Obesity-Associated Hypoventilation in Hospitalized Patients: Prevalence, Effects, and Outcome

Sogol Nowbar, MD, Kristin M. Burkart, MD, Ralph Gonzales, MD, Andrew Fedorowicz, MD, Wendolyn S. Gozansky, MD, MPH, Jon C. Gaudio, MD, Matthew R. G. Taylor, MD, Clifford W. Zwillich, MD

BACKGROUND: Severe obesity is associated with hypoventilation, a disorder that may adversely affect morbidity and mortality. We sought to determine the prevalence and effects of obesity-associated hypoventilation in hospitalized patients.

METHODS: Consecutive admissions to internal medicine services were screened over a 6-month period. In all eligible subjects with severe obesity (body mass index $\geq$35 kg/m^2), we administered a sleep questionnaire, and performed neuropsychological, arterial blood gas, and pulmonary function testing. Hospital course and mortality at 18 months was also determined.

RESULTS: Of 4332 admissions, 6% (n = 277) of patients were severely obese, of whom 150 were enrolled, 75 refused to participate, and 52 met the exclusion criteria. Hypoventilation (mean [$\pm$ SD] arterial partial pressure of carbon dioxide [$PaCO_2$], 52 $\pm$ 7 mm Hg) was present in 31% (n = 47) of subjects who did not have other reasons for hypercapnia. Decreased objective attention/concentration and increased subjective sleepiness were present in patients with obesity-associated hypoventilation compared with in severely obese hospitalized patients without hypoventilation (simple obesity group; mean $PaCO_2$, 37 $\pm$ 6 mm Hg). There were higher rates of intensive care ($P = 0.08$), long-term care at discharge ($P = 0.01$), and mechanical ventilation ($P = 0.01$) among subjects with obesity-associated hypoventilation. Therapy for hypoventilation at discharge was initiated in only 6 (13%) of the patients with obesity-associated hypoventilation. At 18 months following hospital discharge, mortality was 23% in the obesity-associated hypoventilation group as compared with 9% in the simple obesity group (hazard ratio = 4.0; 95% confidence interval: 1.5 to 10.4].

CONCLUSION: Hypoventilation frequently complicates severe obesity among hospitalized adults and is associated with excess morbidity and mortality. **Am J Med. 2004;116:1–7.**
©2004 by Excerpta Medica Inc.

Obesity is common in the United States (1), and high body weight is an independent risk factor for increased mortality (2,3). Severe obesity is associated with hypoventilation. However, hypoventilation may not be recognized in a large number of severely obese inpatients, and therefore appropriate treatment and follow-up may not be instituted at discharge. Furthermore, the diagnosis and treatment of obese patients with the hypoventilation syndrome reduces health care resources (4).

We hypothesized that hypoventilation is common among severely obese inpatients and is associated with higher morbidity and mortality. Accordingly, we prospectively examined a cohort of hospitalized adults to determine the frequency, effects, and outcome of hypoventilation (hypercapnia) associated with obesity. We compared these findings to that found in hospitalized patients who had severe obesity but no hypoventilation.

METHODS

Study Sample

We evaluated consecutive adults older than 18 years of age with a body mass index $\geq$35 kg/m^2, who were admitted to medical services of three teaching hospitals (the Denver Veterans Affairs Medical Center, Denver Health Medical Center, and University of Colorado Hospital). The criterion for body mass index was based on initial pilot data gathered over a 1-month period and literature review suggesting that most previously reported obesity-associated hypoventilation subjects have a body mass index $\geq$35 kg/m^2. Investigators directly screened all admis-

From the University of Colorado Health Sciences Center (SN, KMB, WSG, MRGT, CWZ), Denver Health Medical Center (KMB), and Denver Veterans Affairs Medical Center (CWZ), Denver, Colorado; Division of General Internal Medicine (RG), Department of Medicine, University of California, San Francisco, School of Medicine; Rose Medical Center (AF), Denver, Colorado; and Brown University (JCG), Providence, Rhode Island.

Funding was provided by the Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado.

Requests for reprints should be addressed to Clifford W. Zwillich, MD, Denver Veterans Affairs Medical Center, 1055 Clermont Street, 111, Denver, Colorado 80220, or clifford.zwillich@med.va.gov.

Manuscript submitted January 24, 2003, and accepted in revised form August 18, 2003.

© 2004 by Excerpta Medica Inc.
All rights reserved.

0002-9343/04/$–see front matter
doi:10.1016/j.amjmed.2003.08.022

sions. Subjects were asked to participate in a study designed to determine the influence of obesity on lung function and memory. There was no mention of sleep apnea or sleep quality. Determining the chronicity of hypoventilation or the presence of sleep-disordered breathing was beyond the scope of the study. The study was approved by the Institutional Review Board of each institution.

Hypoventilation was defined as an arterial partial pressure of carbon dioxide ($PaCO_2$) $\geq$43 mm Hg and a pH $\leq$7.42. The specific pH level was selected to eliminate primary metabolic alkalosis and secondary elevation in $PaCO_2$. A $PaCO_2$ $\geq$43 mm Hg is greater than 2 SD higher than the mean reference values at an altitude of 1400 meters (33 mm Hg for women and 34 mm Hg for men) and 2 SD higher than the mean reference values at sea level (37 mm Hg for women and 38 mm Hg for men) (5). Obesity-associated hypoventilation was defined as severe obesity and awake hypoventilation (hypercapnia) in the absence of other known causes of hypoventilation. Simple obesity was defined as severe obesity without the above evidence of hypoventilation. Erythrocytosis was defined as a hemoglobin level >16.3 g/dL in women and >18 g/dL in men, which are more than 2 SD higher than those at both sea level and an altitude of 1400 meters (5).

Exclusion criteria included the inability to give consent, other reasons for hypoventilation, severe chronic obstructive pulmonary disease (COPD) or asthma (forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] $\leq$50%), interstitial lung disease, lung resection, and use of opiate or opiate antagonists. In addition, subjects who had been readmitted were excluded.

Weight/Height and Neck Measurement

We measured height in 88% (n = 132) and weight in 93% (n = 140) of subjects. We used stated values for those in whom weight or height could not be measured. Seated neck circumference at the level of the thyroid cartilage was recorded. Investigators (blinded to outcome measures) assessing height and neck circumference were trained to use uniform techniques.

Medical History

Information on past medical history was obtained by reviewing residents' admission notes. We obtained data from the patient regarding menopausal status, hormone replacement therapy, birth control pills, oxygen, current alcohol consumption, and previous or current tobacco use.

Laboratory Data

Results of the laboratory testing on admission were recorded. Thyroid-stimulating hormone and spirometry values were obtained during the admission if they had not been performed in the previous 6 months. Arterial blood gas was obtained in 95% (91% room air, 9% breathing oxygen) of subjects during the admission when subjects were awake but in a supine position. The supine position was chosen because obese patients have their worst gas exchange during sleep. For the 5% (n = 8) of subjects who refused testing, an arterial blood gas measurement obtained within the previous 6 months was accepted.

Symptoms

Subjective symptoms of hypersomnolence, headache, snoring, and altered concentration were recorded in a standardized fashion. Attention and concentration ability was evaluated using a modified version of the validated Digit Span Test (subset of the Wechsler Adult Intelligence Scale) (6). The Epworth Sleepiness Scale was used to evaluate hypersomnolence (7,8).

Hospital Course

Data were gathered on the duration of hospitalization, and the occurrence of thromboembolism, cardiac arrest, respiratory failure requiring endotracheal intubation, transfer to intensive care units, discharge disposition, or death. In addition, the initiation of obesity-associated hypoventilation-specific treatments, such as continuous positive airway pressure, noninvasive ventilation, tracheostomy, and progesterone use, as well as discharge diagnoses, were recorded.

Mortality Data

The names and social security numbers of all 150 original participants were searched for in the Colorado Death Certificate Master Files for the period from 1999 to 2001. National data on death were obtained using the website www.ancestry.com, which contains complete information provided by the Social Security Administration through 18 months after the last hospital discharge.

Statistical Analysis

Data were incomplete in 7% of the study sample (8 missing spirometry data, 1 missing thyroid-stimulating hormone data, 1 missing a symptom-related questionnaire, and 1 missing data on neck circumference). Bivariate analysis was performed using chi-squared tests, unpaired *t* tests, and Pearson correlations. Multivariate Cox proportional hazards regression was used to compare mortality between groups, adjusting for age, sex, body mass index, history of thromboembolism, history of hypothyroidism, electrolyte abnormalities, and renal insufficiency (serum creatinine level >1.5 mg/dL). These possible confounders were included in the multivariate analyses if they were associated with obesity-associated hypoventilation or mortality in bivariate analyses at a P value <0.20 (9), or if they had been previously known to be associated with obesity-associated hypoventilation or mortality (10,11). Statistical significance was set at P <0.05 (two-tailed). Analyses were performed using SAS, version 6.12 (SAS Institute, Cary, North Carolina).

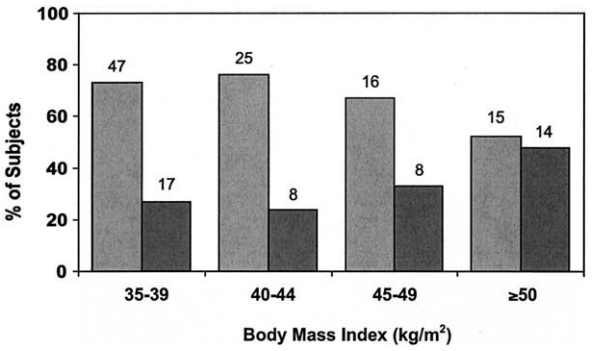

Figure 1. Association between body mass index and the frequency of obesity-associated hypoventilation in 150 patients. $P = 0.05$ using logistic regression. The numbers above each bar represent the number of patients. Light-colored bars indicate simple obesity; dark gray bars indicate obesity-associated hypoventilation.

RESULTS

Of 4332 consecutive admissions, 277 subjects (6%) had a body mass index ≥35 kg/m^2. Among these severely obese inpatients, 127 were excluded: 10 had an FEV_1/FVC ≤50% or prior lung resection, 10 could not give informed consent, 32 used opiates, and 75 refused to participate because they were unwilling to undergo arterial puncture. The remaining 150 were enrolled.

Of the 150 patients, 47 (31%) met the criteria for obesity-associated hypoventilation, whereas the remaining 103 had simple obesity. As body mass index increased, the prevalence of obesity-associated hypoventilation also increased significantly ($P = 0.05$). When the body mass index was >50 kg/m^2, hypoventilation was found in 48% (14/29) of obese subjects (Figure 1). However, obesity-associated hypoventilation was still quite prevalent in the lower body mass index categories.

Patients in the obesity-associated hypoventilation group were slightly heavier, and had higher mean serum bicarbonate levels, higher mean $PaCO_2$ values, and lower pH, than did patients in the simple obesity group (Table 1). A significant relation between body mass index and $PaCO_2$ was found for both patients with obesity-associated hypoventilation ($r = 0.52$, $P < 0.01$) and simple obesity ($r = 0.29$, $P < 0.01$) (Figure 2). Patients in the obesity-associated hypoventilation group were significantly more likely to have a previous diagnosis of obesity hypoventilation syndrome (usually defined as hypoventilation complicating sleep apnea), obstructive sleep apnea, or polycythemia, or to use a diuretic (Table 1). Documentation of a past history of sleep-disordered breathing accompanying hypoventilation or obstructive sleep apnea was not possible in the majority of subjects with this history.

The mean FEV_1 and FVC values were significantly lower in the obesity-associated hypoventilation group (Table 1). However, the FEV_1/FVC ratio was similar between the two groups. In addition, when the presence of severe obstruction was assessed using a more strict criterion from the American Thoracic Society (FEV_1/FVC ratio ≤70% with FEV_1 ≤50% predicted), there was no difference in the prevalence of moderately severe or severe airway obstruction in the obesity-associated hypoventilation and simple obesity groups (15% [n = 7] vs. 7% [n = 7], $P = 0.16$).

The majority of admissions in both groups were for dyspnea ($P = 0.06$, obesity-associated hypoventilation vs. simple obesity) or chest pain ($P = 0.44$). There was no significant difference in discharge diagnoses between the two groups. Also, the frequency of a discharge diagnosis of COPD or asthma exacerbation (6 in the obesity-associated hypoventilation group vs. 11 in the simple obesity group, $P = 0.71$) did not differ between groups, and neither did the presence of severe airflow limitation (FEV_1/FVC ≤70% and FEV_1 ≤50% predicted) differ (3 each in the obesity-associated hypoventilation and simple obesity groups, $P = 0.37$). No patient was discharged with a diagnosis of neuromuscular disease, and only 2 patients with simple obesity were discharged with a diagnosis of interstitial/restrictive lung disease.

Subjects with obesity-associated hypoventilation had more daytime somnolence than did those with simple obesity (mean [± SD] score, 12 ± 5 vs. 10 ± 5, $P = 0.01$). Testing of memory and concentration ability revealed lower scores in the obesity-associated hypoventilation group (7 ± 2 vs. 8 ± 2, $P = 0.01$). There was no difference in the symptoms of hypersomnolence, headache, snoring, or altered concentration between the two groups.

Subjects with obesity-associated hypoventilation were more likely to require invasive mechanical ventilation, tended to need more intensive care unit management, and showed a trend towards longer lengths of stay (Table 2). Furthermore, they were more likely to require long-term care at discharge (Table 2). There were no hospital-related deaths or cardiac arrests in either group. However, critically ill patients (n = 10) had been excluded because informed consent was not readily obtainable.

Although physicians were informed of subjects who had hypercapnia and normal or low pH, only 23% of patients (n = 11) were given the diagnosis of obesity-associated hypoventilation or obesity hypoventilation syndrome at discharge, about one quarter of whom (n = 3) had a previous diagnosis of obesity hypoventilation syndrome. Furthermore, only 13% (6/47) were discharged with a recommendation for long-term treatment for hypoventilation, such as noninvasive ventilatory assist (n = 5) or tracheostomy (n = 1). Of the patients recognized by hospital personnel as having obesity-associated hypoventilation, 36% (n = 4) were discharged with specific treatment compared with 6% (2/36) of those in whom the diagnosis went unrecognized ($P = 0.02$).

Table 1. Characteristics of the 150 Patients with Simple Obesity or Obesity-Associated Hypoventilation

Characteristic	Simple Obesity (n = 103)	Obesity-Associated Hypoventilation (n = 47)	*P* Value
	Number (%) or Mean ± SD		
Age (years)	53 ± 13	55 ± 14	0.28
Male sex	57 (55)	23 (49)	0.47
Race			0.73
White	67 (65)	31 (66)	
Black	20 (19)	7 (15)	
Hispanic	16 (16)	9 (19)	
Body mass index (kg/m^2)	42 ± 8	45 ± 9	0.04
Unemployed	86 (84)	36 (77)	0.31
Past medical history			
Hypertension	58 (56)	30 (64)	0.39
Chronic obstructive pulmonary disease	29 (28)	18 (38)	0.21
Coronary artery disease	26 (25)	13 (28)	0.75
Heart failure	25 (24)	15 (32)	0.33
Obstructive sleep apnea	22 (21)	18 (38)	0.03
Obesity hypoventilation syndrome	2 (2)	6 (13)	0.01
Pulmonary hypertension	4 (4)	5 (11)	0.11
Right-sided heart failure	4 (4)	3 (6)	0.50
Polycythemia	0	2 (4)	0.04
Hypothyroidism	14 (14)	3 (6)	0.20
Diuretic use	47 (46)	30 (64)	0.04
Laboratory measurements			
$PaCO_2$ (mm Hg)	37 ± 6	52 ± 7	0.01
Serum bicarbonate (mEq/L)	24 ± 5	30 ± 4	0.01
PaO_2 (mm Hg)*	62 ± 1.0	51 ± 1.2	0.01
Arterial pH	7.43 ± 0.04	7.38 ± 0.04	0.01
Alveolar-arterial gradient*	16 ± 9	13 ± 9	0.08
Supplemental oxygen†	5 (5)	8 (17)	0.37
Thyroid-stimulating hormone level >5.0 μIU/mL	8 (8)	2 (4)	0.44
Erythrocytosis‡	2 (2)	7 (15)	0.01
FVC (% predicted)	72 ± 20	57 ± 16	0.01
FEV_1 (% predicted)	69 ± 20	53 ± 14	0.01
FEV_1/FVC ratio (%)	77 ± 10	76 ± 9	0.41
Neck circumference (cm)	44 ± 5	47 ± 6	0.01

* Determined on room air only.
† At time of arterial blood gas analysis.
‡ Defined as a hemoglobin level >16.3 g/dL in women and >18 g/dL in men.
COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PaO_2 = arterial partial pressure of carbon dioxide.

At 18 months, mortality was 23% (n = 11) among patients with obesity-associated hypoventilation compared with 9% (n = 9) among patients with simple obesity (Figure 3). After adjusting for age, sex, body mass index, electrolyte abnormalities, renal insufficiency, history of thromboembolism, and history of hypothyroidism, patients with obesity-associated hypoventilation had a hazard ratio for mortality of 4.0 (95% confidence interval [CI]: 1.5 to 10.4). Most of the deaths associated with obesity-associated hypoventilation occurred in the first 3 months following hospital discharge (Figure 3). History of thromboembolism was independently associated with mortality (relative risk [RR] = 4.6; 95% CI: 1.6 to 13.7), as was hyponatremia (sodium level <130 mEq/L; RR = 7.0; 95% CI: 2.2 to 22.1) and renal insufficiency (RR = 2.8; 95% CI: 1.0 to 7.6). However, none of these variables confounded the effect of hypoventilation on mortality.

DISCUSSION

In the present study, 6% of patients hospitalized on medical services of three teaching hospitals were severely obese (body mass index ≥35 kg/ m^2) and 31% (1% of all screened admissions) had hypercapnia unexplained by

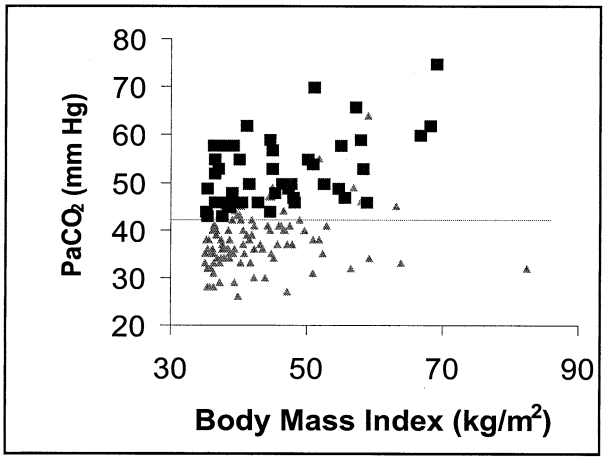

Figure 2. $PaCO_2$ values and body mass index in patients with obesity-associated hypoventilation or simple obesity. Some subjects with simple obesity had elevated $PaCO_2$ values; these patients were not classified as having obesity-associated hypoventilation because each had a pH level >7.42, suggesting that the increased $PaCO_2$ could have been in compensation for metabolic alkalosis. $PaCO_2$ = arterial partial pressure of carbon dioxide. Triangles indicate simple obesity; squares indicate obesity-associated hypoventilation.

other disorders. These patients more often required intensive care and invasive mechanical ventilation, and had a significantly greater likelihood of discharge to long-term care facilities. Most notably, mortality at 18 months following discharge was 23%, which was nearly twice the rate in patients with simple obesity. Moreover, the adjusted relative risk of death in patients with hypercapnia was fourfold greater than for simple obesity.

Although several studies have demonstrated increased mortality among obese persons (2,3,12), the association between hypoventilation and mortality in relation to obesity has not been well defined. Two small retrospective studies of patients with characteristics similar to the patients we studied reported an average in-hospital mortality of 30% (13,14). Although there were no in-hospital deaths in our study, critically ill patients were not included because informed consent was not readily obtainable. Thus, our finding of increased mortality at 18 months supports an additional mortality burden when hypoventilation is superimposed on obesity.

In the current study, physicians usually did not respond to the presence of hypoventilation (hypercapnia); as a result, effective treatment was only instituted in 13% of patients. This lack of attention is of concern because studies have demonstrated that noninvasive ventilatory support administered during sleep often results in normalization of awake unassisted blood gas values and resolution of hypersomnolence in obese patients with hypoventilation and episodes of apnea (15-18), although the effect of noninvasive ventilation on mortality in such patients is not known.

Subjects with obesity-associated hypoventilation had more severe restrictive respiratory defects than did those with simple obesity, as others have also demonstrated (19,20). Although almost half of patients with a body mass index ≥50 kg/m^2 had hypoventilation, this condition was distributed throughout the body mass index range. Still, many subjects did not have hypoventilation, which suggests that obesity alone does not fully explain the respiratory failure in these patients. Furthermore, there has been one report of similar hypercapnic patients being able to normalize their blood gases during voluntary hyperventilation (21), suggesting that physical impediment alone, although substantial and greater than that found in simple obesity (20), does not fully explain the hypercapnia.

The lung function abnormalities that we found in obesity-associated hypoventilation subjects were similar to those recorded in a study of 41 hypercapnic obese patients with obstructive apnea (22). In that study, FVC averaged 60% of predicted, whereas the FEV_1/FVC ratio was 77%, which are very similar to values in our study. Accordingly, we believe that the lung dysfunction in our patients is typical of that found in the obesity hypoventilation syndrome. In addition, subjects with obesity-associated hypoventilation demonstrated lower FEV_1 values than did those with simple obesity. This decrease in FEV_1

Table 2. Adverse Events during Hospitalization, Length of Stay, and Discharge Status among Patients with Simple Obesity or Obesity-Associated Hypoventilation

Variable	Simple Obesity (n = 103)	Obesity-Associated Hypoventilation (n = 47)	*P* Value
	Number (%) or Mean ± SD		
Intensive care management	27 (26)	19 (40)	0.08
Invasive mechanical ventilation	0	3 (6)	0.01
Thromboembolism	3 (3)	2 (4)	0.67
Length of stay (days)	6 ± 9	8 ± 11	0.16
Discharge to long-term care facility	2 (2)	9 (19)	0.01

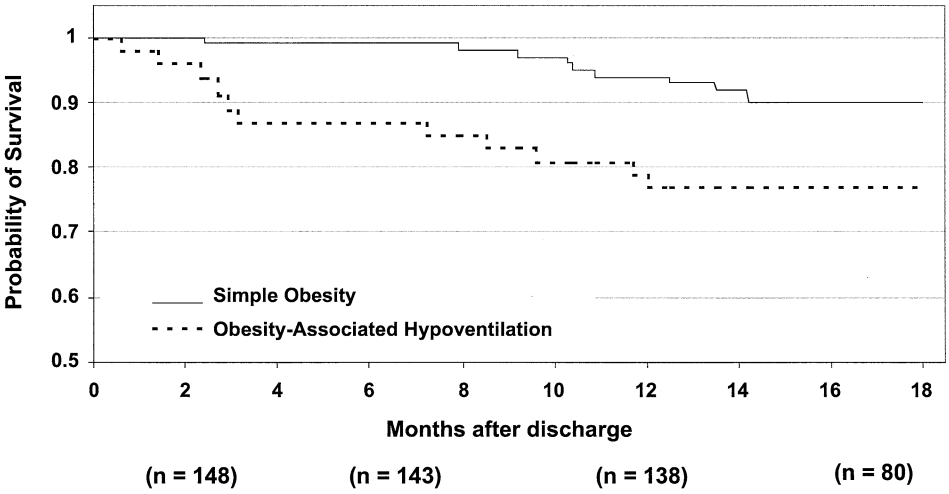

Figure 3. Survival curves for patients with obesity-associated hypoventilation or simple obesity after discharge from hospital, with adjustment for age, sex, body mass index, electrolyte abnormalities, renal insufficiency, history of thromboembolism, and history of hypothyroidism.

is likely in part due to the severity of restriction found in patients with obesity-associated hypoventilation. In addition, there was no difference between the two groups with regards to the severity of airflow limitation when using the American Thoracic Society criteria of obstructive lung disease. If patients with severe obstruction ($FEV_1/FVC \leq 70\%$ and $FEV_1 \leq 50\%$ predicted) were excluded, the prevalence of obesity-associated hypoventilation would still be 31%.

Our study has certain limitations. First, although we did not include subjects with a history of muscle disease or interstitial lung disease, no objective testing was performed to rule out this possibility. Second, our study location (Denver, Colorado), at an altitude of 1609 meters, is more likely to be associated with oxygenation abnormalities and polycythemia for the same degree of hypoventilation than at sea level. Chronic hypoxemia in those living at high altitudes, or as the result of cyanotic congenital heart disease, may result in decreased ventilatory drive (23,24), suggesting that the prevalence of obesity-associated hypoventilation in our community could be higher than at sea level. However, our inability to find any reports of an increased prevalence of hypercapnia in patients with respiratory disease living at a high altitude suggests that altitude has minimal effect on the generalizability of our results. Third, since admissions for acute respiratory conditions such as acute pulmonary edema, COPD/asthma exacerbation, or pneumonia were not exclusionary, it is possible that the increased prevalence of obesity-associated hypoventilation may be partly attributable to these conditions. However, these conditions were equally common between groups, and it is therefore unlikely that this alone would explain our findings.

Lastly, we evaluated subjects for hypoventilation at hospital admission, but did not determine the chronicity of their hypercapnic respiratory failure or the prevalence of sleep-disordered breathing. Accordingly, we are not certain how many had the obesity hypoventilation syndrome in which chronic hypoventilation and sleep-disordered breathing were present. Despite our findings of partially compensated respiratory acidosis (increased serum bicarbonate levels) in the obesity-associated hypoventilation group, there are no data to definitively prove the chronicity of hypercapnic respiratory failure in these patients. In addition, the higher Epworth Sleepiness Scale score and decreased concentration suggest a higher rate of sleep-disordered breathing among those with obesity-associated hypoventilation. Therefore, it is likely, but not proven, that many of these patients had undiagnosed obesity hypoventilation syndrome.

In summary, our findings suggest that hypoventilation is underappreciated and undertreated in severely obese, hospitalized patients. The presence of obesity-associated hypoventilation appears to predict increased mortality and to portend the need for increased intensive and post-discharge care. It may thus be advisable to perform arterial blood gas analysis in severely obese, hospitalized subjects, especially those with dyspnea, who snore, or have headaches or daytime somnolence.

ACKNOWLEDGMENT

We are indebted to Jaclyn Martinez for help in preparing the manuscript; Douglas Robertson, Anna Baron, PhD, and Judy Maselli, MSPH, for assistance in data analysis; to John Weil, William Kaehny, Robert Anderson, and John Steiner for their

critical review of the manuscript; and to Robert W. Schrier for his financial and intellectual support.

REFERENCES

1. NHLBI Obesity Initiative Task Force Members. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res.* 1998;6(suppl 2): 51–82.
2. Solomon CG, Manson JE. Obesity and mortality: a review of the epidemiologic data. *Am J Clin Nutr.* 1997;66(suppl):1044S–1050S.
3. Calle EE, Thun MJ, Petrelli JM, Rodriquez C, Heath CW. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med.* 1999;341:1097–1105.
4. Berg G, Delavie K, Manfreda J, et al. The use of health-care resources in obesity-hypoventilation syndrome. *Chest.* 2001;120: 377–383.
5. Crapo RO, Jensen RL, Hegewald M, Tashkin DP. Arterial blood gas reference values for sea level and at altitude of 1,400 meters. *Am J Respir Crit Care Med.* 1999;160:1525–1531.
6. Wechsler D. *Wechsler Adult Intelligent Scale*. New York, New York: Psychological Corp.; 1955.
7. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* 1991;14:540–545.
8. Johns MW. Reliability and factor analysis of the Epworth sleepiness scale. *Sleep.* 1992;15:376–381.
9. Hosmer DW Jr, Lemeshow S. *Applied Logistic Regression*. New York, New York: Wiley; 1989.
10. Hall WD. Abnormalities of kidney function as a cause and a consequence of cardiovascular disease. *Am J Med Sci.* 1999;317:176–182.
11. Chin MH, Goldman L. Correlates of major complications or death in patients admitted to the hospital with congestive heart failure. *Arch Intern Med.* 1996;156:1814–1820.
12. Bender R, Trautner C, Spraul M, Berger M. Assessment of excess mortality in obesity. *Am J Epidemiol.* 1998;147:42–48.
13. Miller A, Granada M. In-hospital mortality in the Pickwickian Syndrome. *Am J Med.* 1974;56:144–150.
14. MacGregor M, Block A, Ball W Jr. Serious complications and sudden death in the Pickwickian Syndrome. *Top Clin Med.* 1970;126: 279–295.
15. Piper AJ, Sullivan CE. Effects of short-term NIPPV in the treatment of subjects with severe obstructive sleep apnea and hypercapnia. *Chest.* 1994;105:434–440.
16. Resta O, Guido P, Picca V, et al. Prescription of nCPAP and nBIPAP in obstructive sleep apnea syndrome: Italian experience in 105 subjects. A prospective two centre study. *Respir Med.* 1998;92:820–827.
17. Schafer H, Ewig S, Hasper E, Luderitz B. Failure of CPAP therapy in obstructive sleep apnea syndrome: predictive factors and treatment with bilevel-positive airway pressure. *Respir Med.* 1998;92:208–215.
18. Laursen SB, Dreijer B, Hemmingsen C, Jacobsen E. Bi-level positive airway pressure treatment of obstructive sleep apnea syndrome. *Respiration.* 1998;65:114–119.
19. Luce JM. Respiratory complications of obesity. *Chest.* 1980;78:626–631.
20. Rochester DF, Enson Y. Current concepts in the pathogenesis of the obesity hypoventilation syndrome. *Am J Med.* 1974;57:402–420.
21. Leech JA, Onal E, Swanson R, Lopata M. Voluntary hyperventilation in obesity hypoventilation. *Chest.* 1991;100:1334–1338.
22. Leech JA, Onal E, Baer P, Lopata M. Determinants of hypercapnia in occlusive sleep apnea syndrome. *Chest.* 1987;92:807–813.
23. Weil VJ, Byrne-Quinn E, Sodal IE, Filley GF, Grover RF. Acquired attenuation of chemoreceptor function in chronically hypoxic man at high altitude. *J Clin Invest.* 1971;50:186–195.
24. Blesa MI, Lahiri S, Rashkind WJ, Fishman AF. Normalization of the blunted ventilatory response to hypoxia in congenital cyanotic heart disease. *N Engl J Med.* 1977;296:237–241.