David S. Warner, M.D., Editor

Obesity Hypoventilation Syndrome

A Review of Epidemiology, Pathophysiology, and Perioperative Considerations

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ABSTRACT

Obesity hypoventilation syndrome (OHS) is defined by the triad of obesity, daytime hypoventilation, and sleep-disordered breathing without an alternative neuromuscular, mechanical, or metabolic cause of hypoventilation. It is a disease entity distinct from simple obesity and obstructive sleep apnea. OHS is often undiagnosed but its prevalence is estimated to be 10–20% in obese patients with obstructive sleep apnea and 0.15–0.3% in the general adult population. Compared with eucapnic obese patients, those with OHS present with severe upper airway obstruction, restrictive chest physiology, blunted central respiratory drive, pulmonary hypertension, and increased mortality. The mainstay of therapy is noninvasive positive airway pressure. Currently, information regarding OHS is extremely limited in the anesthesiology literature. This review will examine the epidemiology, pathophysiology, clinical characteristics, screening, and treatment of OHS. Perioperative management of OHS will be discussed last.

OBESITY is a growing global concern. One of the consequences of morbid obesity is obesity hypoventilation syndrome (OHS). This syndrome is characterized by the combination of obesity (body mass index (BMI) $\geq$30 kg/m^2), daytime awake hypercapnia (partial pressure of arterial carbon dioxide (Pa_{CO_2}) $\geq$45 mmHg at sea level) and hypoxemia (partial pressure of arterial oxygen (Pa_{O_2}) $<$70 mmHg at sea level), in the presence of sleep-disordered breathing without other known causes of hypoventilation, such as severe obstructive or restrictive parenchymal lung disease, kyphoscoliosis, severe hypothyroidism, neuromuscular disease, and congenital central hypoventilation syndrome.[1] It is estimated that 90% of patients with OHS also have obstructive sleep apnea (OSA).[2] Although the precise prevalence of OHS in the general adult population is unknown, it is estimated to be between 0.15–0.3%.[3]

OHS is a disease entity distinct from simple obesity and OSA. Patients in whom OHS is diagnosed consume greater levels of healthcare resources than eucapnic patients with OSA.[4] Although OHS is associated with excess morbidity and mortality,[5] screening in high-risk individuals is not routinely performed preoperatively. This lack of vigilance may

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lead to increased perioperative morbidity and mortality. Currently, information regarding the perioperative evaluation and management of OHS is extremely limited in the anesthesiology literature. The prevalence of OHS is likely to rise as a result of the current global obesity epidemic, and it is crucial for anesthesiologists to recognize and manage patients with this syndrome. Therefore, the objectives of this review are to examine the prevalence of OHS; review the current data on disease mechanisms, screening, and treatment; and discuss the optimal perioperative management of OHS.

Materials and Methods

With the help of a research librarian, we searched Medline (January 1948 – May 2011), Medline in-process & Other Nonindexed Citations (May 2011), EMBASE (January 1980 – May 2011), Cochrane Database of Systematic Reviews (January 2005 – April 2011) and the Cochrane Central Register of Controlled Trials (May 2011). Searches were conducted using the following components: "Obesity Hypoventilation Syndrome and related terms," "Anesthesia and related terms," "Screening or Preoperative Assessment and related terms," and "Therapy or Treatment or Management and related terms." The following key terms were used for the literature search: "obesity hypoventilation syndrome," "OHS," "Pickwick," "hypoventilation," "obesity," "overweight," "anesthesia," "anesthesiology," "preoperative care," "screening," "therapeutics," "disease management," "treatment outcome," and "therapy." The results of the search were limited to adult human studies published in the English language. To ensure that all potentially relevant articles were included, the reference lists of relevant reviews and included articles were searched manually for further studies.

Study Selection

Studies were selected independently by three reviewers (EC, DL, JW) who screened the titles and abstracts to identify studies reporting prevalence and treatment of patients with OHS. OHS was defined as daytime hypercapnia and hypoxemia (Pa_{CO_2} ≥45 mmHg and Pa_{O_2} <70 mmHg at sea level) in obese patients (BMI ≥30 kg/m^2) with sleep-disordered breathing in the absence of any other cause of hypoventilation. Any disagreements were resolved by consensus or by consulting the senior author (FC). All study designs including randomized control trials and observational studies were included.

Data Extraction

Data extraction was performed independently by two reviewers (DL, EC). Disagreements were resolved by consensus or by consulting the senior author (FC). The following data were extracted from each study: first author, publication year, study design, sample size, treatment method, and treatment duration. The following parameters were collected from the studies: age, sex, neck circumference, waist/hip ratio, arterial oxygen tension, arterial carbon dioxide tension, pH, serum bicarbonate (HCO_3^-), hemoglobin, and hematocrit. Lung function such as percent predicted forced expiratory volume in the first second (FEV_1 % pred), percent predicted forced vital capacity (FVC % pred), FEV_1/FVC, carbon dioxide sensitivity, and sleep parameters such as apnea-hypopnea index (AHI), percentage of total sleep time with oxygen saturation (Sp_{O_2}) <90%, average awake Sp_{O_2}, and minimum Sp_{O_2} were tabulated. Mean values of the collected parameters were calculated for patients with OHS and eucapnic obese individuals. Statistical significance of each parameter between the two groups was tested with the Student *t* test. Pooled SD was calculated as previously described.[6]

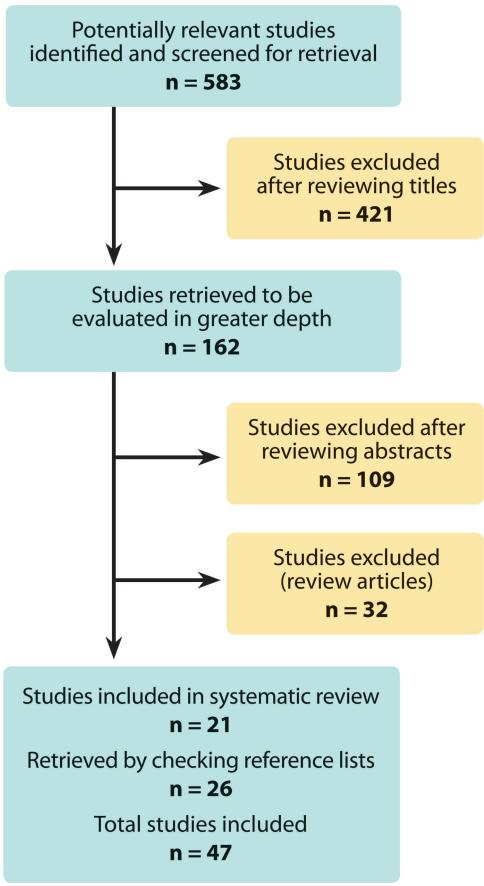

Fig. 1. Literature search strategy.

Results and Discussion

The search strategy identified 583 articles (fig. 1). After screening the abstracts, 21 studies were included and another 26 studies were manually retrieved from the reference lists. There were 30 prospective studies, 12 retrospective studies, 4 randomized controlled studies, and 1 case-control study. Of the 47 studies, 5 prospective studies and 4 randomized controlled trials investigated pharmacologic treatment of OHS. The remainder examined ventilation therapy. In total there were 1,077 patients in whom OHS was diagnosed by fulfilling three criteria: (1) daytime hypercapnia and hypoxemia (Pa_{CO_2} >45 mmHg and Pa_{O_2} <70 mmHg at sea level) in

Table 1. Prevalence of OHS

First Author, Publication Year, Country	Design	Population	Total Patients	Diagnosed with OHS	Age* (yr)	BMI* (kg/m^2)	AHI* (Events/h)	Prevalence of OHS (%)
Resta *et al.* 2000 Italy[11]	Prospective	Pts referred to sleep lab	219	37	51	40	42	17
Kessler *et al.* 2001 France[2]	Prospective	Pts referred to sleep lab	254	34	54	33	76	13
Verin *et al.* 2001 France[13]	Retrospective	Pts referred to sleep lab	218	24	55	34	55	11
Mokhlesi *et al.* 2007 US[10]	Prospective	Pts referred to sleep lab	359	72	48	43	62	20
Trakada *et al.* 2010 Greece[12]	Prospective	Pts referred to sleep lab	276	39	57	40	44	14
Overall Prevalence of OHS in Pts Referred to Sleep Lab (%)†	—	—	1,326	206	—	—	—	16
Golpe *et al.* 2002 Spain[15]	Retrospective	OSA pts	175	24	N/A	32	42	14
Laaban *et al.* 2005 France[16]	Retrospective	OSA pts	1,141	125	56	34	55	11
Akashiba *et al.* 2006 Japan[14]	Retrospective	OSA pts	611	55	48	29	52	9
Overall Prevalence of OHS in OSA pts (%)†	—	—	1,927	204	—	—	—	11
Sugerman *et al.* 1986 US[19]	Retrospective	Bariatric surgical pts	263	18	41	N/A	44	7
Dominguez-Cherit *et al.* 1998 Mexico[17]	Retrospective	Bariatric surgical pts	37	8	38	50	N/A	22
Lecube *et al.* 2010 Spain[18]	Prospective	Bariatric surgical pts	88	6	38	48	18	7
Overall Prevalence of OHS in Bariatric Surgery Pts (%)†	—	—	388	32	—	—	—	8

The overall prevalence of OHS in patients referred to sleep laboratory, patients with OSA, and patients undergoing bariatric surgery were 16, 11, and 8%, respectively.

* Age, BMI, and AHI are mean values for all patients, calculated from the data provided by the authors in the article. † Overall prevalence is calculated by dividing total patients diagnosed with OHS by total patients studied.

AHI = apnea-hypopnea index; BMI = body mass index; OHS = obesity hypoventilation syndrome; OSA = obstructive sleep apnea; pts = patients; US = United States.

the absence of any other cause of hypoventilation; (2) obesity (BMI ≥30 kg/m^2); and (3) sleep-disordered breathing.[7]

What Is the Prevalence of OHS?

The prevalence of OHS in the general population is unknown because it has not been studied. Because approximately 1.5% of the general United States population has severe obesity and OSA, and 10–20% of the severely obese patients with OSA have OHS,[8,9] the prevalence of OHS among the general adult population in the United States is estimated to be 0.15–0.3%.[3] Five studies (four prospective and one retrospective) including a total of 1,326 patients, evaluated patients referred to sleep centers with clinical symptoms of OSA[10–13] (table 1). The prevalence of OHS ranged from 11% to 20%, with an overall prevalence of 16%. Three retrospective studies including a total of 1,927 patients evaluated patients with a known diagnosis of OSA.[14–16] The prevalence of OHS ranged from 9% to 14%, with an overall prevalence of 11%. Finally, in three studies (one prospective and two retrospective) of a total of 388 patients awaiting bariatric surgery, the prevalence of OHS was found to be 7–22% with an overall prevalence of 8%.[17–19]

In summary, the prevalence of OHS is 11% in patients with known OSA and 8% in bariatric surgical patients.

What Are the Mechanisms Leading to the Development of OHS?

Daytime hypercapnia is the distinguishing feature of OHS that separates it from simple obesity and OSA. It is entirely due to hypoventilation given that a short course of noninvasive positive airway pressure therapy (less than 2 weeks) improves hypercapnia without any significant changes in body weight, carbon dioxide production, or the volume of dead space.[20] There are three leading hypotheses for the pathogenesis of chronic daytime hypoventilation in OHS: impaired

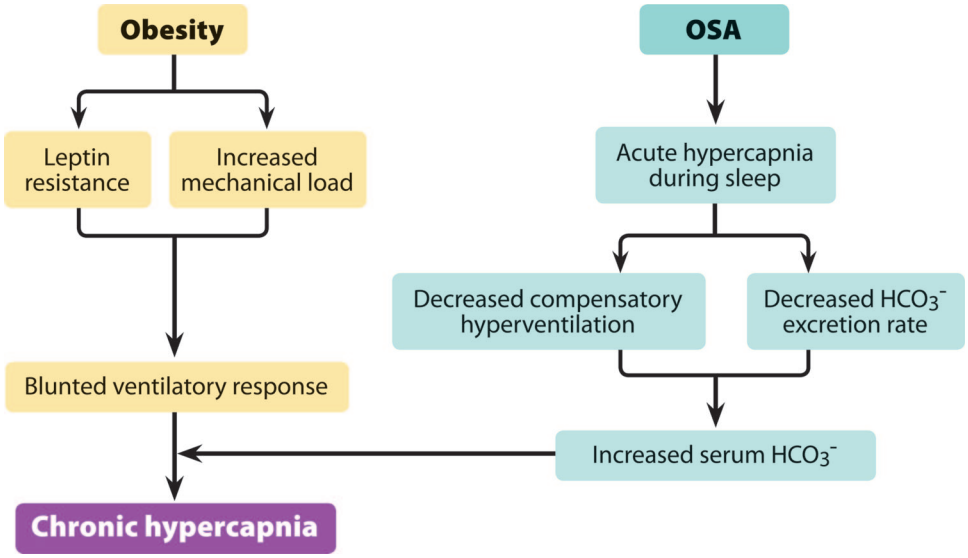

Fig. 2. Mechanisms by which obesity and OSA result in chronic hypercapnia. HCO3$^-$ = serum bicarbonate; OSA = obstructive sleep apnea.

respiratory mechanics because of obesity, leptin resistance leading to central hypoventilation, and impaired compensatory response to acute hypercapnia in OSA (fig. 2).[3,21]

Increased Mechanical Load and Impaired Respiratory Mechanics

Obesity imposes a significant load on the respiratory system and could result in hypoventilation secondary to fatigue and the relative weakness of the respiratory muscles.[22–24] Several studies that compare patients with OHS with individuals who are eucapnic and obese have noted a significantly higher BMI in the OHS group.[10,14,16,25] However, because less than a third of the morbidly obese individuals develop hypercapnia, other mechanisms may result in hypoventilation.[10,16,26]

Leptin Resistance

Leptin is a protein produced specifically by the adipose tissue that regulates appetite and energy expenditure.[27–29] It crosses the blood-brain barrier and exerts its effect through binding to leptin receptors in various areas of the brain.[28] In obese patients, a higher level of leptin is found causing an increase in ventilation to compensate for the increased carbon dioxide production associated with excess body mass.[27,30,31] Patients with OHS exhibit an even higher serum leptin level than eucapnic individuals matched for BMI, and their serum leptin level drops after positive airway pressure (PAP) therapy.[32,33] These observations suggest leptin resistance may contribute to the hypoventilation in OHS.

Impaired Compensation of Acute Hypercapnia in Sleep-disordered Breathing

Obstructive apneas, hypopneas, and long periods of hypoventilation during sleep result in transient episodes of acute hypercapnia. Compensatory mechanisms, including hyperventilation during brief periods of arousal between the obstructive events and renal bicarbonate retention, are required to maintain carbon dioxide homeostasis.[34] Chronic hypercapnia in OHS may occur if these compensatory responses are impaired. In eucapnic subjects with OSA, periods of apnea are separated by periods of hyperventilation such that the accumulated carbon dioxide load is eliminated.[35] However, when apneas become three times longer than the breathing interval, carbon dioxide accumulates (fig. 3).[35]

Patients with OHS, in comparison with those with eucapnia, have a reduced duration of ventilation between periods of apnea.[36] This is possibly related to a gradual adaptation of chemoreceptors secondary to mild elevation of serum HCO_3^- that can occur even during acute hypercapnia. In eucapnic individuals, arterial carbon dioxide tension is restored to normal during wakefulness and the excess HCO_3^- is excreted. However, a transition from acute to chronic hypercapnia may result if the small amount of retained HCO_3^- is not excreted by the kidneys, leading to a reduction of ventilatory carbon dioxide responsiveness. In a computer model, when both carbon dioxide response and the rate of renal HCO_3^- excretion was abnormally low, a rise in awake arterial carbon dioxide tension and HCO_3^- developed over multiple days.[37]

Do Patients with OHS Possess Different Clinical Features than Obese Patients with Eucapnia?

Compared with obese patients with eucapnia, patients with OHS demonstrate four main clinical features: more severe upper airway obstruction, impaired respiratory mechanics, blunted central respiratory drive, and increased incidence of pulmonary hypertension. Table 2 compares various reported demographic and physiologic parameters between patients with OHS and obese patients with eucapnia.[5,10,11,14,16,25,26,38–46] The clinical features of OHS are summarized in figure 4.

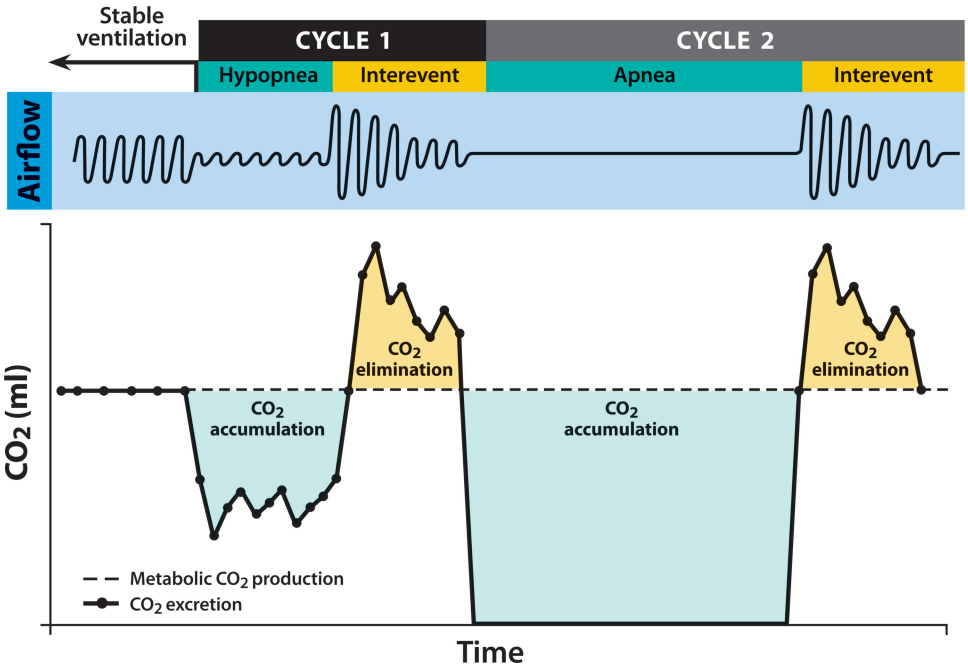

Fig. 3. Interapnea/hypopnea hyperventilation and carbon dioxide (CO_2) excretion. In the first cycle, the interevent hyperpnea is sufficient to excrete the carbon dioxide accumulated during hypopnea. In the second cycle, much more carbon dioxide is accumulated during apnea than is excreted after the event. Multiple cycles of excessive carbon dioxide accumulation during the apneic period lead to hypercapnia. (Adapted from reference 35 with permission.)

Upper Airway Obstruction

Patients with OHS display increased upper airway resistance in both the sitting and supine position in comparison with obese individuals with eucapnia.[47] This may contribute to the increased work of breathing found in OHS patients.[48]

Respiratory Mechanics

Simple obesity impairs respiratory mechanics leading to reduced lung volumes, decreased chest wall compliance, increased respiratory resistance, and increased work of breathing.[49,50] These parameters are further impaired in OHS patients (table 2). Spirometric values from patients with OHS typically reveal a restrictive pattern with a reduction in FEV_1 and FVC but normal FEV_1/FVC. Functional residual capacity, total lung capacity, and expiratory reserve volume are also reduced in OHS compared with eucapnic obesity.

Studies on OHS respiratory mechanics reveal an excessive load imposed on the respiratory system. Chest wall compliance was reduced 2.5-fold in patients with OHS *versus* those with eucapnic obesity.[51] In addition, pulmonary resistance is increased in OHS, likely secondary to the reduction in functional residual capacity. These alterations in respiratory mechanics double the work of breathing in OHS patients compared with patients with eucapnic obesity.[48,51] The work of breathing is further increased when these patients adopt the supine position from sitting due to the cephalad shift of abdominal contents.[48,50]

Central Respiratory Drive

Obese individuals need to generate higher levels of minute ventilation to maintain eucapnia due to their higher basal oxygen consumption, carbon dioxide production, and work of breathing.[30,31,49] Obese individuals have a substantially increased central respiratory drive compared with normal-weight patients to compensate for the increased ventilatory requirements.[50] In contrast, patients with OHS have a blunted central respiratory drive to both hypercapnia and hypoxia. They do not hyperventilate to the same degree as obese individuals with eucapnia when forced to rebreathe carbon dioxide[43,52,53] or breathe a hypoxic gas mixture.[53] The blunting of central respiratory drive may result from leptin resistance and sleep-disordered breathing.[29,34]

Pulmonary Hypertension

The incidence of pulmonary hypertension, as defined by a mean pulmonary arterial pressure ≥20 mmHg, is higher in patients with OHS than in obese patients with eucapnia, ranging from 30% to 88%.[2,4,45] The etiology of pulmonary hypertension is likely secondary to chronic alveolar hypoxia and hypercapnia. In some OHS patients, pulmonary hypertension may result from left-heart failure because left ventricular hypertrophy is a common finding due to associated cardiomyopathy in severe obesity,[54] and pulmonary arterial occlusion pressure has been reported to be increased in OHS.[45]

Do Patients with OHS Experience Higher Morbidity and Mortality than Obese Patients with OSA and Comparable BMI?

Obesity and OSA are associated with a spectrum of comorbidities such as coronary artery disease, heart failure, stroke

Table 2. Demographic and Clinical Differences between Patients with Obesity Hypoventilation Syndrome and Obese Patients with Eucapnia

Parameters*	OHS (Mean ± SD)	Eucapnic obesity (Mean ± SD)	*P* Value	References
N	741	2,972	—	—
Age (yr)	50.1 ± 9.3	51.3 ± 8.5	<0.0001	5,10,11,14,16,25,26,38–45
Male (%)	70.5	78.6	N/A	5, 10, 11, 14, 16, 25, 26, 38–45
Female (%)	29.5	21.4	N/A	5, 10, 11, 14, 16, 25, 26, 38–45
BMI (kg/m^2)	39.6 ± 7.7	33.4 ± 5.9	<0.0001	5, 10, 11, 14, 16, 25, 26, 38–45
Neck circumference (cm)	47 ± 6	44 ± 5	0.01	5, 25
Waist-to-hip ratio	1.0 ± 0.06	0.9 ± 0.1	<0.0001	38
Gas exchange	—	—	—	—
Pa_{O_2} (mmHg)	66.8 ± 8.7	78.7 ± 8.0	<0.0001	5, 10, 11, 14, 16, 25, 26, 39–42, 44–46
Pa_{CO_2} (mmHg)	49.8 ± 6.4	39.7 ± 2.7	<0.0001	5, 10, 11, 14, 16, 25, 26, 39–46
HCO_3^- (mM)	30.9 ± 3.8	25.9 ± 3.4	<0.0001	5, 10, 26, 40, 41, 43
Pulmonary function	—	—	—	—
FEV_1 (% pred)	71.0 ± 13.1	87.8 ± 13.2	<0.0001	5, 10, 11, 14, 16, 25, 38–44, 46
FVC (% pred)	80.3 ± 12.4	92.8 ± 10.4	<0.0001	5, 10, 11, 14, 16, 25, 38–44, 46
FEV_1/FVC	79.4 ± 7.2	80.7 ± 5.3	<0.0001	5, 10, 11, 14, 16, 25, 38–44, 46
FRC (% pred)	80.8 ± 7.3	83.5 ± 3.6	0.0156	42, 44
TLC (% pred)	77 ± 14.7	95 ± 11.5	<0.0001	11, 38, 40
Sleep-disordered breathing	—	—	—	—
AHI (events/h)	66.4 ± 21.6	47.5 ± 18.2	<0.0001	5, 10, 11, 14, 16, 25, 26, 38–43
TST Spo_2 <90% (%)	49.2 ± 31.8	17.1 ± 21.1	<0.0001	10, 11, 14, 25, 38, 40, 41
Min nocturnal Spo_2 (%)	65.1 ± 10.4	74.5 ± 7.7	<0.0001	10, 11, 14, 25, 38, 40, 41
Central respiratory drive to CO_2	—	—	—	—
CO_2 sensitivity (l/min/mmHg)	1.2 ± 0.8	2.4 ± 1.5	<0.0001	38, 40, 43, 46

Compared with obese patients with eucapnia, patients with obesity hypoventilation syndrome have significantly higher BMI, increased hypoxemia and hypercapnia, more restrictive respiratory mechanics, and more severe sleep-disordered breathing.

* Values represent pooled mean ± SD by computing values from the stated references.

AHI = apnea-hypopnea index; BMI = body mass index; CO_2 = carbon dioxide; FEV_1 = forced expiratory volume in 1 s; FRC = functional residual capacity; FVC = forced vital capacity; HCO_3^- = bicarbonate; OHS = obesity hypoventilation syndrome; Pa_{CO_2} = arterial partial pressure of carbon dioxide; Pa_{O_2} = arterial partial pressure of oxygen; SD = standard deviation; Spo_2 = pulse oximeter oxygen saturation; TLC = total lung capacity; TST Spo_2 <90% = total sleep time with pulse oximeter oxygen saturation less than 90%.

and metabolic syndrome, which result in increased morbidity and mortality.[55–59] Furthermore, patients with OSA are at increased risk of developing postoperative complications including arrhythmias and hypoxemia.[60–62] An increased risk of intensive care unit transfer and increased length of hospital stay were also observed among patients with OSA who underwent noncardiac surgery.[61]

Several studies showed that patients with OHS may experience higher morbidity and mortality than patients who are similarly obese and have OSA. Compared with obese individuals with eucapnia, patients with OHS were more likely to develop heart failure (odds ratio (OR) 9, 95% CI 2.3–35), angina pectoris (OR 9, 95% CI 1.4–57.1) and cor pulmonale (OR 9, 95% CI 1.4–57.1).[4] They also received higher rates of long-term care at discharge (19% *vs.* 2%, $P = 0.01$), and invasive mechanical ventilation (6% *vs.* 0%, $P = 0.01$).[5]

The mortality rate in patients with untreated OHS is high. A retrospective study described a mortality rate of 46% during an average 50-month follow-up period in OHS patients without therapy.[63] In addition, patients with OHS exhibit a higher mortality rate than obese patients with eucapnia. A group of patients with OHS and obese patients with eucapnia were followed after hospital discharge for 18 months. Those with OHS had a mortality rate of 23% compared with 9% in the eucapnic obesity group.[5] Most patients in the OHS group were discharged without any therapy. In a 1992 study evaluating open bariatric surgery, patients with either OHS or OSA suffered a surgical mortality rate of 4%, significantly higher than that reported in patients without OHS or OSA (0.2%, $P < 0.01$).[64] The major causes of death include pulmonary embolus and peritonitis from leaks. Perioperative safety of bariatric surgery has improved since.[65,66] However, in high-risk patients (OHS, previous history of venous thromboembolism, BMI ≥ 50 kg/m^2, male sex, hypertension, and age ≥ 45 yr) undergoing gastric bypass, mortality ranges between 2–8%.[67–69]

In summary, patients with OHS experience higher morbidity and mortality than those who are obese with eucapnia. Previous history of venous thromboembolism, morbid obesity, male sex, hypertension, increasing age, and noncompliance with PAP treatment may further increase mortality risk. Surgical mortality rate in high-risk OHS patients undergoing bariatric surgery is between 2–8%.

What Is the Mainstay of Therapy for OHS?

Therapeutic interventions for OHS therapy include four main components: PAP therapy, supplemental oxygen,

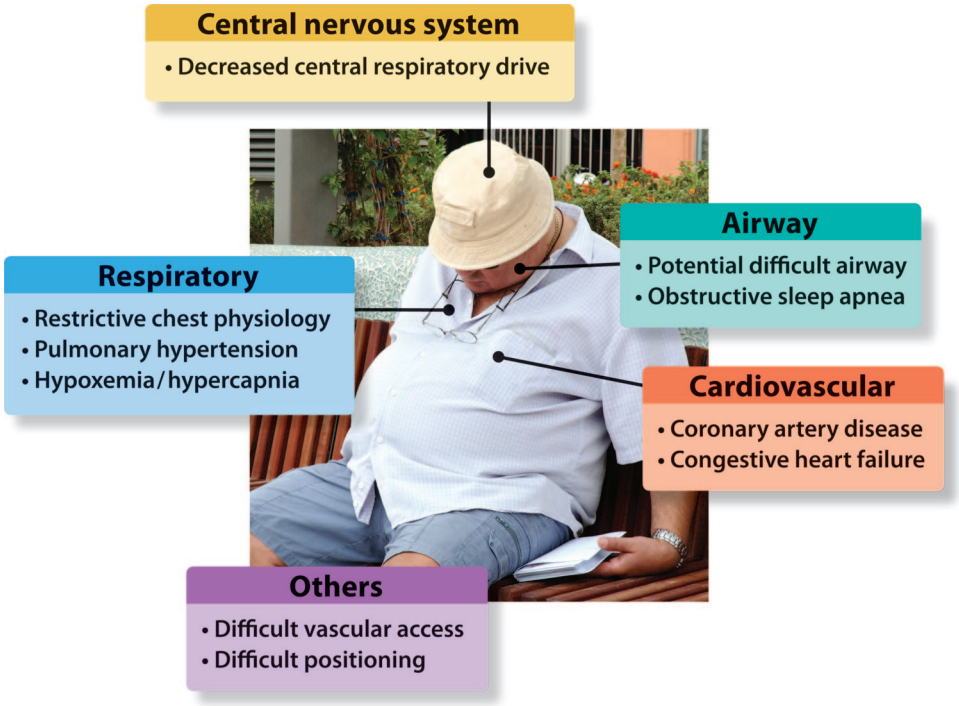

Fig. 4. Clinical features of the patient with obesity hypoventilation syndrome.

weight reduction surgery, and pharmacologic respiratory stimulants.

PAP Therapy: Short-term and Long-term Benefits

The two main forms of PAP therapy currently being used are continuous positive airway pressure (CPAP) and bilevel PAP.

Short-term benefits of PAP include an improvement in gas exchange and sleep-disordered breathing (tables 3 and 4). There were five studies that evaluated the effects of a short course (≤ 3 weeks) of PAP on $Paco_2$ and Pao_2.[63,70–73] All five studies reported a significant decrease in $Paco_2$ and four studies reported a significant increase in Pao_2. One possible explanation for the single study that showed a nonsignificant change in Pao_2 could be related to the short duration of therapy (five nights).[70] There were four studies that studied the benefits of short-term PAP on sleep-disordered breathing.[70–72,74] All four studies reported a significant improvement in AHI and oxygen saturation during sleep.

Long-term benefits of PAP include an improvement in gas exchange, lung volumes, and central respiratory drive to carbon dioxide. Nine studies examined the relationship between long-term PAP (≥4 weeks) and gas exchange (table 3).[75–83] All but one study showed a significant improvement in $Paco_2$ and Pao_2.

There were four studies that investigated the effects of long-term PAP on FEV_1 and FVC (table 5).[71,76,77,84] Three of the four studies found a significant improvement in pulmonary function. Two of the positive studies did not report a significant change in BMI. This improvement of restrictive ventilatory defect is assumed to be due to a decrease in the premature closure of dependent airways during expiration and to an opening of microatelectasis. Lin only reported a trend toward improved FEV_1 with 4 weeks of CPAP.[71] However, the course of treatment was much shorter than that examined by the other three studies (24–48 weeks).

Five studies evaluated the effects of PAP on central respiratory drive, as measured by carbon dioxide sensitivity, calculated as the change in minute ventilation per unit change in end-tidal carbon dioxide (table 4).[41,70,71,77,80] Three studies demonstrated a significant increase in carbon dioxide sensitivity, whereas the other two studies reported a trend toward an increase in carbon dioxide sensitivity.

PAP may also reduce mortality in OHS. Two retrospective studies have demonstrated a mortality rate of 13–19% in patients with OHS on PAP throughout a mean period of 4 yr.[76,79] Through indirect comparison, this mortality rate is lower than the 23% mortality rate reported in patients with untreated OHS at 18 months of follow-up (fig. 5).[5]

In summary, short-term (≤3 weeks) PAP therapy improves gas exchange and sleep-disordered breathing. In addition, long-term (≥4 weeks) PAP therapy improves lung volumes and central respiratory drive to carbon dioxide and lowers mortality. Because of its noninvasiveness and effectiveness, PAP is considered the first-line therapy for OHS.

Efficacy of Bilevel PAP versus CPAP

CPAP failure, defined by a residual AHI ≥5 or a mean nocturnal Spo_2 <90%, has been documented in some patients with OHS. These nonresponders improved after treatment with bilevel PAP.[81]

Table 3. Effects of Positive Airway Pressure Therapy on Arterial Blood Gases

Author	Design	N	Type	Duration (Weeks)	Pa_{O_2} (mmHg)		Pa_{CO_2} (mmHg)	
					Pretreatment	Posttreatment	Pretreatment	Posttreatment
Short-term Therapy								
Chouri-Pontarollo *et al.* 2007[70]	Prospective	15	Bilevel PAP	<1	77.3 ± 6.8	74.3 ± 6.8	47.3 ± 2.3	41.3 ± 3‡
Perez de Llano *et al.* 2008[72]	Prospective	13	Bilevel PAP	<1	49.9 ± 7.7	63.3 ± 10.6*	58.1 ± 5.9	44.3 ± 5.5*
		11	CPAP	<1	51.3 ± 6.7	68.9 ± 3.8*	59.6 ± 11	41.6 ± 4.5*
Perez de Llano *et al.* 2005[63]	Retrospective	54	Bilevel PAP	1	45.8 ± 9.1	55.9 ± 5.6†	60.3 ± 9.9	50.4 ± 4.7†
Piper *et al.* 1994[73]	Prospective	13	Bilevel PAP	1–3	50	66†	62	46‡
Lin 1994[71]	Prospective	30	CPAP	2	75 ± 5.2	90.7 ± 5.2*	47.2 ± 1.5	39 ± 3.00*
			CPAP	4	75 ± 5.2	90.7 ± 5.2*	47.2 ± 1.5	39 ± 3.00*
Long-term Therapy								
Mokhlesi *et al.* 2006[83]	Retrospective	75	CPAP 80%/ Bi-level PAP 20%	4	59 ± 11	64 ± 11†	54 ± 7	49 ± 7†
Storre *et al.* 2006[82]	Prospective Crossover	10	Bi-level PAP	6	73.3 ± 6.3	76.3 ± 12.4	47.4 ± 2.0	45.9 ± 3.7[ns]
			Bi-level PAP + AVAPS	6	73.3 ± 6.3	72.8 ± 9.1	47.4 ± 2.0	42.0 ± 5.2*
Piper *et al.* 2008[78]	Prospective	18	CPAP	12	N/A	N/A	52	46.2*
		18	Bilevel PAP	12	N/A	N/A	49	42.1*
Budweiser *et al.* 2007[76]	Retrospective	126	Bilevel PAP	24	57.8 ± 11.5	65.6 ± 10.4†	55.5 ± 7.7	42.1 ± 5.5†
Priou *et al.* 2010[79]	Retrospective	130	Bilevel PAP	24	63.5 ± 13	72.5 ± 9.4‡	55.9 ± 10.5	45.3 ± 5.3‡
Redolfi *et al.* 2007[80]	Retrospective	6	Bi-level PAP	40	51.3 ± 6.7	75.0 ± 10.3§	55.5 ± 4.8	43.7 ± 1.2§
De Lucas-Ramos *et al.* 2004[77]	Prospective	13	Bilevel PAP	48	55.9 ± 6.4	64 ± 8.6*	49.9 ± 3.67	40.3 ± 3.37*
Heinemann *et al.* 2007[84]	Prospective	32	Bilevel PAP	52	50.1 ± 6.2	63.6 ± 9.3	51.9 ± 3.6	41.6 ± 6.2†
Berger *et al.* 2001[75]	Retrospective	8	CPAP	56 ± 76	N/A	N/A	56 ± 7	41 ± 5§
		10	Bilevel PAP		N/A	N/A	58 ± 4	42 ± 4§

Both short-term and long-term positive airway pressure therapy increase Pa_{O_2} and decrease Pa_{CO_2} in patients with obesity hypoventilation syndrome. Values are given in mean ± SD.

* $P < 0.05$; † $P < 0.001$; ‡ $P < 0.0001$; § $P < 0.01$ (Pre *vs.* Post).

AVAPS = average volume assured pressure support; Bi-level PAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; Pa_{CO_2} = arterial partial pressure of carbon dioxide; Pa_{O_2} = arterial partial pressure of oxygen.

A recent prospective randomized study compared the long-term efficacy of bilevel PAP *versus* CPAP after excluding nine patients with OHS in whom CPAP titration failed.[78] Two groups of 18 patients with OHS who underwent successful CPAP titration study were randomized to either bilevel PAP or CPAP for 3 months. Both groups experienced a similar degree of improvement in Pa_{CO_2} and daytime sleepiness. Overall, bilevel PAP was not considerably superior to CPAP if CPAP titration was successful. However, if CPAP titration is unsuccessful, the bilevel PAP should be strongly considered and treatment should be individualized to each patient.[3] Bilevel PAP should be instituted if the patient is intolerant of higher CPAP pressure (more than 15 cm H_2O) or if hypoxemia persists despite adequate resolution of obstructive respiratory events.[85]

The various degrees of response to CPAP suggests that OHS is a heterogeneous disease. Patients with OHS who were prescribed bilevel PAP due to failed CPAP trial had significantly reduced FEV_1 and FVC *versus* CPAP responders.[72] In contrast, AHI was significantly higher in the CPAP group. It seems that in some patients, severe OSA is a major contributor to OHS and these patients could be successfully treated with long-term CPAP therapy. In other patients with severe restrictive defect secondary to morbid obesity, long-term bilevel PAP may be required.

Supplemental Oxygen

Approximately 40% of patients with OHS continue to desaturate to Sp_{O_2} <90% during sleep while on adequate CPAP settings, thereby requiring supplemental oxygen.[74] Oxygen therapy may act as a double-edged sword, as the administration of high-concentration supplemental oxygen without any form of positive airway pressure therapy may worsen hypercapnia by reducing minute ventilation.[86,87] In a recent study, some patients with OHS whose condition is stable experienced a significant increase in transcutaneous carbon dioxide tension when administered 100% oxygen compared with room air.[88] This was associated with a significant decrease in minute ventilation. Therefore, clinicians should administer the lowest concentration of oxygen to OHS patients to avoid worsening of hypercapnia while maintaining optimized oxygenation, particularly in patients

Table 4. Effects of Positive Airway Pressure Therapy on Sleep Parameters

Author	Design	N	Type	Duration (Weeks)	AHI	
					Pretreatment	Posttreatment
Short-term Therapy						
Banerjee *et al.* 2007[74]	Prospective	23	CPAP	<1	78 ± 8.4	16.4 ± 6.1‡
Chouri-Pontarollo *et al.* 2007[70]	Prospective	15	Bilevel PAP	<1	62 ± 32	11 ± 13†
Perez de Llano *et al.* 2008[72]	Prospective	13	Bilevel PAP	<1	36.5 ± 23.1	N/A
		11	CPAP	<1	56 ± 23	N/A
Lin 1994[71]	Prospective	30	CPAP	2	87 ± 14	8 ± 4*
			CPAP	4	87 ± 14	8 ± 4*
Long-term Therapy						
Storre *et al.* 2006[82]	Prospective Crossover	10	Bilevel PAP	6	74 ± 25	21 ± 15*
			Bilevel PAP + AVAPS	6	74 ± 25	31 ± 21*
Han *et al.* 2001[41]	Prospective	5	CPAP	6	52.4 ± 23.2	2.8 ± 1.6*
Priou *et al.* 2010[79]	Retrospective	130	Bilevel PAP	24	86.6 ± 32	13 ± 14†

Both short-term and long-term positive airway pressure therapy improve AHI and oxygen saturation during sleep in patients with obesity hypoventilation syndrome. Values are given in mean ± SD.

* $P < 0.05$; † $P < 0.001$; ‡ $P < 0.005$ (Pre *vs.* Post).

AHI = apnea-hypopnea index; AVAPS = average volume assured pressure support; Bi-level PAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; Spo_2 = pulse oximeter oxygen saturation; TST = total sleep time.

with OHS experiencing an exacerbation or recovering from sedatives/narcotics or general anesthesia.[89]

Weight Reduction Surgery

Bariatric surgery is now widely accepted as a mainstay treatment in the management of obesity, especially for morbidly obese patients in whom more conservative approaches have failed or who have developed comorbidities. Bariatric surgery improves gas exchange and pulmonary function in OHS. At 1 yr after surgery, Pa_{O_2}, Pa_{CO_2}, FEV_1, and FVC all improved significantly.[64,90] To better understand the effect of surgical weight loss on OSA, Greenburg *et al.* performed a meta-analysis of 12 studies including a total of 342 patients in whom polysomnography pre- and postmaximum weight loss were available.[91] They found that bariatric surgery led to significant weight loss with a mean reduction in BMI from 55.3 kg/m^2 to 37.7 kg/m^2. This robust weight loss was accompanied by a 71% reduction in the AHI from baseline

Table 5. Effects of Positive Airway Pressure Therapy on Pulmonary Function

Author	Design	N	Type	Duration (Weeks)	FEV_1 (% pred)		FVC (% pred)		CO_2 sensitivity (l/min/mmHg)	
					Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Short-term Therapy										
Chouri-Pontarollo *et al.* 2007[70]	Prospective	15	Bilevel PAP	<1	N/A	N/A	90	89	2.0 ± 1.3	2.4 ± 1.9
Lin 1994[71]	Prospective	6	CPAP	2	70 ± 3.8	N/A	N/A	N/A	0.46 ± 0.2	2.46 ± 0.5*
		6	CPAP	4	70 ± 3.8	71 ± 3.9	N/A	N/A	0.46 ± 0.2	2.5 ± 0.48*
Han *et al.* 2001[41]	Prospective	5	CPAP	2	N/A	N/A	N/A	N/A	1.32 ± 0.7	1.46 ± 0.973
		5	CPAP	4	N/A	N/A	N/A	N/A	1.32 ± 0.7	1.40 ± 0.49
Long-term Therapy										
Han *et al.* 2001[41]	Prospective	5	CPAP	6	N/A	N/A	N/A	N/A	1.32 ± 0.7	1.80 ± 1.02*
Budweiser *et al.* 2007[76]	Retrospective	126	Bilevel PAP	24	59.8 ± 16.5	72.6 ± 17.6†	64.2 ± 15.6	78.8 ± 16.6†	N/A	N/A
Redolfi *et al.* 2007[80]	Retrospective	6	Bilevel PAP	40	N/A	N/A	N/A	N/A	0.4 ± 0.3	0.9 ± 0.5
De Lucas-Ramos *et al.* 2004[77]	Prospective	13	Bilevel PAP	48	77.6 ± 12.4	86.6 ± 22.2	80.8 ± 12.7	92.6 ± 14.5*	0.5 ± 0.24	0.78 ± 0.4*
Heinemann *et al.* 2007[84]	Prospective	32	Bilevel PAP	52	63.2 ± 16.3	79.1 ± 17.6†	65.8 ± 15.3	81.9 ± 15.4†	N/A	N/A

Long-term positive airway pressure therapy improves FEV_1, FVC, and CO_2 sensitivity in patients with obesity hypoventilation syndrome. Values are given in mean ± SD.

* $P < 0.05$; † $P < 0.001$ (Pre *vs.* Post).

Bilevel PAP = bilevel positive airway pressure; CO_2 = carbon dioxide; CPAP = continuous positive airway pressure; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity.

Table 4. Continued

% TST with Spo_2 <90%		Average Spo_2 (%)		Minimum Spo_2 (%)	
Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
75	18‡	89.9 ± 1.1	92.4 ± 0.8‡	61.9 ± 3.9	75.4 ± 4.2‡
38 ± 32	5 ± 10‡	89 ± 3	93 ± 1†	65 ± 14	87 ± 6†
92.1 ± 14.1	14.8 ± 14.4*	78.7 ± 5	92.3 ± 2*	N/A	N/A
76.3 ± 19.5	5.2 ± 4.5*	82.3 ± 4.4	92.4 ± 1.2*	N/A	N/A
N/A	N/A	81 ± 2.1	93 ± 0.4*	N/A	N/A
N/A	N/A	81 ± 2.1	94 ± 0.4*	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A
46.1 ± 5.2	0.35 ± 0.46*	88.7 ± 0.8	94 ± 1.4*	51.8 ± 17.3	88.8 ± 1.5*
N/A	N/A	85.3 ± 5.5	92.4 ± 2.2†	N/A	N/A

values of 55 events/h (95% CI 49–60) to 16 events per hour (95% CI 13–19). Only 38% achieved cure defined as AHI less than 5. In contrast, 62% of patients had residual disease with the mean residual AHI of 16 events/h. Many of these patients had persistent OSA of moderate severity (AHI ≥ 15 events/h). Thus, although improvements should be anticipated, OSA will not resolve in all patients after surgically achieved weight loss but it should be noted that, despite weight loss, most patients were still obese at the time of the second sleep assessment. Although there is a drastic reduction in OSA severity, some patients still have moderate OSA

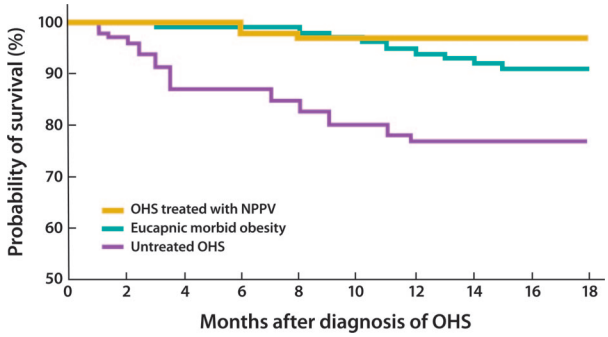

Fig. 5. Survival curves for patients with untreated obesity hypoventilation syndrome (OHS) and morbidly obese patients with eucapnia as reported by Nowbar *et al.*,[5] compared with patients with OHS treated with positive airway pressure therapy.[76] NPPV = noninvasive positive pressure ventilation. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Mokhlesi B, Kryger MH, Grunstein RR, 2008, Assessment and Management of Patients with Obesity Hypoventilation Syndrome, Proceedings of the American Thoracic Society, 5:218–25, Official Journal of the American Thoracic Society[7].)

after maximum weight loss and could therefore benefit from CPAP therapy.[91] Similarly, 14% of OHS patients still require PAP therapy after weight loss.[90] Therefore, OHS patients should undergo reevaluation postbariatric surgery before discontinuing PAP therapy.

Bariatric surgery is associated with significant risk. The overall perioperative mortality ranges between 0.5–1.5%.[66,92] The presence of OSA and extreme preoperative weight are independent risk factors associated with perioperative death and adverse events including venous thromboembolism, surgical reintervention, and prolonged hospital stay.[65,66]

Pharmacotherapy

Medications that increase respiratory drive have been investigated for the treatment of OHS. Limited evidence was available for two respiratory stimulants: medroxyprogesterone acetate and acetazolamide.

Medroxyprogesterone acetate stimulates respiration at the hypothalamic level.[93] Its role in OHS is uncertain. An early study reported an increase in Pa_{O_2} and a decrease in Pa_{CO_2} in OHS patients treated with medroxyprogesterone acetate.[94] However, a later study did not demonstrate the same benefits.[20] Because medroxyprogesterone acetate increases the risk of venous thromboembolism,[95] administration to OHS patients whose mobility is limited may be unsafe.

Acetazolamide is a carbonic anhydrase inhibitor that increases minute ventilation by inducing metabolic acidosis through increased excretion of bicarbonate by the kidneys. Acetazolamide has been shown to improve AHI, increase Pa_{O_2}, and reduce Pa_{CO_2} in patients with OSA.[96,97] More recently, in mechanically ventilated patients with OHS, ac-

etazolamide reduced plasma HCO_3^- and increased hypercapnic drive response.[98] Given the very limited data on pharmacotherapy and the fact that it is not used widely, we do not recommend it as a mainstay therapy in patients with OHS.

Perioperative Management of Patients with OHS

How Do We Screen for OHS in the Preoperative Settings?

Although there is increased awareness of OSA among anesthesiologists, OHS is often undiagnosed and may greatly increase perioperative risk. A high level of suspicion can lead to early recognition and treatment. Routine screening for hypercapnia in obese patients with OSA may help to identify OHS and allow for referral to sleep medicine for appropriate PAP therapy, modifications in the surgical approach, anesthetic technique, and postoperative monitoring.

Several findings are supportive of OHS, yet the definitive test for alveolar hypoventilation is an arterial blood gas performed on room air during wakefulness. Three clinical predictors of OHS have been suggested: serum HCO_3, AHI, and lowest oxygen saturation during sleep.[10] Increased serum bicarbonate level due to metabolic compensation of respiratory acidosis is common in patients with OHS and points toward the chronic nature of hypercapnia. In a cohort of obese patients with OSA referred to the sleep laboratory for suspicion of OSA, a serum HCO_3^- threshold of 27 mEq/L demonstrated a 92% sensitivity in predicting hypercapnia on arterial blood gas.[10] To complement the highly sensitive serum HCO_3^-, a highly specific (95%) AHI threshold of 100 was identified. A two-step screening process was proposed, with serum HCO_3^- as the initial test to exclude patients without OHS and then AHI as the second test to improve specificity. In addition, hypoxemia (Sp_{O_2} <90%, corresponding to Pa_{O_2} < 60 mmHg)[99] during wakefulness should lead clinicians to suspect OHS in patients with OSA. In a recent meta-analysis, OSA patients with higher BMI, higher AHI, and more restrictive chest wall mechanics were more likely to develop OHS.[100] In these patients with OHS, the mean BMI, AHI, FEV_1 % pred,and FVC % pred were 39 kg/m^2, 64 events/h, 71%, and 85%, respectively.

In summary, patients presenting with a high BMI and AHI should alert the physician to screen for OHS. The serum HCO_3^- level is an easy test to screen for hypercapnia before elective surgery. If the serum HCO_3^- is increased or there is presence of hypoxemia by room air Sp_{O_2} during wakefulness, a confirmatory test with a measurement of arterial blood gases is recommended. Once hypercapnia is confirmed, referral to sleep medicine and further testing, such as pulmonary function testing, chest imaging, thyroid-stimulating hormone, and clinical assessment of neuromuscular strength, is recommended to rule out other important causes of hypoventilation.

How Do We Assess and Optimize a Patient with Suspected OHS before Elective Surgery?

An algorithm for screening and perioperative management of OHS is provided in figure 6. For patients at high risk of OHS undergoing major surgery, additional testing for sleep-disordered breathing and pulmonary hypertension should be sought. Perioperative OHS precautions should also be considered.

General Considerations

The three main challenges in OHS are OSA, obesity, and hypoventilation (hypercapnia and hypoxemia). The preoperative assessment of the patient with suspected OHS should begin with a history and physical examination directed to identify comorbidities in OSA and obesity. Patients with untreated OSA and obesity are at greater risk of developing coronary artery disease, congestive heart failure, and diabetes mellitus.[56–58] The frequency and severity of comorbidities increase proportionally with the weight of the patient. Due to the changes in cardiac hemodynamics associated with obesity, severely obese patients may develop a cardiomyopathy characterized by both diastolic and systolic dysfunction.[101]

A focused cardiopulmonary examination should be directed at discovering signs of congestive heart failure (rales, S3, jugular venous distension) and pulmonary hypertension (loud P2, right ventricular heave, congestive hepatomegaly). A detailed examination of the airway and sites for venous access should be performed.

Screening for OSA

The diagnosis of OSA is established by polysomnography. Because most sleep clinics typically have long wait lists for polysomnography, multiple screening tools were developed to evaluate patients at risk for OSA. The STOP-Bang questionnaire was used in preoperative patients.[102,103] It is a scoring model combining the STOP (*s*noring, *t*iredness, *o*bserved apneas, and increased blood *p*ressure) questionnaire and Bang (*B*MI ≥35, *a*ge more than 50 yr, *n*eck circumference more than 40 cm, and male *g*ender). A positive screen (three or more questions answered yes) indicates high risk for OSA. A systematic review has suggested using the STOP-Bang questionnaire in the surgical population due to its high methodologic quality and easy-to-use features.[104]

Patients identified as at high risk for OSA who present for major elective surgery should be referred to the sleep clinic to establish the diagnosis and to titrate PAP therapy. Therapy should be started during the few days or weeks before surgery. Even with a period as short as 5 days, gas exchange and sleep-disordered breathing can improve significantly with either CPAP or bi-level PAP in OHS.[70] Ideally, an early consultation would allow the sleep physician adequate time to devise a management plan. If this is not achieved, these "high-risk" patients should proceed to surgery and be managed cautiously as if they were known to have OSA.[105,106]

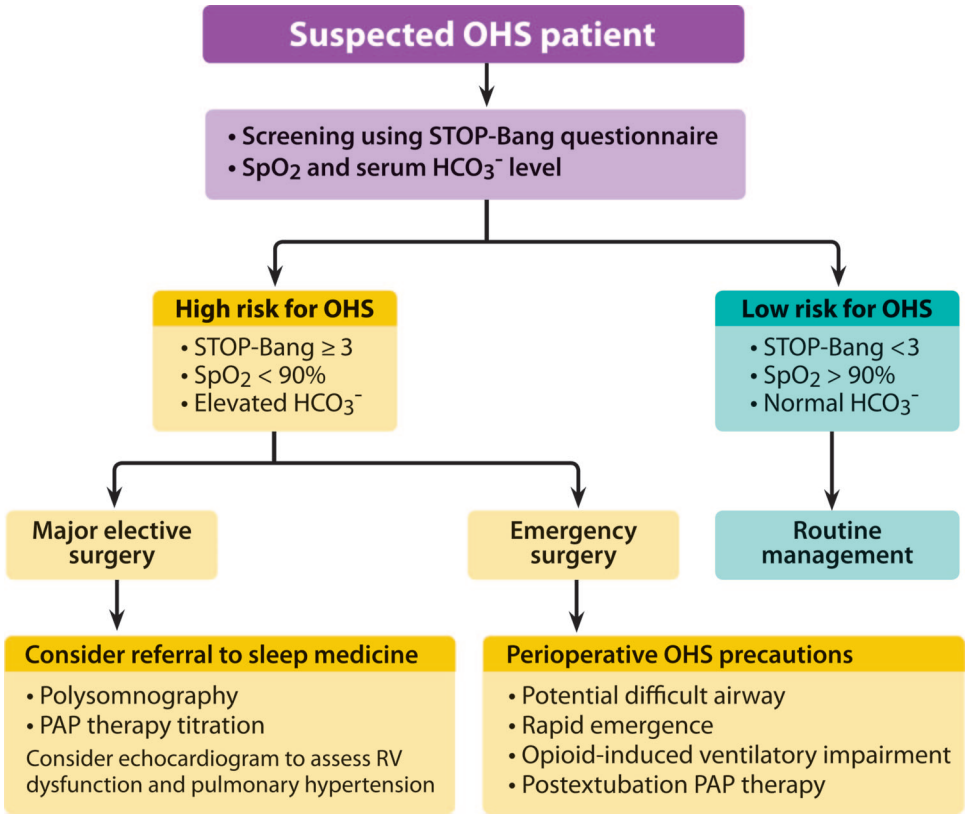

Fig. 6. Suggested algorithm for preoperative evaluation and management of the suspected OHS patient. In a cohort of obese patients with OSA referred to a sleep laboratory, a serum bicarbonate threshold of 27 mEq/l was suggested as a screening test (sensitivity 92%; specificity 50%) for obesity hypoventilation syndrome.[9] HCO_3^- = serum bicarbonate; OHS = obesity hypoventilation syndrome; PAP = positive airway pressure; RV = right ventricular; Spo_2 = pulse oximeter oxygen saturation.

Preoperative Risk Stratification and Cardiovascular Testing

The Lee revised cardiac risk index represents a valuable tool to predict cardiac risk for elective major noncardiac surgery in the general population.[107] However, other risk factors specifically related to OHS, such as pulmonary hypertension and history of venous thromboembolism, should be considered when evaluating perioperative risk. Most of the data on evaluating surgical risk in severely obese patients are derived from bariatric surgical studies. A mortality risk score for patients undergoing gastric bypass include hypertension, BMI ≥ 50 kg/m^2, male sex, age ≥ 45 yr, and known risk factors for pulmonary embolism (OHS, previous thromboembolism, preoperative vena cava filter, pulmonary hypertension).[67–69] The obesity surgery mortality risk score stratifies mortality risk into low (zero or one comorbidity), intermediate (two to three comorbidities) and high (four to five comorbidities). Mortality rates were 0.2%, 1.2%, and 2.4% for low, intermediate, and high risk class, respectively.[68] The most common causes of death were pulmonary embolism (30%), cardiac causes (27%) and gastrointestinal leak (21%).

A 12-lead electrocardiogram should be obtained in patients suspected to have OHS. Signs of right ventricular hypertrophy on electrocardiogram including right-axis deviation and right bundle-branch block suggest pulmonary hypertension. In contrast, a left bundle-branch block on electrocardiogram suggests occult coronary artery disease. Preoperative chest x-ray should also be considered. A chest x-ray showing cardiomegaly or abnormal pulmonary vascularity suggests undiagnosed heart failure and pulmonary hypertension. Furthermore, it could act as a baseline study when evaluating for causes of postoperative respiratory difficulties.

Indications for further cardiovascular testing should be based on patient cardiovascular risk factors and the invasiveness of surgery according to current American Heart Association guidelines.[107,108] The assessment of functional capacity is of particular importance in obese individuals because cardiorespiratory fitness levels and postoperative complication rate are inversely related to BMI.[109,110] Functional exercise testing is the preferred evaluation modality but its use may be limited in the severely obese who cannot exercise due to their weight or orthopedic issues. If these patients are undergoing major surgery and present with multiple cardiac risk factors, pharmacologic stress testing and transthoracic echocardiogram may be considered if management will be changed.[108]

Preoperative Pulmonary Testing

Studies evaluating postoperative pulmonary complications have generally found no increased risk attributable to obesity.[111] In a recent retrospective study of a National Inpatient

Surgical sample of 110,000 OSA patients, patients with OSA were found to have a higher risk of pulmonary complications than patients without OSA.[112] Routine pulmonary function tests may not translate into an effective risk prediction for postoperative pulmonary complications in noncardiothoracic surgery.[113] However, if coexisting chronic obstructive pulmonary disease is suspected in the patient with OHS, spirometry may be considered for diagnosis and subsequent optimization. Arterial blood gas measurements should be obtained to confirm the presence and severity of daytime hypercapnia in obese patients with hypoxemia during wakefulness or an increased serum bicarbonate level.

What Are the Key Considerations Specific to Intraoperative Management of OHS?

Airway Management

OSA is a risk factor for both difficult mask ventilation and tracheal intubation.[114] In addition, patients with severe OSA (AHI $\geq$ 40 events/h) showed a significantly higher prevalence of difficult intubation than patients with lower AHI.[115]

Obesity results in a threefold increase in difficulty with mask ventilation.[116] Whether obesity increases the difficulty of tracheal intubation is more controversial. A retrospective study of 18,500 surgical patients reported that obesity is a risk factor for difficult intubation.[117] However, other studies have not found an association between BMI and intubation difficulties.[118,119] More recently, Kheterpal *et al.* identified five risk factors (limited mandibular protrusion, thick/obese neck anatomy, OSA, snoring, and BMI more than 30 kg/m^2) as independent predictors of difficult mask ventilation and intubation during anesthesia induction.[120] This suggests that OHS patients with limited mandibular protrusion are in the highest risk group for airway complications.

During induction of anesthesia, patients with OHS should be placed in the ramp position with elevation of the torso and head. This has been shown to improve the ease of ventilation and glottic view from the neutral position.[121] Preoxygenation for more than 3 min with a tightly fitted mask can increase apnea tolerance time. Strategies to reduce atelectasis during preoxygenation include optimal patient positioning and the application of PAP. When the patient is in a 25° head-up tilt position, Pa_{O_2} was higher and the time to desaturate to 92% during apnea was increased when compared with preoxygenation while supine.[122] The application of CPAP and positive end-expiratory pressure during preoxygenation also achieved a higher oxygen tension and longer time to desaturation.[123] A variety of airway adjuncts and skilled anesthesiology assistance should be made available in advance. Awake intubation should be considered when mandible advancement, neck extension, or mouth opening is limited in OHS patients.

Emergence from Anesthesia

Patients with OHS are sensitive to the respiratory depressant effects of anesthetic agents due to the propensity of airway collapse, sleep deprivation, and blunting of physiologic response to hypercapnia and hypoxemia. A semiupright or lateral position is recommended at the end of surgery for better oxygenation and airway maintenance.[124] Rapid emergence from anesthesia is preferred because tracheal extubation should be performed only after the patient is fully conscious. A systematic analysis of the literature comparing postoperative recovery after propofol, isoflurane, desflurane, and sevoflurane-based anesthesia in adults demonstrated that early recovery was faster in the desflurane and sevoflurane groups.[125] Another strategy to accelerate emergence is to decrease volatile anesthetic requirement and minimize washout time from fat/muscle by using other short-acting anesthetic adjuvants, such as remifentanil, or a combined general-regional anesthetic.[106]

What Are the Key Considerations Specific to Postoperative Management of OHS?

Opioid-induced Ventilatory Impairment

Opioid-induced ventilatory impairment (OIVI) is a term describing opioid-induced central respiratory depression, decreased level of consciousness, and upper airway obstruction. The end-result of OIVI is a decrease in alveolar ventilation. The incidence of OIVI after major surgery varies with the different routes of opioid administration. The incidence of decreased respiratory rate was 0.8, 1.2, and 1.1% for intramuscular, intravenous patient-controlled analgesia and epidural analgesia, respectively.[126] The incidence of oxygen desaturation was 37, 11.5, and 15.1% for intramuscular, intravenous patient-controlled analgesia and epidural analgesia, respectively.[126] Patients with OHS could be at significant risk for OIVI due to their susceptibility to upper airway obstruction, depressed central respiratory drive, and impaired pulmonary mechanics. An opioid-sparing analgesic regimen, including local anesthetic infused nerve block catheters and nonopioid adjuncts (acetaminophen, nonsteroidal antiinflammatory drugs), should be considered in these patients.

Improved postoperative monitoring is key in reducing the risk of OIVI. Patient-specific, anesthetic, and surgical factors determine the requirements for postoperative monitoring. OHS patients undergoing major surgery who require high doses of postoperative opioid should be monitored with continuous oximetry. Recurrent respiratory events in the postanesthesia care unit, including apnea for $\geq$10 s, bradypnea of less than 8 breaths/min, pain-sedation mismatch, or desaturations to less than 90%, can be used to identify patients at high risk of postoperative respiratory complications.[127] Recently, Macintyre *et al.* proposed that sedation level is a more reliable sign of OIVI than respiratory rate[128] because multiple reports suggest that OIVI is not always accompanied by a decrease in respiratory rate.[128–130] Thus, sedation scoring systems should be used postoperatively to recognize OIVI so that appropriate interventions are triggered. In patients with OHS requiring high doses of postoperative opioids,

sedation monitoring should be considered every 1 to 2 h for the first 24 h.[131]

Postoperative PAP Therapy

There is limited evidence demonstrating a reduction in postoperative complications with PAP in patients with OHS. However, a case series of 14 patients with OSA suggested that the use of CPAP continuously for 24 to 48 h postextubation may reduce the risk of postoperative complications.[132] In addition, PAP was found to decrease postextubation respiratory failure in severely obese patients admitted to the intensive care unit (absolute risk reduction of 16%).[133] Subgroup analysis of patients with hypercapnia showed reduced hospital mortality in the PAP group compared with the control group. Other potential benefits of perioperative CPAP include reduced hemodynamic fluctuations and arrhythmia related to hypoxemia.

A recent case report described a 59-yr-old patient with OHS who suffered multiple orthopedic injuries secondary to a mechanical fall (a simple fall not associated with any cardiac or neurologic event [*e.g.,* heart attacks or stroke]).[134] In the emergency department, she received opioid analgesics and subsequently developed severe hypoxemia refractory to naloxone. The initiation of bilevel PAP promptly restored adequate ventilation.

In summary, patients with OHS who were previously on PAP should resume therapy as soon as possible postoperatively. In patients suspected to have OHS experiencing postoperative ventilatory impairment, PAP should be considered as a rescue device. Based on the available literature, patients with OHS typically require an inspiratory PAP and the expiratory PAP of 16–18 cm H_2O and 9–10 cm H_2O, respectively, to achieve adequate resolution of upper airway obstruction and to improve ventilation. If previous PAP titration has not been performed or the data are unavailable to the anesthesiologists, bilevel PAP can be empirically set at these pressures in patients suspected of having OHS.

Conclusion

OHS is a disease entity that anesthesiologists need to have a thorough understanding of. The prevalence of OHS is estimated to be 0.15–0.3% in the general population[3] and 8% in patients undergoing bariatric surgery.[17] Patients with OHS have a syndrome distinct from mere obesity and OSA, as indicated by the severe upper airway obstruction, restrictive chest physiology, blunted central respiratory drive, and pulmonary hypertension. The mainstay of therapy for OHS is PAP therapy because it improves gas exchange, lung volumes, and sleep-disordered breathing, and reduces mortality.

Perioperative management begins with a high index of suspicion for OHS in the morbidly obese patient. Screening questionnaires such as the validated STOP-Bang questionnaire can identify patients at high risk of OSA. This screening tool can be further complemented by the presence of low Spo_2, increased $Paco_2$, and serum HCO_3^- level to identify patients at high risk of OHS. Before major elective surgery, these patients should be referred to sleep medicine for polysomnography and PAP titration. An echocardiogram should be considered to assess right ventricular function and pulmonary hypertension. Perioperative precautions of OHS include prudent airway management, rapid emergence, monitoring for ventilatory impairment and early resumption of PAP therapy. Future research should focus on the perioperative strategies of screening, monitoring and treatment of OHS and associated complications.

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