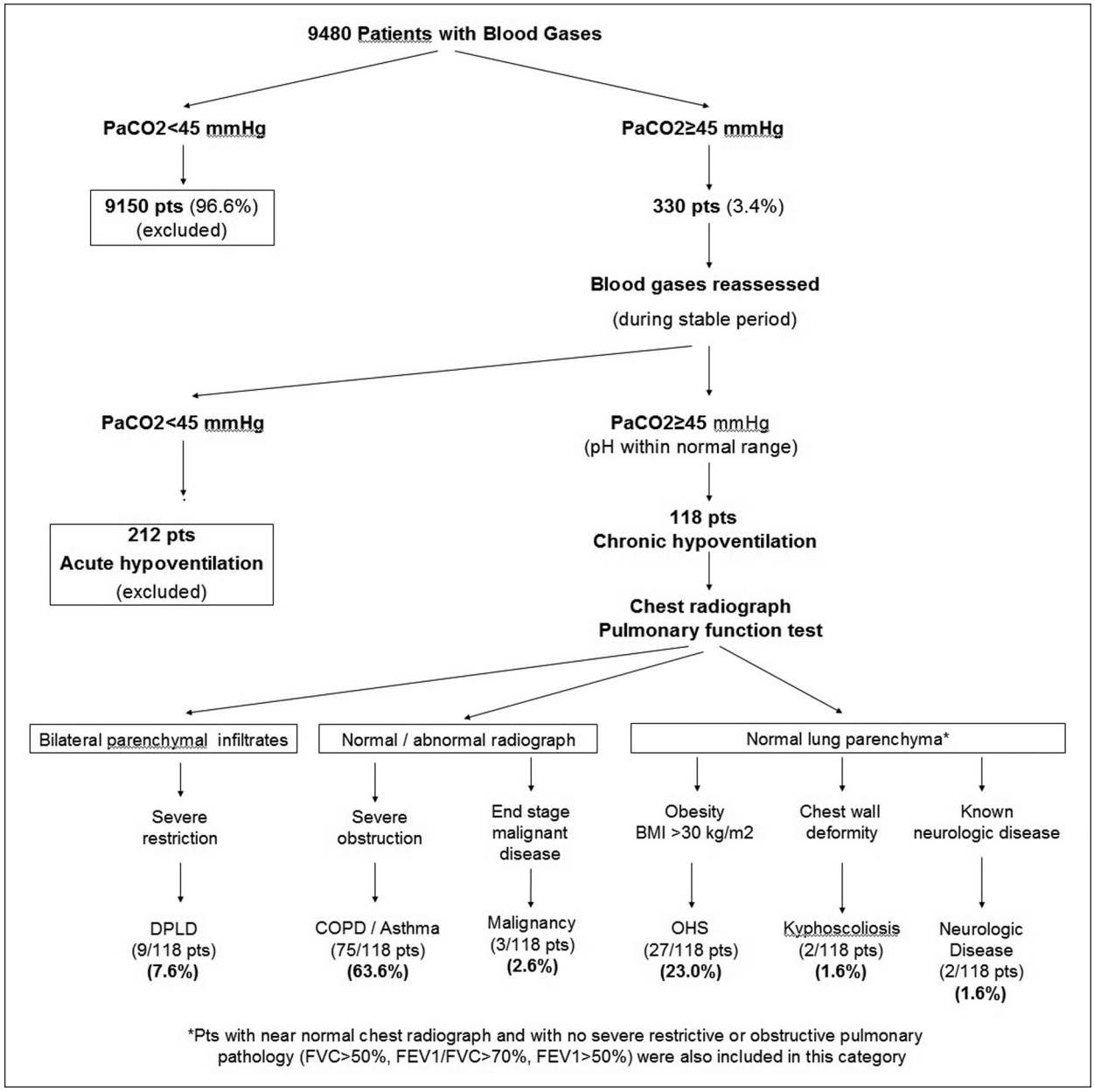


**Figure 1:** The diagnostic steps in patients with hypercapnia. FVC = Forced vital capacity, FEV1 = Forced expiratory volume in 1 second, COPD = Chronic obstructive pulmonary disease, OHS = Obesity hypoventilation syndrome, DPLD = Diffuse parenchymal lung diseases, BMI = Body mass index, pts = patients

distribution. The Mann-Whitney-U and Kruskal-Wallis tests were used for the comparison of non-normally distributed data. Discrete variables were compared using the Chi-square test. Factors that were potential predictors of OHS were analyzed using logistic regression. Multivariate logistic regression analysis was used as a stepwise descending method from predictive factors with significance ≤0.05 in the univariate analysis. Diagnostic accuracies of parameters for identifying OHS were assessed using the area under the receiver operating characteristic (ROC) curve area under curve (AUC). $P < 0.05$ were considered to be significant. Data were analyzed using SPSS statistical software (version 13.01, serial number 9069728, SPSS Inc., Chicago).

## Results

During the period of study, a total of 9480 patients' arterial blood gases were evaluated and 330 patients (3.4%) that met the selection criteria were included in the analysis. Of patients with hypoventilation, 122 (37%) were female and the mean age was 62.3 ± 17.5 years. BMI was low in 8.2% (BMI <20 kg/m$^2$), normal in 29.7% (BMI 20-24.9 kg/m$^2$) and overweight in 35.5% (BMI 25-29.9 kg/m$^2$) and obese in 26.7% (BMI ≥30 kg/m$^2$) of the cases. Of the patients, 54.9% had a smoking history.

Hypoventilation was found to be associated with acute diseases in 212 patients (64.2%) and chronic diseases in 118 (35.8%) patients. Of patients with chronic hypoventilation, 63.6% patients were related to obstructive lung diseases and 24.6% were related to OHS [Table 1]. Patients in the OHS group had significantly higher BMI (42.7 ± 9.4 vs. 25.5 ± 5.1 kg/m$^2$, $P < 0.001$) and had lower smoking rates (41.4% vs. 68.5%, $P = 0.017$), than did patients in other chronic hypoventilation groups [Table 2]. OHS was misdiagnosed as COPD in 14 patients and congestive heart failure in six patients. Only five cases (17.2%) had been diagnosed correctly as OHS.

**Table 1: Causes of chronic alveolar hypoventilation**

| Disease category | Disease | No. (%) | Total no. (%) |
|---|---|---|---|
| Obstructive lung diseases | COPD | 70 (59.4) | 75 (63.6) |
| | Severe asthma | 5 (4.2) | |
| Parenchymal diseases | DPLD | 9 (7.6) | 9 (7.6) |
| Chest wall-obesity | OHS | 27 (23.0) | 29 (24.6) |
| | Chest wall | 2 (1.6) | |
| Neurological diseases | ALS | 1 (0.8) | 2 (1.6) |
| | Guillain-Barre | 1 (0.8) | |
| Other | Malignancy | 3 (2.6) | 3 (2.6) |
| Total | | 118 (100) | 118 (100) |

COPD = Chronic obstructive pulmonary disease, OHS = Obesity hypoventilation syndrome, DPLD = Diffuse parenchymal lung diseases, ALS = Amyotrophic lateral sclerosis

$PaO_2$ and $SaO_2$ levels were significantly lower in the OHS group (median 60 mmHg [range: 34.2-168.5] vs. median 80.8 mmHg [range: 34.3-395.0], $P = 0.002$ and median 89.9% [range: 54.0-98.9] vs. median 94.9% [range: 52.7-99.5], $P = 0.001$, respectively) [Table 2]. ROC analysis indicated that the optimal cutoff value of $SaO_2$ predicting OHS was <91.4%. $SaO_2$ had an AUC of 0.702 (95% confidence interval [CI]: 0.601-0.825, $P = 0.001$) and sensitivity and specificity were 70.8% and 59%, respectively. $HCO_3^-$ (32.5 ± 5.6 mmol/L vs. 34.8 ± 7.8 mmol/L) and $PaCO_2$ (median 56.8 mmHg [range: 45.2-120.0] vs. median 55.2 mmHg [range: 45.5-102.3]) were the same between groups. The ratio of partial arterial carbon dioxide pressure to body mass index ($PaCO_2$/BMI) had the highest diagnostic accuracy for identifying OHS as measured by area under ROC curve analysis (AUC: 0.90, 95% CI: 0.835-0.977, $P < 0.001$). The sensitivity and the specificity of $PaCO_2$/BMI ratio for diagnosing OHS at the optimal cut-off level <1.5 was 96.6% and 69%, respectively.

Univariate logistic regression analysis showed that, female gender, BMI, smoking, $PaO_2$, $SaO_2$ and a $PaCO_2$/BMI <1.5 to be significantly related to OHS [Table 3]. In multivariate logistic regression analysis BMI >35 kg/m$^2$, $SaO_2$ <91.4% and $PaCO_2$/BMI <1.5 were found to be significantly related to OHS [Table 4]. A $PaCO_2$/BMI <1.5 was an independent variable strongly predicting OHS (odds ratio: 36.9, 95% CI: 2.75-492.95, $P = 0.007$).

## Discussion

In current practice, hypoventilation is often used synonymously with hypercapnic respiratory failure. It is known that pulmonary and many extra-pulmonary pathological conditions lead to the development of hypoventilation. In our study, among the 9480 hospitalized patients, 330 patients (3.4%) were detected to have alveolar hypoventilation. Except in specific patients groups, the exact prevalence of hypoventilation in the general population is unknown. A study by Ray *et al*. demonstrated hypercapnia in 44 (9%) of the 514 emergency department patients with acute respiratory failure.[9] In a similar study conducted by Hussain

**Table 2: Demographic and laboratory characteristics of patients with chronic alveolar hypoventilation**

| Variable | OHS (29 patients) (%) | Non-OHS (89 patients) (%) | Total (118 patients) (%) | *P* |
|---|---|---|---|---|
| Demography | | | | |
| Age | 64.3±11.2 | 65.1±14.8 | 64.9±14.0 | 0.788 |
| Gender (F) | 18 (62.1) | 23 (25.8) | 41 (34.7) | <0.001* |
| BMI | 42.7±9.4 | 25.5±5.1 | 29.6±9.8 | <0.001* |
| Smoking | 12 (41.4) | 61 (68.5) | 73 (61.9) | 0.017* |
| Arterial blood gases | | | | |
| $PaO_2$ | 67.3±31.1 | 94.4±53.7 | 87.7±50.3 | 0.002* |
| $PaCO_2$ | 59.7±16.2 | 59.7±13.2 | 59.7±13.9 | 0.687 |
| $HCO_3^-$ | 32.5±5.6 | 34.8±7.8 | 34.2±7.3 | 0.084 |
| $SaO_2$ | 85.4±11.9 | 92.4±7.7 | 90.7±9.4 | 0.001* |
| $PCO_2$/BMI | 1.46±0.5 | 2.42±0.6 | 2.2±0.7 | <0.001* |

*Statistically significant ($P$<0.05), OHS = Obesity hypoventilation syndrome, BMI = Body mass index

**Table 3: Univariate logistic regression analysis of demographic and laboratory parameters predicting OHS**

| Variable | OHS | | *P* value |
|---|---|---|---|
| | OR | 95.0% CI | |
| Demography | | | |
| Age | 0.986 | 0.951-1.022 | 0.437 |
| Gender | 4.696 | 1.933-11.407 | <0.001* |
| BMI | 1.600 | 1.309-1.956 | <0.001* |
| BMI >35 kg/m$^2$ | 109.889 | 25.513-473.310 | <0.001* |
| Smoking | 0.324 | 0.137-0.769 | 0.011* |
| Arterial blood gases | | | |
| $PaO_2$ (mmHg) | 0.981 | 0.966-0.996 | 0.012* |
| $PaCO_2$ (mmHg) | 1.000 | 0.970-1.031 | 0.992 |
| $HCO_3^-$ (mmol/L) | 0.956 | 0.900-1.015 | 0.142 |
| $SaO_2$ (%) | 0.929 | 0.887-0.972 | <0.002* |
| $SaO_2$ <%91.4 | 3.965 | 1.647-9.543 | 0.002* |
| $PCO_2$/BMI <1.5 | 54.466 | 13.667-217.054 | <0.001* |

*Statistically significant (*P*<0.05). BMI = Body mass index, F = Female, CI = Confidence interval, OR = Odds ratio, OHS = Obesity hypoventilation syndrome

**Table 4: Multivariate logistic regression analysis of demographic and laboratory parameters predicting OHS**

| Variable | OHS | | *P* |
|---|---|---|---|
| | OR | 95.0% CI | |
| Gender (F) | 0.693 | 0.033-14.383 | 0.813 |
| BMI >35 kg/m$^2$ | 24.771 | 3.509-174.874 | 0.001* |
| Smoking | 0.907 | 0.044-18.649 | 0.949 |
| $PaO_2$ (mmHg) | 1.007 | 0.984-1.031 | 0.539 |
| $SaO_2$ <%91.4 | 22.929 | 1.266-415.297 | 0.034* |
| $PCO_2$/BMI <1.5 | 46.497 | 2.791-732.145 | 0.007* |

*Statistically significant (*P*<0.05). BMI = Body mass index, F = Female, CI = Confidence interval, OR = Odds ratio, OHS = Obesity hypoventilation syndrome

*et al*. in Pakistan, hypercapnia was found in 69% of 270 cases with acute respiratory failure.[10] Perhaps because we used a different methodology in our study, we found lower rates of hypercapnia compared with these studies.

In clinical practice, COPD is the most common cause of chronic hypoventilation.[5] In our study, of patients with chronic hypoventilation, 63.6% were associated with chronic obstructive lung diseases. The rates of chronic hypercapnia in COPD patients are reported to a range from 60% to 70% respectively.[11,12] The second most common cause of hypoventilation was OHS and was detected in 24.4% of our patients. The precise prevalence of OHS in the general population is unknown; however, it is estimated to be between 0.15% and 0.3% and some studies have reported the prevalence rates between 19% and 31% in obese patients.[13,14]

Patients with OHS have been reported to have the most severe arterial blood gas disturbances compared with the other chronic pulmonary groups and they exhibited the most severe nocturnal oxygen desaturations.[15] In our study, although we did not study nocturnal oxygenation, OHS cases had significantly lower daytime $PaO_2$ and $SaO_2$ levels. Furthermore, a $SaO_2$ <91.4% was found to be a significant predictor of OHS. Mokhlesi *et al*. in their study have reported the lowest oxygen saturation during sleep as an independent predictor of OHS in obstructive sleep apnea patients.[4] They also found a clear correlation between serum bicarbonate level and OHS in patients with obstructive sleep apnea syndrome (OSAS). In the present study, serum bicarbonate level was also elevated but was comparable between groups and $PaCO_2$ levels alone had no significance in predicting OHS. However, a $PaCO_2$/BMI ratio <1.5 had a strong correlation for OHS.

It is known that OHS and OSAS are often associated and the majority of patients with OHS have severe OSAS.[13] However, due to the methodological design of our study, the rate of OSAS could not be determined. Approximately, 80% of OHS cases have been shown to have OSAS in the literature.[3] On the contrary, the prevalence of OHS in patients with obstructive sleep apnea was found to be 30% in a retrospective random sample and 20% in a prospective sample by Mokhlesi *et al*.[4] In a meta-analysis including 4250 OSAS patients by Kaw *et al*., day-time hypercapnia was present in 788 patients (19%).[13] Laaban and Chailleux have reported the prevalence of day-time hypercapnia as 11% among 1141 OSAS patients.[16] However, in both study, day-time hypercapnia was related to the severity of obesity and obesity-related impairment in lung function.[13,16]

Whereas most patients with OHS have had prior hospitalizations and have higher healthcare utilization, the formal diagnosis of OHS is established late in the fifth or sixth decade of life.[17] The most common presentations of the patients are an acute-on-chronic exacerbation with acute respiratory acidosis leading to admission to an intensive care unit, or during a routine outpatient evaluation by a sleep specialist or pulmonologist.[17] Nowbar *et al*. in their study have reported that patients with OHS were mostly identified during systematic screening of hospitalized patients and that the vast majority were discharged from the hospital without any form of therapy for hypoventilation.[14] Therapy for hypoventilation at discharge was initiated in only 6 (13%) of patients with OHS.[14] Similarly, only 17.2% of OHS patients in our study had a formal diagnosis of OHS and the majority of the remaining OHS patients were mistakenly treated as COPD, heart failure or both.

There were some limitations of the present study. First, this study was performed in a specific patient group in a tertiary health care institution and may not represent OHS prevalence in the general population. However, we think our results are valuable since it provides information on causes of chronic alveolar hypoventilation in order of frequency. The second limitation is the lack of polysomnography testing in some patients (due to the observational design of the study) to clarify associated OSAS. We think the lack of polysomnographic examination does not influence our results since OSAS in non-obese patients is not expected to cause day-time hypercapnia.[13,16,18]

## Conclusion

Our study showed that the $SaO_2$ level and $PaCO_2$/BMI ratio were strong predictors for OHS in obese hospitalized patients in a tertiary health care institution. Hypoventilation was observed in 3.4% of hospitalized patients who participated in the study. Of these patients, 35.8% had chronic alveolar

hypoventilation that was mostly associated with chronic obstructive lung diseases and OHS. Because misdiagnoses are common among OHS patients, a careful examination of body mass index, $SaO_2$ level and particularly $PaCO_2$/BMI ratio may reduce misdiagnoses among hypercapnic patients.

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**How to cite this article:** Bülbül Y, Ayik S, Ozlu T, Orem A. Frequency and predictors of obesity hypoventilation in hospitalized patients at a tertiary health care institution. Ann Thorac Med 2014;9:87-91.

**Source of Support:** Nil, **Conflict of Interest:** None declared.