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Is a Raised Bicarbonate, Without Hypercapnia, Part of the Physiologic Spectrum of Obesity-Related Hypoventilation?

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BACKGROUND: Obesity hypoventilation syndrome (OHS) conventionally includes awake hypercapnia, but an isolated raised bicarbonate, even in the absence of awake hypercapnia, may represent evidence of "early" OHS. We investigated whether such individuals exhibit certain features characteristic of established OHS.

METHODS: Obese subjects (BMI > 30 kg/m^2) were identified from a variety of sources and divided into those with (1) normal blood gas measurements and normal acid-base balance, (2) an isolated raised base excess (BE) (≥ 2 mmol/L), and (3) awake hypercapnia (> 6 kPa; ie, established OHS). Two-point ventilatory responses to hypoxia and hypercapnia were performed. Polygraphic sleep studies were done to identify intermittent and prolonged hypoxia.

RESULTS: Seventy-one subjects (BMI, 47.2; SD, 9.8; age, 52.1 years; SD, 8.8 years) were recruited into three groups (33, 22, and 16 respectively). The $Paco_2$ and BE values were 5.15, 5.42, 6.62 kPa, and +0.12, +3.01, +4.78 mmol/L, respectively. For nearly all the ventilatory response and sleep study measures, group 2 (with only an isolated raised BE) represented an intermediate group, and for some of the measures they were more similar to the third group with established OHS.

CONCLUSIONS: These data suggest that obese individuals with a raised BE, despite normocapnia while awake, should probably be regarded as having early obesity-related hypoventilation. This has important implications for clinical management as well as randomized controlled treatment trials, as they may represent a group with a more reversible disease process.

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ABBREVIATIONS: AHI = apnea/hypopnea index; ANOVA = analysis of variance; BE = base excess; $Etco_2$ = end-tidal CO_2; [HCO_3^-] = bicarbonate concentration; ODI = oxygen desaturation index; OHS = obesity hypoventilation syndrome; Sao_2 = arterial oxygen saturation; SDB = sleep-disordered breathing; Spo_2 = oxygen saturation by pulse oximetry

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Obesity hypoventilation syndrome (OHS) has been defined conventionally by the combination of obesity (BMI > 30 kg/m^2), daytime hypercapnia ($Paco_2$ > 45 mm Hg or > 6 kPa) during wakefulness, and usually (but not always) the presence of sleep-disordered breathing (SDB), such as OSA, with or without sleep-related central hypoventilation, which is usually most pronounced during rapid-eye-movement sleep.[1] More importantly for the clinician, patients with OHS have a higher morbidity, mortality, and health-care use compared with nonhypercapnic obese subjects.[2]

Respiratory acidosis from CO_2 retention in patients with chronic respiratory disease is partially compensated for by the generation of bicarbonate and a sustained elevation of the threshold for renal bicarbonate reabsorption.[3] Frequently, when these patients are admitted with acute hypercapnic respiratory failure, an elevated plasma bicarbonate concentration ($[HCO_3^-]$) is present, indicating established chronic respiratory failure.[4]

The control of plasma $[HCO_3^-]$ by the kidneys and the removal of CO_2 by the alveoli have markedly different time constants. In clinical practice, a situation occurs in which the plasma $[HCO_3^-]$, generated to partially compensate for the respiratory acidosis resulting from an elevated $Paco_2$ during the night, becomes superfluous when the hypercapnia resolves on awakening (following improvements in respiratory drive muscle load and/or drive). This diurnal variation in the metabolic response to offset nocturnal hypercapnia may result in a residual metabolic alkalosis during the day. Norman et al[5] used a computer model to simulate CO_2 and renal bicarbonate kinetics resulting from periods of nocturnal hypoventilation. Transient hypercapnia during SDB, causing some renal compensation, was assumed. Changes in $Paco_2$ can of course occur rapidly within minutes and even seconds, whereas changes in bicarbonate take hours

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and days. A transition from acute hypoventilation to chronic hypoventilation occurred over several days if either renal excretion of $[HCO_3^-]$ or ventilatory response to hypercapnia were reduced.

Correctly recognizing the whole spectrum of the obese population with impending or chronic respiratory failure is important for designing the most appropriate long-term respiratory management. There is a clinical priority to recognize the different stages and phenotypes of OHS to determine both what dictates a poorer prognosis and which treatments to use (such as noninvasive ventilation or ventilatory stimulants[6]). We hypothesized, even in the absence of a raised daytime $Paco_2$, that the presence of a raised plasma standard $[HCO_3^-]$, or base excess (BE), and, thus, a biomarker of whole-body acid-base balance,[7] would be associated with reduced ventilatory drive and nocturnal hypoventilation in obese patients,[8] thus suggesting the presence of "early" OHS. We have, therefore, investigated the relationship between daytime ventilatory drive, nocturnal hypoventilation, and metabolic acid-base status in a range of obese subjects.

Materials and Methods

Study Design and Setting

This was an open cross-sectional study of obese subjects with and without conventionally defined OHS. The work was carried out in the Oxford Sleep Unit, Oxford Centre for Respiratory Medicine, Churchill Hospital, England, which is a National Health Service secondary and tertiary referral center. Subjects were recruited and studied between June 2011 and September 2013. The study was registered prospectively with a global trials registry site (NCT01380418). It has been reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[9] The study was approved by the Oxford research ethics committee (Oxfordshire REC B 11/H0605/9). After an initial approach, all subjects interested in participating in the study were invited to a screening appointment, and written informed consent was obtained from all participants.

Participants

Obese subjects (BMI > 30 kg/m^2) with or without conventionally defined OHS were included. Patients were referred to the Oxford Sleep Unit, Oxford Centre for Respiratory Medicine, England, by general practitioners or other hospital consultants. Subjects were recruited from the following sources: (1) following a recent admission to hospital after the diagnosis of OHS had been made, (2) after referral to the sleep and ventilation clinic for assessment of possible SDB and/or OHS, and (3) during assessment for bariatric surgery.

Participants were excluded for any of the following: (1) current treatment with respiratory stimulants or depressants, diuretics, theophylline; (2) presence of obstructive lung disease (FEV_1/FVC < 70% predicted); (3) other severe comorbidities, such as congestive cardiac failure, primary CNS or neuromuscular diseases, untreated hypothyroidism; or (4) currently on treatment of OHS including continuous positive airways pressure or noninvasive ventilation.

Demographic and Anthropometric Data

Data were collected on all participants, including age, sex, height, weight, BMI, and resting oxygen saturation by pulse oximetry (Spo_2) measured with a standard pulse oximeter (Masimo Corporation). Daytime somnolence was assessed using the Epworth sleepiness score.[10]

Physiologic Measurements

Outcome variables for this study included the BE, derivatives from the measured ventilatory responses to hypercapnia and hypoxia (see later), and derivatives from an overnight sleep study, including measures of overall hypoxia (total time with Spo_2 < 90%) and intermittent hypoxia (oxygen desaturation index [ODI] and apnea/hypopnea index [AHI]). All participants had all measurements made.

BE Measurements: Arterial blood gas sampling was performed from the radial artery with subjects in a seated position breathing room air between 8:00 AM and 10:00 AM after at least 15 min of rest. Analysis of Pao_2, $Paco_2$, arterial standard $[HCO_3^-]$, BE, and pH were performed

using an analyzer maintained and calibrated according to the manufacturer's recommendations (ABL 90; Radiometer Medical ApS).

Subject Grouping: Following arterial blood gas analysis, subjects were divided a priori into three groups according to the following criteria.

1. Normal daytime $Paco_2$ ($\leq$ 6 kPa) and BE ($<$ 2 mmol/L)
2. Normal daytime $Paco_2$ ($\leq$ 6 kPa) and elevated BE ($\geq$ 2 mmol/L)
3. Elevated daytime $Paco_2$ ($>$ 6 kPa)

Ventilatory Response Testing: Instrument calibrations preceded the study of each patient, and the studies were performed after the overnight sleep study. Both the hypoxic and the hypercapnic challenge test were performed on the same day, with the subject having a 30-min interval between each test. Subjects were seated comfortably in a chair at rest, wearing a full face mask (Respironics Gel Comfort; Koninklijke Philips N.V.) initially delivering air only, through a two-way, non-rebreathing valve (T-shape; Hans Rudolph, Inc). Baseline measurements of resting Spo_2, end-tidal CO_2 ($ETCO_2$) levels, and resting ventilation (NICO 2; Koninklijke Philips N.V.) were made over at least a 15-min period until stable. The expiratory limb of the circuit was attached to the NICO 2 capnograph and oximeter, whose digital output was connected to a PC (Dell), allowing breath-by-breath measurements to be taken continuously over this period.

Hypoxic Ventilatory Response Test: After this baseline period, subjects first inhaled a hypoxic gas mix of 15% oxygen, balance nitrogen (BOC), through the two-way, non-rebreathing valve from a gas reservoir (100 L nondiffusing Douglas collection bag). The effect of this hypoxic gas mixture on Spo_2, $ETCO_2$, and ventilation was followed over at least 15 min until the subject's ventilation was stable. During the hypoxic challenge the subject's Spo_2 was monitored continuously to prevent severe hypoxemia, with the test being terminated if Spo_2 values fell below 70% (one subject) or the patient became distressed (no subjects). Thus, a two-point steady-state, poikilocapnic estimate of the hypoxic response was made.

Hypercapnic Ventilatory Response Test: The ventilatory response to 5% CO_2, balance oxygen (BOC), was then measured using the same technique as described previously. The subjects inhaled the hypercapnic gas mix through the two-way, non-rebreathing valve from the gas reservoir. The effect of this hypercapnic gas mixture on Spo_2, $ETCO_2$, and ventilation was followed over at least 15 min until the subject's ventilation was stable, unless the patient became distressed (no subjects). Thus a two-point steady-state, hyperoxic estimate of the hypercapnic response was made.

In addition to the two-point ventilatory responses to hypoxia and hypercapnia (L/min increase per fall in Spo_2 or rise in Pco_2), other simpler derivatives were calculated. The degree to which the Spo_2 was defended during the hypoxic challenge test was taken as a simple measure of poikilocapnic hypoxic sensitivity (this measure can be obtained during a simple "fitness to fly" assessment[11] without the need to measure the minute ventilation); similarly, the end-tidal Pco_2 reached during the challenge was recorded. The average of the final stable 5-min period of each study was used for all these analyses.

Sleep Study: SDB was assessed from a one-night, in-hospital respiratory polygraphic sleep study. Subjects' body movements (derived automatically from the video signal), heart rate, and pulse transit time changes were routinely recorded as markers of arousal from sleep. The sleep study equipment also measured nasal pressure via nasal cannula, Spo_2, pulse rate, and respiratory effort via thoracic and abdominal bands (Win-Visi monitoring system; Stowood Scientific Instruments Ltd). From these measurements, AHI per hour in bed and oxygen desaturation events per hour in bed were automatically calculated, with manual review and editing (including removal of clear awake periods) to ensure accuracy of the data as previously described.[12] The variables derived for this study were: (1) number of oxygen desaturations ($\geq$4%) per hour of study (ODI); (2) mean arterial oxygen saturation (Sao_2) overnight, AHI; and (3) time, or percent of time, during the overnight study spent with a $Spo_2 <$ 90%.

Statistical Analysis

Data analyses were performed using SPSS (version 22; IBM). Data are presented as the mean and SD for normally distributed data. Data were tested for normality and parametric analyses conducted when appropriate.

Any differences between the three groups (normal, raised BE only, and raised $Paco_2$) were explored using analysis of variance (ANOVA) with post hoc assessment of any significant intergroup differences using Duncan post hoc comparison test. For the ANOVA, any non-normally distributed data were first converted using a logarithmic transformation.

Results

Seventy-one obese subjects (37, 52%, men) were studied during the 27-month recruitment period. Demographic and anthropometric data are reported for each group in Table 1. There were no differences in age, weight, or BMI between the groups, although the *P* value for BMI approached significance ($P = .056$) between groups.

The ventilatory drive measurements at baseline and after hypoxic and hypercapnic challenge testing are shown in Tables 2-4, respectively. Table 5 shows the sleep data for each group.

For most of the ventilatory response and sleep measurements, the group with only a raised BE are a middling group, between the normal and OHS groups. The ANOVA and Duncan post hoc comparison tests suggest for some measures that the raised BE group is more similar to the OHS group rather than to the normal group. For example: the fall in Sao_2 and the rise in $ETCO_2$ during the hypoxic and hypercapnic challenges, respectively, and the time spent at $<$ 90% Sao_2 overnight (despite similar values for the awake baseline Sao_2) (Table 2).

Discussion

In this prospective observational cohort study, we have demonstrated that obese subjects with a raised BE, but with a normal daytime $Paco_2$, have a ventilatory response between those of normal obese subjects (without evidence of awake hypoventilation) and those with hypercapnia and, thus, conventionally defined OHS. This evidence suggests that these subjects are in the middle of a spectrum, and indeed they could be considered as patients with "early OHS," albeit we do not have longitudinal data showing that they will progress and, if so, over what time scale. These data challenge the conventional threshold-based definition of OHS, in so much as

TABLE 1] Demographic, Anthropometric, and Gas Exchange Data for Each Group

Measure	Groups 1, 2, and 3 Combined	Group 1	Group 2	Group 3	ANOVA *P* Value
		Normal $Paco_2$ and Normal BE (n = 33)	Normal $Paco_2$ and Elevated BE (n = 22)	Elevated $Paco_2$ (n = 16)	
Age, y	52.1 (8.8)	53.6 (9.4)	48.7 (7.9)	53.7 (7.6)	.09
Weight, kg	136 (29.5)	130 (28.9)	135 (22.6)	148 (35.1)	.09
BMI, kg/m^2	47.2 (9.80)	45.2 (9.1)	46.5 (7.9)	51.6 (11.7)	.056
pH, log [H^+]	7.42 (0.03)	7.41 (0.02)[a]	7.44 (0.01)[a]	7.41 (0.03)[a]	< .001
Pao_2, kPa	9.87 (1.39)	10.26 (1.38)[a]	9.77 (1.35)[a]	9.17 (1.26)[a]	.031
$Paco_2$, kPa	5.57 (0.79)	5.15 (0.47)[a]	5.42 (0.32)[a]	6.62 (0.91)[a]	< .001
BE, mmol/L	+2.08 (2.41)	+0.12 (1.38)[a]	+3.01 (0.98)[a]	+4.78 (2.10)[a]	< .001
Standard bicarbonate, mmol/L	26.2 (2.11)	24.4 (1.18)[a]	27.0 (0.87)[a]	28.5 (2.11)[a]	< .001
Creatinine, mmol/L	70.6 (12.9)	82.1 (28.7)	70.6 (12.9)	76.8 (17.9)	.19
Hematocrit, fraction	0.43 (0.04)	0.42 (0.04)[a]	0.45 (0.04)[a]	0.44 (0.05)[a]	.02

Data are expressed as mean (SD). Normal daytime $Paco_2$ was a $Paco_2 \leq 6$ kPa, and normal BE was a BE < 2 mmol/L. ANOVA = analysis of variance; BE = base excess.
[a]Grouping of data as determined by Duncan post hoc comparison.

patients with daytime hypercapnia may represent only the severe end of the obesity-related hypoventilation spectrum.

Physiologic Similarities and Difference Across the Spectrum of Obesity-Related Hypoventilation

The most striking example of the similarity between the group with overt OHS and the group with only a raised BE occurred in the hypoxic ventilatory response test. The subjects with a raised BE level, but daytime normocapnia, showed a greater fall in oxygen saturation than was observed in the normocapnic obese subjects without an elevated BE, and, furthermore, there was no significant difference between those subjects with only an elevated BE and the patients with hypercapnia. It is possible that the failure to increase ventilation and defend the oxygen level, in the face of nocturnal hypoxia, could be a contributory cause to the gradual development of daytime hypercapnia. However, it is also conceivable that the reverse might be true, and our interpretation remains a hypothesis that needs to be tested.

Although the results of the hypercapnic ventilatory response tests also showed that the obese subjects with only a raised BE have similarity with those fulfilling the conventional criteria for OHS, causality is particularly difficult to establish; once there is a raised plasma bicarbonate level, the ventilatory response to inhaled CO_2 will be attenuated.[13] Therefore, we can only comment that there was greater similarity between the subjects with metabolic compensation, with and without chronic hypercapnia, than with the subjects with normocapnia and a normal acid-base balance.

TABLE 2] Baseline Ventilation Data

Measure	Group 1	Group 2	Group 3	ANOVA *P* Value
	Normal $Paco_2$ and Normal BE (n = 33)	Normal $Paco_2$ and Elevated BE (n = 22)	Elevated $Paco_2$ (n = 16)	
Minute ventilation, L/min	8.05 (1.84)	8.33 (2.26)	7.54 (1.61)	.47
Respiratory rate, breaths/min	14.7 (4.01)	16.1 (4.93)	14.3 (5.89)	.48
% Spo_2	96.0[a] (1.83)	96.3[a] (1.62)	92.4[a] (1.69)	.007
$ETCO_2$, kPa	5.3[a] (0.40)	5.4[a] (0.35)	6.2[a] (0.6)	< .001

Data shown from average of the final 5 min of the challenge. Data are expressed as mean (SD). Normal daytime $Paco_2$ was a $Paco_2 \leq 6$ kPa, and a normal BE was a BE < 2 mmol/L. $ETCO_2$ = end-tidal partial pressure of CO_2; Spo_2 = arterial oxygen saturation from oximetry. See Table 1 legend for expansion of other abbreviations.
[a]Grouping of data as determined by Duncan post hoc comparison.

TABLE 3] Results From the Hypoxic Ventilatory Response Test

Measure	Group 1 Normal $Paco_2$ and Normal BE (n = 33)	Group 2 Normal $Paco_2$ and Elevated BE (n = 22)	Group 3 Elevated $Paco_2$ (n = 16)	ANOVA *P* Value
Minute ventilation, L/min	10.12 (3.27)	9.26 (2.31)	9.21 (2.28)	.45
Respiratory rate, breaths/min	14.8 (3.91)	15.6 (4.90)	13.8 (5.11)	.55
% Spo_2	93.4[a] (2.36)	92.6[a] (2.50)	87.2[a] (1.50)	.001
$ETCO_2$, kPa	5.18[a] (3.01)	5.21[a] (2.60)	6.03[a] (0.54)	< .001
Decrease in % Spo_2	2.50[a] (1.64)	3.68[a] (2.07)	5.01[a] (0.40)	.002
Rise in minute ventilation, L/min	2.12 (1.01)	0.97 (0.96)	1.39 (1.02)	.20
Ventilatory response, L/min/% Spo_2	2.42 (4.48)	0.40 (0.41)	0.66 (1.20)	.058

Data shown from average of the final 5 min of the challenge. Data are expressed as mean (SD). Normal daytime $Paco_2$ was a $Paco_2 \leq 6$ kPa, and a normal BE was a BE < 2 mmol/L. See Table 1 and 2 legends for expansion of abbreviations.
[a]Grouping of data as determined by Duncan post hoc comparison.

Comparison With Previous Studies

The unstimulated central drive to breathe during rest has been found to be higher in normocapnic subjects with morbid obesity than in normal-weight control individuals, presumably because of compensation for the increased mechanical load.[14] An impaired ventilatory response to hypercapnia is also a common feature of obesity-related hypoventilation,[14] although hypercapnic ventilatory responses are highly variable between individuals and are sometimes even within the normal range in patients with only mild hypercapnia. The ventilatory response to hypoxia is also known to be blunted in subjects with obesity-related hypoventilation.[14] Thus, our observations of generally reduced hypoxic and hypercapnic ventilatory responses across the spectrum of obesity-related hypoventilation, from normocapnia with some metabolic compensation through to metabolically compensated chronic hypercapnia, are supported by previous data.

Differences in Respiratory Physiologic Parameters During Sleep

There was no difference across the groups in daytime somnolence, ODI, AHI, and overall oxygenation (mean Spo_2 overnight). Despite this, there were, however, differences observed in both the absolute time and percent of time spent below an Spo_2 level of 90% between the three groups, with the raised BE only and chronic hypercapnia groups being the most similar. Although this greater nocturnal hypoventilation would be expected in the chronic hypercapnia group as a consequence of their lower baseline oxygen saturation level, this would not be the explanation for the subjects with normocapnia and metabolic compensation as their awake Spo_2 values were similar. Again, it is difficult to infer the

TABLE 4] Results From the Hypercapnic Ventilatory Response Test

Measure	Group 1 Normal $Paco_2$ and Normal BE (n = 33)	Group 2 Normal $Paco_2$ and Elevated BE (n = 22)	Group 3 Elevated $Paco_2$ (n = 16)	ANOVA *P* Value
Minute ventilation, L/min	14.6[a] (5.43)	11.96[a] (2.31)	11.76[a] (3.30)	.035
Respiratory rate, breaths/min	14.3 (4.09)	16.6 (4.90)	15.0 (5.11)	.15
% Spo_2	99.0 (1.61)	98.4 (2.20)	98.3 (2.30)	.40
$ETCO_2$, kPa	6.03[a] (0.44)	6.03[a] (0.47)	7.09[a] (0.81)	< .001
Rise in end-tidal CO_2, kPa	0.73 (0.33)	0.65 (0.39)	0.80 (0.46)	.14
Rise in minute ventilation, L/min	6.73[a] (0.72)	3.64[a] (0.37)	3.51[a] (0.43)	.026
Ventilatory response to CO_2, L/min/kPa	1.57 (0.91)	0.87 (0.69)	0.70 (0.59)	.50

Data shown from average of the final 5 min of the challenge. Data are expressed as mean (SD). Normal daytime $Paco_2$ was a $Paco_2 \leq 6$ kPa, and a normal BE was a BE < 2 mmol/L. See Table 1 and 2 legends for expansion of abbreviations.
[a]Grouping of data as determined by Duncan post hoc comparison.

TABLE 5] Sleep Data

Measure	Group 1 Normal $Paco_2$ and Normal BE (n = 33)	Group 2 Normal $Paco_2$ and Elevated BE (n = 22)	Group 3 Elevated $Paco_2$ (n = 16)	ANOVA *P* Value
Epworth sleepiness score	12.2 (5.5)	12.1 (5.0)	11.9 (6.2)	.99
4% ODI, events/h	40.6 (26.3)	53.9 (44.5)	55.7 (40.8)	.28
Apnea/hypopnea index, events/h	20.6 (26.0)	34.0 (33.7)	29.5 (28.5)	.25
Mean % Spo_2	92.6[a] (2.6)	90.7[a] (5.24)	88.0[a] (7.17)	.007
Time spent with % $Spo_2 < 90\%$, h:min:s	1:14:20[a] (1:23:35)	1:59:20[a] (2:02:20)	2:43:49[a] (2:28:46)	.04
Percentage of time spent with % $Spo_2 < 90\%$	17.3[a] (19.3)	27.7[a] (28.7)	42.3[a] (34.7)	.012

Data are expressed as mean (SD). ODI = oxygen desaturation index. Normal daytime $Paco_2$ was a $Paco_2 \leq 6$ kPa, and a normal BE was a BE < 2 mmol/L. See Table 1 and 2 legends for expansion of other abbreviations.
[a]Grouping of data as determined by Duncan post hoc comparison.

direction of causality in a cross-sectional study, but the group with an elevated BE but normal daytime CO_2 levels is likely to represent the patients at an early stage in the obesity-related hypoventilation spectrum and be those patients at risk for developing chronic hypercapnic respiratory failure if there were further deteriorations in the balance between neural respiratory drive, respiratory muscle load, and respiratory muscle capacity (as would be expected, for example, with a further increase in weight). These findings suggest that sustained hypoventilation may be more relevant than intermittent hypoxia, such as occurs with purely obstructive or central sleep apnea. This is physiologically plausible, as brief transient periods of hypoventilation, seen in upper airways obstruction, only leads to a rise in CO_2 to mixed venous levels, with the rise thereafter very much slower.[15,16] More prolonged hypoventilation, with attendant rises in the partial pressure of arterial CO_2, are required to promote bicarbonate generation and renal reabsorption of bicarbonate.

Limitations of the Study

The measurement of ventilatory control has many challenges, and we acknowledge that our simple approach has a number of limitations. The very presence of chronic hypercapnia in a patient almost certainly confirms reduced ventilatory drive, unless the respiratory load on the system is extremely high, as can sometimes be observed in morbid obesity. Any measurements of ventilatory control performed in the presence of ventilatory failure, with or without an increased ventilatory load, are difficult to interpret. However, if a test of ventilatory control is to be useful clinically to identify patients with "early" OHS, then the requirement is for a simple test that could be applied in ordinary practice. The simple procedures we have used, assessing a patient's ability to defend their gas exchange in response to hypoxia and hypercapnia, appear appropriate and clearly have paralleled increasing degrees of obesity-related hypoventilation. Furthermore, there are other potential sources of bicarbonate that could interfere with metabolic status as a marker of early OHS and also reduce ventilatory drive itself. Diuretic-induced potassium depletion, and the use of sedatives and oxygen, may contribute to the development of both acute and chronic hypercapnia through effects on renal bicarbonate kinetics, even in the absence of preexisting hypercapnia. Patients with OHS often retain salt and water because of cardiorespiratory failure and/or the metabolic syndrome, which may also contribute to this.[5] However, we specifically excluded patients on diuretics and respiratory depressants and those with significant cardiac failure.

These data were collected from a single center specializing in the management of patients with SDB and chronic respiratory failure. However, we believe the heterogeneous nature of the whole study group reduced any selection bias and reflected the clinical picture seen in obese subjects with and without OHS. On the other hand, the exclusion of subjects with the potential for a raised plasma bicarbonate for reasons other than obesity-related hypoventilation lowers the general applicability of an isolated raised BE level to identify early OHS.

Clinical Implications

With the increasing incidence of obesity, physicians need to be cognisant of the respiratory consequences that are associated with increasing body mass and, in particular, the propensity to cause chronic respiratory failure. When the Pco_2 is elevated, then this alone will

clearly raise clinical concern. We have shown considerable similarities between obese subjects with only an elevated BE and no daytime hypercapnia and those obese patients with hypercapnic chronic respiratory failure, supporting the concept that obesity-related hypoventilation has a clinical spectrum and that metabolic compensation in the presence of normocapnia probably identifies subjects with "early OHS" at a milder end of the spectrum. Thus, in the obese, an isolated BE without awake hypercapnia should not be dismissed as normal. Whether early detection of obesity-related hypoventilation allows useful therapeutic interventions to be used will need to be tested in appropriate randomized controlled trials. From these current data, we recommend that future treatment trials include those subjects with a raised plasma standard bicarbonate concentration, or BE, whether the $Paco_2$ is increased.

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References

1. Berger KI, Ayappa I, Chatr-Amontri B, et al. Obesity hypoventilation syndrome as a spectrum of respiratory disturbances during sleep. *Chest*. 2001;120(4):1231-1238.
2. Nowbar S, Burkart KM, Gonzales R, et al. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. *Am J Med*. 2004;116(1):1-7.
3. Berger KI, Norman RG, Ayappa I, Oppenheimer BW, Rapoport DM, Goldring RM. Potential mechanism for transition between acute hypercapnia during sleep to chronic hypercapnia during wakefulness in obstructive sleep apnea. *Adv Exp Med Biol*. 2008;605:431-436.
4. Epstein SK, Singh N. Respiratory acidosis. *Respir Care*. 2001;46(4):366-383.
5. Norman RG, Goldring RM, Clain JM, et al. Transition from acute to chronic hypercapnia in patients with periodic breathing: predictions from a computer model. *J Appl Physiol (1985)*. 2006;100(5):1733-1741.
6. Raurich JM, Rialp G, Ibáñez J, Llompart-Pou JA, Ayestarán I. Hypercapnic respiratory failure in obesity-hypoventilation syndrome: CO_2 response and acetazolamide treatment effects. *Respir Care*. 2010;55(11):1442-1448.
7. Siggaard-Andersen O. Acute experimental acid-base disturbances in dogs. An investigation of the acid-base and electrolyte content of blood and urine. *Scand J Clin Lab Invest*. 1962;14(suppl 66):1-20.
8. Hart N, Mandal S, Manuel A, et al. Obesity hypoventilation syndrome: does the current definition need revisiting? *Thorax*. 2014;69(1):83-84.
9. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Bull World Health Organ*. 2007;85(11):867-872.
10. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-545.
11. Seccombe LM, Kelly PT, Wong CK, Rogers PG, Lim S, Peters MJ. Effect of simulated commercial flight on oxygenation in patients with interstitial lung disease and chronic obstructive pulmonary disease. *Thorax*. 2004;59(11):966-970.
12. Stradling JR, Barbour C, Pitson DJ, Davies RJ. Automatic nasal continuous positive airway pressure titration in the laboratory: patient outcomes. *Thorax*. 1997;52(1):72-75.
13. Fahey PJ, Hyde RW. "Won't breathe" vs "can't breathe." Detection of depressed ventilatory drive in patients with obstructive pulmonary disease. *Chest*. 1983;84(1):19-25.
14. Verbraecken J, McNicholas WT. Respiratory mechanics and ventilatory control in overlap syndrome and obesity hypoventilation. *Respir Res*. 2013;14:132.
15. Mahutte CK, Woodley WE, Rebuck AS. A comparison of the effects of steady-state and progressive hypoxia on the ventilatory and frequency response. *Adv Exp Med Biol*. 1978;99:315-324.
16. Trueb TJ, Cherniack NS, D'Souza AF, Fishman AP. A mathematical model of the controlled plant of the respiratory system. *Biophys J*. 1971;11(10):810-834.