RESPIRATORY COMPLICATIONS OF OBESITY

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INTRODUCTION

In 1977 a Select Committee on Nutrition and Human Needs of the U. S. Senate estimated that over 50 million Americans exceed ideal body weight by ten percent or more and should therefore be classified as obese. Fifteen million of these persons are sufficiently obese to increase their risk of ill health (1). The medical problems most often attributed to obesity include diabetes, degenerative joint disease and hypertension. Less appreciated are the unique respiratory complications of this extremely common medical problem.

Most physicians are familiar with Joe "the fat boy" in the Pickwick papers of 1837 in whom Charles Dickens personified the unique hypersomnolence of excessive obesity (2). The term Pickwickian syndrome was first coined in the medical literature by Sir William Osler in 1918 (3), but it was not until 1956 that Burwell and associates documented the alveolar hypoventilation syndrome that occurs with obesity and described the accompanying periodic breathing, hypoxemia, polycythemia and cor pulmonale (4). Burwell clearly documented that this syndrome could be reversed by weight reduction and thus attributed the pathogenesis to the mechanical dysfunction imposed by obesity. Interest in a diverse pathophysiology began in 1965 when Gastaut and colleagues introduced the concept of sleep apnea (5). Since that time many studies indicate that the interactions of several diverse physiologic abnormalities contribute to the unique respiratory complications of obesity and these interactions are the subject of this review.

MECHANICAL ABNORMALITIES

Metabolic Demands - Obesity, generally defined as an excessive accumulation of fat, results in an increased body mass. Although fat is not as metabolically active as muscle and other tissues, work must be performed to move an obese body, imposing higher metabolic demands than in a normal person. These demands are reflected in the obese subject's oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) which are higher than normal at rest and exercise.

Table 1

Metabolic Demands of Obese Subjects at Rest and Bicycle Exercise of 670 KPM

	$\dot{V}_E$ L/min	F B/min	$\dot{V}_{O_2}$ ℓ/min	$\dot{P}_{aCO_2}$ mm Hg	$\dot{V}_E/\dot{V}_{O_2}$
Control					
Rest	8.91	10	0.27	38.7	33.3
Exercise	33.1	18	1.54	35.0	21.5
Obese					
Rest	10.83	15	0.35	42.3	31.4
Exercise	51.8	27	2.01	37.6	25.8

As Dempsey and colleagues have shown, Table 1, minute ventilation ($\dot{V}_E$) increases at a relatively faster rate during exercise, producing a significantly greater ventilation equivalent for oxygen consumption ($\dot{V}_E/\dot{V}_{O_2}$) in obese subjects (6, 7). This increased minute ventilation is accompanied by an excessively increased respiratory rate. These parameters indicate inefficient ventilation. These findings also indicate that most obese persons are eucapneic at rest and exercise but must ventilate excessively to maintain a normal P_{aCO_2} in the face of high CO_2 production.

Work of Breathing - Excess ventilation suggests an increase in mechanical work of breathing. Sharp and colleagues have demonstrated an increase in inspiratory work per breath in addition to that imposed by overbreathing, Table 2 (8).

Table 2

Respiratory Work
kg-m/1L breath
(n = 22)

	Lung	Thorax	Total
Normal	0.035	0.038	0.073
Obese	0.043	0.054	0.095

The increase in total work per breath is mainly caused by an increase in energy expended to move the chest wall and extrapulmonary structures. In some subjects such expenditures were four times that required for lighter individuals.

The marked increase in mechanical work per breath is predominantly due to a marked reduction of chest wall compliance in obese persons as demonstrated by Cherniack, Table 3 (10).

Table 3

Respiratory Compliance in Normal and Obese Persons
L/cm H_2O
(n = 36)

	Lung	Chest Wall	Total
Normal	0.211	0.214	0.104
Obese	0.157	0.106	0.063

Lung compliance was reduced on average 26 percent, whereas chest wall compliance was reduced on average 51 percent. However, the

chest wall "stiffness" cannot fully account for the total increased work of breathing that has been demonstrated by other investigators. Fritts and colleagues performed similar measurements in subjects whose oxygen consumption was simultaneously determined at rest and voluntary hyperpnea. Both mechanical and oxygen consumption values were elevated above normal, but since the excess oxygen consumption was greater than the excess mechanical work, it was reasoned that the obese subjects did not ventilate efficiently (9). This inefficiency was explained by the extra energy needed to impart motion to the chest wall and extrapulmonary structures or to inefficiency of the respiratory muscles.

Other factors that may contribute to an increased work of breathing are listed in Table 4.

Table 4

Factors Further Compromising Mechanical Function in the Obese

Recumbency
Air-flow obstruction
Inefficiency of respiratory muscles

Several authors have confirmed that there is a further reduction in chest wall compliance with recumbency leading to additional mechanical impairment (8, 10).

Since overcoming the resistance of the chest wall cannot account for the total increase in the oxygen consumption caused by the work of breathing, the remaining increase must be due either to an increase in non-elastic work to make flow in airways or to

inefficiency of the respiratory muscles. Since none of the reported studies used subjects with air-flow obstruction, it seems unlikely that there is a significant increase in non-elastic work. However, several reports have addressed the efficiency of both the diaphragm and the intercostal muscles.

Inefficiency of Respiratory Muscles - Fritts, et al., and Cherniack have found a decreased efficiency of respiratory muscles in obese subjects (9, 11). Fritts (9) has calculated the percent efficiency of the respiratory muscles in both normal and obese patients, Table 5.

Table 5

Efficiency of Respiratory Muscles in Normals and Obese

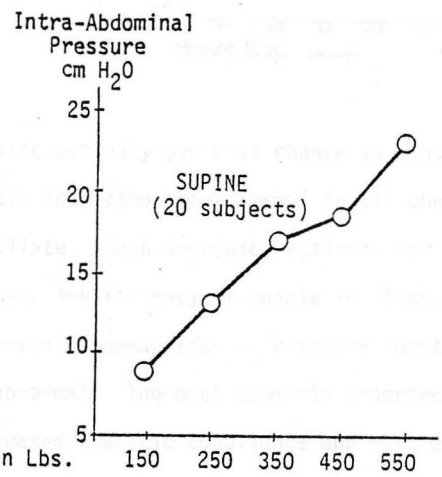
	Ventilation $L/min/M^2$	Energy $kgM/min/M^2$	Work $kgM/min/M^2$	Efficiency %
Normal				
Resting $\bar{m}$	6.4	8.4	0.30	3.77
Hyperpnea $\bar{m}$	26.0	121.8	2.07	1.93
Obese				
Resting $\bar{m}$	5.4	73.9	0.64	1.02
Hyperpnea $\bar{m}$	15.4	220.0	2.42	1.08

The values for efficiency in obese patients were low both at rest and at increased ventilatory levels, because the increased energy cost of breathing exceeded the increase in the mechanical work. Both groups of investigators attributed this inefficiency to energy

required to move adipose tissue overlying the chest wall, but other explanations have been suggested.

For example, Hackney has shown a linear increase in end-expiratory abdominal pressure with increasing weight, Figure 1 (12). These pressures represent a progressively severe preload for inspiratory muscles. The decreased compliance of the respiratory system

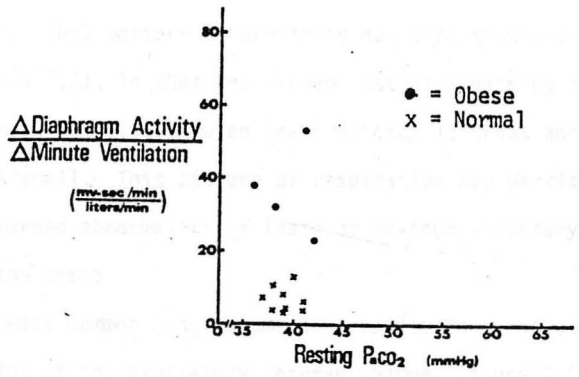
Figure 1



causes an increased afterload, and Hackney suggests that such loading leads to inefficient muscular contraction.

Further, Lourenco's studies of diaphragmatic function in obese persons have demonstrated increased diaphragmatic activity for any given level of ventilation, Figure 2 (13).

Figure 2



The diaphragmatic activity per unit change in minute ventilation is significantly increased above normal in all obese patients who do not hypoventilate. Such increased activity may also be interpreted to suggest inefficiency of muscle function.

Pulmonary Function Abnormalities - Pulmonary function in obese persons is always abnormal. The most commonly reported abnormalities in addition to decreased thoracic compliance and muscle inefficiency are listed in Table 6.

Table 6

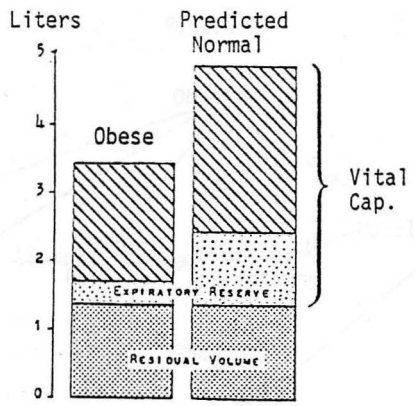
Pulmonary Function Abnormalities in Obesity

1. Abnormal pattern of respiration
2. Reduction of lung volumes
3. Regional gas abnormalities
4. Hypoxemia

Whether it be due to respiratory muscle dysfunction or insurmountable mass loading, obese persons tend to breathe rapidly and shallowly. This pattern of breathing has been shown by Cournand to be adaptive (14), in that the oxygen cost of breathing is less for a given minute ventilation when the frequency is great and the tidal volume is small. This pattern of respiration may partially account for the marked abnormality of tests of maximum voluntary ventilation seen in the obese.

The most common lung volume abnormality in obese subjects is a reduction of the expiratory reserve volume, Figure 3 (15).

Figure 3



The mass of the chest wall decreases total lung capacity and functionaly residual capacity but does not reduce residual volume; these changes result in a decrease of both the vital capacity and expiratory reserve volume. The reduction is greater in the supine position when expiratory reserve volume may be less than closing volume

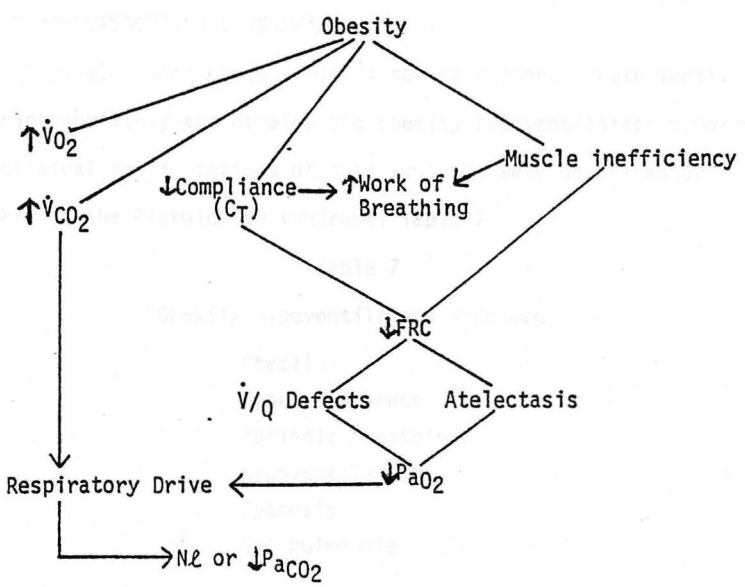
resulting in regional gas trapping (8, 16).

Regional gas trapping causes a delayed nitrogen washout of poorly ventilating lung units resulting in ventilation-perfusion mismatch (17). Further, each tidal volume in the obese subject is distributed to the apex rather than the base of the lung accentuating the mismatch. This abnormality is even more marked in the supine position (18, 19). Thus, ventilation-perfusion abnormalities accentuated by posture account for the hypoxemia that is common in obese patients.

SIMPLE OBESITY

A possible schematic of the respiratory consequences of obesity is presented in Figure 4.

Figure 4



This schema may be useful in understanding the respiratory manifestations of the syndrome of simple obesity. With an increase in body mass there is an increase in oxygen consumption and CO_2 production. Total thoracic compliance decreases and respiratory muscles function less efficiently, and thus work of breathing is increased. There is a decrease in functional residual capacity resulting in ventilation-perfusion abnormalities and areas of atelectasis, and these changes cause arterial hypoxemia, particularly in the recumbent position. However, individuals with simple obesity are able to appropriately increase minute ventilation to meet the excess requirements for CO_2 excretion resulting in a normal or low arterial carbon dioxide tension. Nevertheless, obese persons have dyspnea on exertion out of proportion to normal persons.

OBESITY HYPOVENTILATION SYNDROME (OHS)

Clinical - Some obese patients do not augment minute ventilation appropriately and develop the obesity hypoventilation syndrome. The clinical manifestations of this syndrome were described by Burwell as the Pickwickian syndrome, Table 7.

Table 7

Obesity Hypoventilation Syndrome

Obesity
Hypersomnolence
Periodic breathing
Hypoventilation
Cyanosis
Cor pulmonale

These patients are not only obese but also demonstrate hypersomnolence, periodic respirations, alveolar hypoventilation, cyanosis, and they develop cor pulmonale due to pulmonary hypertension.

Etiology - Although the syndrome was initially attributed only to mechanical limitations that prevent adequate ventilation, three apparently interrelated etiologies are now thought to be important in its genesis, Table 8.

Table 8

Etiologies of Obesity Hypoventilation Syndrome

Decreased mechanical efficiency of respiratory system

Respiratory center abnormalities

Sleep apnea and upper airway obstruction

Decreased Mechanical Efficiency of Respiratory System - Several investigators have documented a decreased mechanical efficiency of the respiratory system in patients with obesity hypoventilation syndrome compared to persons with simple obesity. Table 9 presents the results of Sharp who has calculated respiratory work in two such groups of persons (8).

Table 9

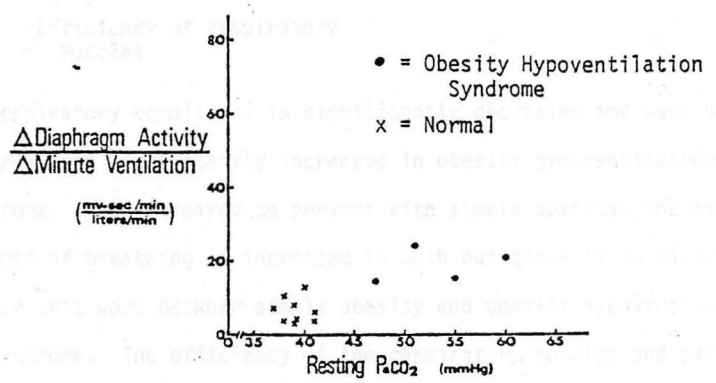
Respiratory Work
kg-m/1L breath
(n = 22)

	Lung	Thorax	Total
Normal obese	0.043	0.054	0.095
Obesity hypoventilation syndrome	0.085	0.127	0.212

Work was calculated from the change in pressure across the respiratory system compared to the change in volume. In persons with simple obesity work measured in this manner was about 30 percent above that in persons of normal weight, but respiratory work was almost three times normal in those with obesity hypoventilation syndrome. Additionally, investigators have documented a lower total respiratory system compliance and a greater inertance of the respiratory system in the obesity hypoventilation syndrome when compared with simple obesity (8, 10, 20). Although significantly elevated above normal in each group, no difference in the oxygen cost of breathing per unit respiratory work has been demonstrated between simple obesity and obesity hypoventilation syndrome.

In contrast to simple obese persons a decrease in diaphragmatic activity in the obesity hypoventilation syndrome has been demonstrated by Lourenco, Figure 5 (13).

Figure 5



The lack of increased diaphragmatic activity of hypercapnic patients has been interpreted as an inability of the inspiratory muscles to meet the demands of an elevated CO_2 production. The contribution of the respiratory center was not addressed in this study, however. Rochester and Enson have also described heightened demands for diaphragmatic work in obese persons and have demonstrated that static inspiratory pressures were only 60 to 70 percent of normal in obese hypercapnic patients (20).

A summary of the magnitude of mechanical alterations in simple obesity and obesity hypoventilation syndrome is given in Table 10.

Table 10

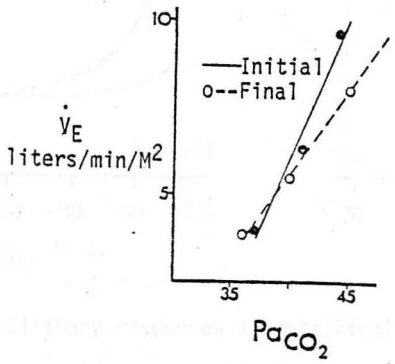
Mechanical Alteration of Respiratory System in Obesity

	Simple Obesity	Obesity Hypoventilation Syndrome
Respiratory Compliance	↓	↓↓↓
Work of Breathing	↑	↑↑↑
O_2 Cost of Breathing	↑↑↑	↑↑↑
Efficiency of Respiratory Muscles	↓	↓↓

Respiratory compliance is significantly decreased and work of breathing significantly increased in obesity hypoventilation syndrome. When compared to persons with simple obesity, the oxygen cost of breathing is increased in both but there is no difference per unit work between simple obesity and obesity hypoventilation syndrome. The efficiency of the respiratory muscles and particularly the diaphragm is decreased in obesity hypoventilation syndrome.

Respiratory Center Abnormalities - Several authors have demonstrated that respiratory center responsiveness both to hypoxemia and CO_2 breathing is normal in subjects with simple obesity (21-23). Figure 6 represents ventilatory responsiveness to carbon dioxide in normal obese persons both before and after significant weight loss (21).

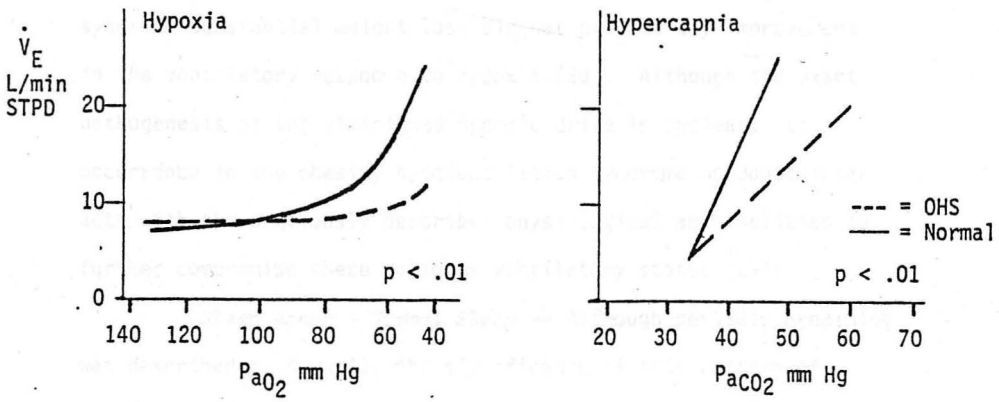
Figure 6



Following weight reduction there was less increment in ventilation per unit increment in P_{aCO_2}. This decrease in responsiveness after weight reduction was attributed to a reduction in ventilatory requirements after the oxygen cost of breathing had diminished. This finding, confirmed by other authors, indicates that obesity per se does not decrease hypercapnic drive (23).

In contrast, it has been established that patients with obesity hypoventilation syndrome have diminished ventilatory responsiveness to both hypoxemia and hypercapnia. Zwillich has studied normal persons and patients with obesity hypoventilation syndrome; his data are presented in Figure 7 (24).

Figure 7



Hypoxic ventilatory responses are strikingly depressed in patients with the obesity hypoventilation syndrome, averaging one-sixth the values found for normal controls. Similarly, ventilatory responses to hypercapnia are markedly depressed, averaging less than one-third of normal. Marked improvement of the ventilatory response to hypercapnia can be demonstrated with weight loss suggesting that the attenuation of hypercapnic drive is secondary to obesity. Furthermore, this is in accord with the observations of Cherniack and Milic-Emili who have both demonstrated that experimental airway obstruction or increased elastic resistance attenuates the ventilatory responsiveness to hypercapnia (25, 26).

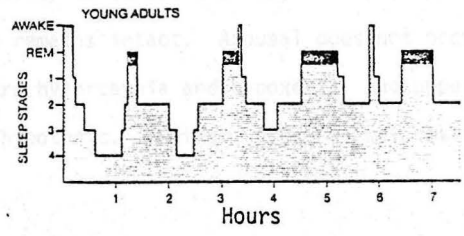
Thus, in obese subjects, loss of hypercapnic responsiveness is the result of the chest wall restriction. Although such may potentiate hypercapnia, it is not likely to be the sole cause.

Although diminished ventilatory responsiveness to carbon dioxide may be acquired in obesity, Levinson and Cherniack have demonstrated that hypoxic drive is relatively resistance to mechanical loading (27). Likewise, in two patients with the obesity hypoventilation syndrome substantial weight loss did not produce any improvement in the ventilatory response to hypoxia (28). Although the exact pathogenesis of the diminished hypoxic drive is unclear, its occurrence in the obesity hypoventilation syndrome no doubt interacts with the previously described physiological abnormalities to further compromise these patients ventilatory status (29).

Sleep Apnea - Normal Sleep -- Although periodic breathing was described by Burwell, the significance of this pattern of respiration in obese patients was not appreciated until 1965, and nocturnal respiratory dysrhythmias in nonobese subjects were not described until 1967 (5, 30).

An understanding of the sleep apnea syndrome in obesity requires a basic understanding of the stages of normal sleep and the associated physiologic changes. Sleep is divided into two major categories, rapid eye movement (REM) sleep and nonrapid eye movement (NREM) sleep.

Figure 8



As illustrated in Figure 8, a normal person fluctuates cyclically through four stages of NREM and REM sleep with a periodicity of 90 to 120 minutes (31). Physiologic differences that occur in REM and NREM sleep are listed in Table 11 (32).

Table 11

Physiologic Differences Between Sleep Stages

	NREM	REM
Respiratory Pattern	Slow regular	Rapid irregular
Apnea	10 sec or less	Up to 20 seconds
Ventilation: CO_2 Response	Normal to mild decrease	Diminished
Ventilation: O_2 Response	Normal	Normal
Arousal		
P_{aCO_2}	54 mm Hg	60 mm Hg
P_{aO_2}	59 mm Hg	44 mm Hg
Tone-Upper Airway Muscles	Present	Absent

The NREM sleep which occupies most of the night is associated with regular breathing with apneic periods of less than 10 seconds. Ventilatory response to carbon dioxide is slightly diminished and hypoxic ventilatory response remains intact. Arousal occurs with mild hypercapnia and hypoxemia. Upper airway muscle tone remains intact. In REM sleep respirations are rapid, shallow and irregular, and apneic periods of up to 20 seconds occur. There is more marked insensitivity to carbon dioxide; however, hypoxemic ventilatory response remains intact. Arousal does not occur with relatively severe hypercapnia and hypoxemia and upper airway muscles become hypotonic. Further, upper airway obstruction during

REM sleep initiates a reflex causing apnea without increasing respiratory effort (32).

Changes in the magnitude of these respiratory variations that occur in normal sleep have been identified as the sleep apnea syndrome (5). However, recent reports demonstrate a distinct sex difference in what should be considered normal physiologic variation during sleep in nonobese persons.

Block has studied 30 asymptomatic men and 19 asymptomatic women of normal body weight during one night's sleep, Table 12 (33).

Table 12

Incidence of Apneic Episodes in Normal Subjects

	Number of Subjects	Number of Episodes	Episodes >20 sec	Episodes Associated With Desaturation
Male	12	51	23	38
Female	3	9	0	0
p value		<0.003		<0.01

Apnea occurred in 12 of 30 males subjects and only 3 of 19 female subjects. Both the number and duration of apneic episodes was significantly greater in men than women. Further, none of the female subjects had an apneic episode associated with arterial oxy-hemoglobin desaturation. When these authors included hypopnea (slowing of respirations) that resulted in desaturation, males had a total of 105 episodes in 11 subjects whereas hypopnea was not seen in any female subject. An analysis of contributing factors to the occurrence of sleep events in men appears in Table 13.

Table 13

Factors Contributing to Sleep Events in Male Subjects

	Desaturation	Hypopnea	Apnea
↑ Age	$p < 0.001$	$p < 0.009$	NS
↑ Wt/ht/ratio	$p < 0.003$	$p < 0.02$	$p < 0.02$
Total Sleep	NS	NS	NS

There is a significant positive relationship between oxygen desaturation and hypopnea and age, and to these events plus apnea and weight/height ratio. There is no correlation with total time of sleep.

Sleep Apnea - Diagnosis -- Although there is a wide variation in normal respiratory patterns during sleep, a considerable literature has accumulated on the sleep apnea syndrome and its clinical manifestations. The currently accepted definition of the sleep apnea syndrome is given in Table 14 (37).

Table 14

Definition of Sleep Apnea Syndrome

1. Thirty apneic episode ($\geq$ 10 secs) during 7 hours in both REM and NREM sleep
2. Repetitive apneic episodes during NREM sleep

Diagnosis of the sleep apnea snydrome requires polygraphic evidence of greater than 30 apneic episodes of at least 10 seconds each occurring during 7 hours of both REM and NREM sleep. Additionally, repetitive apneic episodes must occur during NREM sleep. Apneic episodes at sleep onset or accompanying rapid eye movements in REM

sleep are excluded (38). Applying these rather strict criteria, three types of sleep apnea have been identified, Table 15 (39).

Table 15

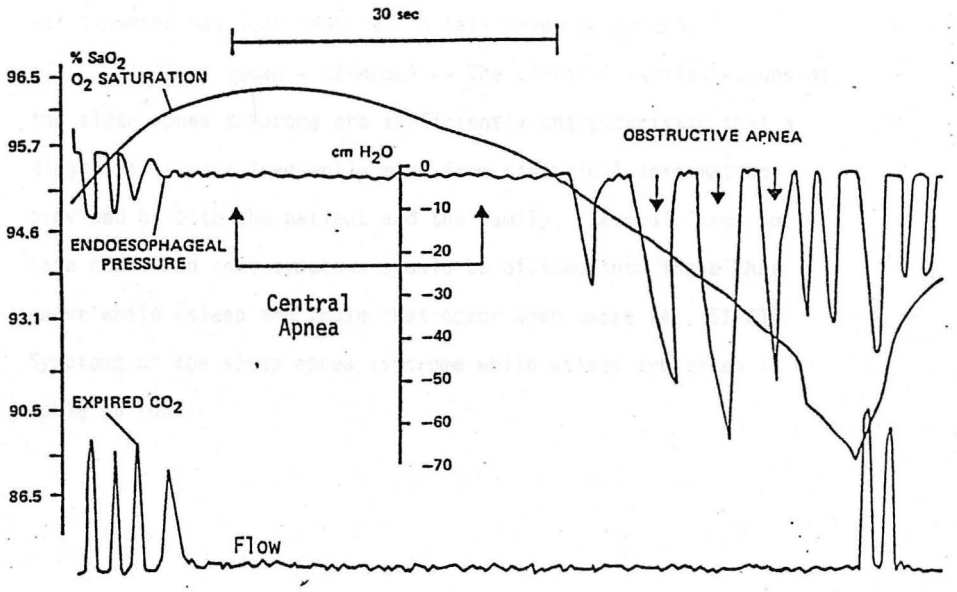
Types of Sleep Apnea

1. Central
2. Obstructive
3. Mixed

These include central or respiratory center apnea, obstructive or upper airway obstruction apnea, and a combination of both central and obstructive apneas.

A polygraphic tracing of mixed apnea incorporates the features of both central and obstructive apnea, Figure 9 (40).

Figure 9



Esophageal pressure reflects pleural pressure and therefore diaphragmatic activity. Central apnea is diagnosed when there are no esophageal pressure fluctuations, and there is cessation of air flow at the nose and mouth. Obstructive apnea is diagnosed when there are increasing subatmospheric swings in esophageal pressure not resulting in air flow at the nose and mouth. The pressure swings represent increased diaphragmatic activity in the presence of upper airway obstruction. Mixed or complex apnea is diagnosed when both central and obstructive apneas appear on the same tracing. In this situation the apneic period is most commonly initiated by a central apnea followed closely by an obstructive period as illustrated in Figure 9. Depending on the length of cessation of air flow, the oxygen saturation as monitored by an ear oximeter has been reported to fall below 60 percent.

Sleep Apnea - Clinical -- The clinical manifestations of the sleep apnea snydrome are sufficiently characteristic that a diagnosis is most frequently made from historical information provided by both the patient and the family. Several large series have confirmed that symptoms should be divided into those that occur while asleep and those that occur when awake (41, 61-63). Symptoms of the sleep apnea syndrome while asleep are given in Table 16 (63).

Table 16

Sleep Apnea Syndromes-Symptoms
While Asleep

Loud snoring nightly

Abnormal sleeping behavior

Unusual movements with apnea
Somnambulism

Difficult Arousal

Nocturnal Enuresis

Regardless of type of apnea 100 percent of patients studied by Guilleminault had pharyngeal snoring during sleep, frequently associated with snorting interrupted by silences (apneic periods) of twenty seconds or longer. The snoring had an onset in childhood in 46 percent of patients and before 21 years in 96 percent.

Abnormal motor activity was also observed in every patient during polygraphic recordings, and the movements were very stereotypic and occurred during apneic periods. Sleep was extremely agitated with frequent abnormal movements of the extremities or gross movements of the whole body. Movements of the arms or legs often caused slaps or kicks of the bed partner and led to separate beds in 40 percent of couples questioned. Occasionally, patients sat up in bed as if struggling to breathe.

Somnabulism occurred weekly to once every 6 months in approximately 60 percent of patients. Occasionally patients stood up in their sleep, walked a few steps and then fell to the floor (64).

Arousal, particularly during somnabulism, was difficult. Even painful stimuli were unsuccessful, and it was not uncommon for

patients to sleep the rest of the night on the floor. If aroused, temporal and spatial disorientation frequently occurred.

A minority of adults (approximately 8 percent) complained of intermittent nocturnal enuretic episodes that had resulted in negative urologic and neurologic evaluations.

Symptoms most disturbing to patients with sleep apnea occurring while awake are listed in Table 17 (63).

Table 17

Sleep Apnea Syndrome-Symptoms
While Awake

Hypersomnolence
Automatic behavior
Hypnagogic hallucinations
Morning headache and "Foggy Mind"
Deterioration of intellectual capacity

According to Guilleminault daytime somnolence and sleep attacks at inappropriate times occur in approximately 85 percent of patients. These symptoms frequently have been present for over five years before presentation.

Automatic behavior is reported in close association with hypersomnolence. During an episode, which may last for hours, it is possible for patients to perform simple repetitive tasks with complete retrograde amnesia for the episode (65). Complex behavior, however, is difficult, perhaps including the ability to speak coherently and appropriately. Polygraphic monitoring has revealed that frequent, repetitive micro sleep episodes are related to the appearance and development of this syndrome (66).

Guilleminault estimates that hypnagogic hallucinations occur in at least 40 percent of patients and are particularly common when the urge to sleep occurs in the daytime. Characteristically, these hallucinatory images persist for only a short time before being recognized as such by the patient and dispelled; however, an occasional patient may react inappropriately before realizing the hallucinatory nature.

Approximately one-half of patients complain of recurrent morning headaches. These usually are described as frontal cephalalgia and dissipate several hours after arousal. Morning headaches are often associated with a "foggy mind", that is, an inability to remember events of the previous day as well as difficulty performing cognitive tasks.

Closely related to automatic behavior is a deterioration of intellectual capacity. This complaint is elicited from the patient or the spouse over 50 percent of the time. They also report a short attention span. These symptoms greatly interfere with work performance.

Obese patients presenting with this constellation of symptoms are virtually all men who have documented sleep disordered breathing (67).

INTERACTIONS OF DEFECTS

The exact pathogenesis of the obesity hypoventilation syndrome remains to be elucidated. However, it seems reasonable at the present to believe that an interaction of the decreased efficiency of the respiratory system, the respiratory center abnormalities

and the sleep apnea syndrome, perhaps to differing degrees in individual patients, result in this syndrome, Table 18.

Table 18

Interaction of Defects in
Obesity Hypoventilation Syndrome

	Decreased Mechanical Efficiency	Respiratory Center Defect	Sleep Apnea
1. Hypoventilation	✓	✓	✓
2. Hypersomnolence		✓	✓
3. Periodic breathing		✓	✓
4. Hypoxemia with cor pulmonale	✓	✓	✓

Weaker inspiratory muscles and lower chest wall compliance has been demonstrated in patients with the obesity hypoventilation syndrome out of proportion to patients of the same weight with simple obesity. This decreased mechanical efficiency leads to a greater reduction in FRC and more marked hypoventilation and hypoxemia in these patients. Pulmonary hypertension, polycythemia and cor pulmonale may occur as a consequence of the severe arterial hypoxemia (20).

Decreased responsiveness of the respiratory center both to hypoxia and hypercapnia is a consistent finding in patients with obesity with hypoventilation. Although this respiratory center insensitivity may be a secondary phenomena, it could account for hypoventilation, hypersomnolence, periodic breathing and hypoxemia with cor pulmonale.

Since the initial description of the sleep apnea syndromes it has become apparent that virtually all patients with the obesity hypoventilation syndrome demonstrate some type of sleep distrubed

respirations. Dysrhythmia of sleep respiration of all types can result in hypoventilation, hypersomnolence, periodic breathing and critical levels of hypoxemia associated with cor pulmonale. Most evidence indicates that sleep apnea is the most important feature of the pathogenesis of obesity hypoventilation syndrome.

Relationship of Obesity Hypoventilation Syndrome to Sleep Apnea

Although there is increasing evidence that obesity hypoventilation syndrome is related to sleep apnea, the exact pathogenesis remains unclear. The positive correlation with an increased weight/height ratio supports the hypothesis that, in men, obesity per se contributes to the obesity hypoventilation syndrome by increasing episodes of sleep apnea with desaturation. Likewise, the marked difference in sex distribution of periodic breathing and desaturation during sleep correlates well with the repeated observation that greater than 80 percent of patients with the obesity hypoventilation syndrome are men (34-36). Variables that have been investigated in an attempt to establish the pathogenesis appear in Table 19.

Table 19

Relationship of OHS to Sleep Apnea

Genetic
Upper airway obstruction
Respiratory center defect

Genetic - It has been well established that hypersomnolence can occur in the nonobese adult as a result of sleep apnea. Additionally, partial airway obstruction in children due to enlarged tonsils and adenoids can cause hypoventilation, cardiomegaly and cor pulmonale (37, 45-50). Recently, however, the sleep apnea syndrome associated with hypersomnolence but without enlarged tonsils and adenoids has been recognized in children and has led to the speculation of a genetic predisposition (51). In support of this speculation is the finding of obstructive sleep apnea in 4 male family members as well as the occurrence of sudden infant death in the same family (52). A genetic predisposition to the sleep apnea syndrome when complicated by obesity may be involved in the pathogenesis of the obesity hypoventilation syndrome.

Airway Obstruction and Pharyngeal Muscle Defects - A good correlation has been demonstrated between the occurrence of the obesity hypoventilation syndrome and sleep apnea (39, 53). Apneic periods commonly result from total airway obstruction and may be relieved by intubation or tracheostomy (41, 54, 55). These features and the anatomic observation that patients with the obesity hypoventilation syndrome have short necks and large tongues has led to investigation of the activity of the genioglossus muscle. The genioglossus has been shown to play an important role in normal persons in the mechanics of maintaining open airway passages in the oropharyngeal region (56). In patients with the obesity hypoventilation syndrome, airway occlusion frequently

occurs during REM sleep with normal loss of activity of the genioglossus muscles. Once collapse has occurred the progressive increase in inspiratory muscle activity results in continued obstruction until hypoxemia results in arousal and preferential activation of the genioglossus muscle with relief of obstruction (55, 57).

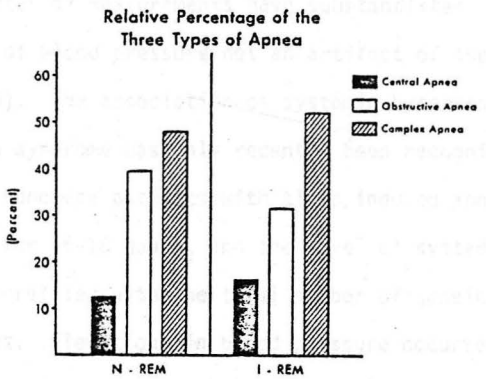
Respiratory Center Defect - Since the initial report by Lyons and Huang that administration of the respiratory stimulant progesterone normalized the P_{aCO_2} in patients with the obesity hypoventilation syndrome, there has been interest in the respiratory center's role in the pathogenesis of the sleep apnea snydrome (58). The occurrence of pure central sleep apnea in some patients with the obesity hyperventilation syndrome and the demonstration that diaphragmatic activity is diminished in patients with an elevated P_{aCO_2} supports a respiratory center defect in some patients (13).

The output of the respiratory center can be assessed by measurement of mouth occlusion pressure at functional residual capacity 150 msec. after onset of an occluded respiration (59). Using this technique a group of patients with obesity hypoventilation syndrome has been identified whose respiratory center output does not increase with carbon dioxide breathing and suggesting a respiratory center defect (60).

Additionally, several authors have reported patients who have developed central apnea after intubation or tracheostomy further suggesting abnormalities of the respiratory center (41, 44).

The relative frequency of the three types of sleep apnea in patients with the obesity hypoventilation syndrome has been studied by Sackner, Figure 10 (41).

Figure 10



Mixed apnea is the most common and central apnea least common in both NREM and REM sleep. The same authors have shown that mixed apneas are the most prolonged, averaging 38 seconds, while obstructive apneas average 28 seconds. The total time spent in apnea in 8 hours of sleep in patients with the obesity hypoventilation syndrome varies from 38 to 72 percent with a mean of 47 percent (42-44).

Regardless of the defect resulting in sleep apnea in the obese, when hypercapnia occurs there is universal hypersomnolence and periodic breathing.

COMPLICATIONS OF OBESITY HYPOVENTILATION SYNDROME

Sleep Apnea Associated Cardiovascular Dysfunction - Systemic Hypertension - Systemic hypertension has been recognized as a complication of obese subjects free of other disease (68). Direct intra-arterial measurements have substantiated that it is a true elevation of blood pressure not an artifact of the method of measurement (69). The association of systemic hypertension with the sleep apnea syndrome has only recently been recognized (70). Both obese and nonobese patients with sleep induced apnea have been monitored for 16-18 hours, and the level of systemic arterial hypertension correlated with the total number of apneic episodes during the night. Elevations in blood pressure occurred following the lowest point of oxygen saturation of an apneic cycle (40, 71, 72). This finding has led to the investigation of asymptomatic normals with a snoring history, and similar hemodynamic changes occur when sleep apnea is documented (62).

Sleep Apnea Associated Cardiovascular Dysfunction - Pulmonary Artery Hypertension - Following documentation of severe degrees of hypoxemia during episodes of apnea it was not unexpected to find a rise in pulmonary artery pressure. Guilleminault has data documenting a progressive increase in both systolic and diastolic pulmonary artery pressures in sleep apnea patients (40). Pulmonary artery pressures reached levels as high as 87 mm Hg systolic and 50 mm Hg diastolic. Pressures began to increase after 15 to 20 seconds of apnea and were highest after 5 to 10 minutes of repetitive apnea.

Sleep Apnea Induced Cardiovascular Dysfunction - Cardiac Arrhythmias-- Sudden death is well known in the Pickwickian syndrome. Recent evidence has suggested sleep apnea as a causative factor in the sudden infant death syndrome, and cardiac arrhythmias in adult sleep apneas have been documented which may add to the risk of sudden death (73). Arrhythmias have been investigated both during wakefulness and sleep, and the relative frequency in 15 male patients with sleep apnea is summarized in Table 20 (74).

Table 20

Arrhythmias During Wakefulness and Sleep

Data	Awake (no.)	Sleep (no.)
Patients	15	15
Normal sinus rhythm	15	0
Marked sinus arrhythmia	0	14
Extreme sinus bradycardia (Heart rate <30/min)	0	6
Asystole (2.5 to 6.3 sec)	0	5
Second degree A-V block	0	2
Complex premature ventricular contractions	6	10
Ventricular tachycardia	0	2

Normal sinus rhythm was present during wakefulness but usually changed to marked sinus arrhythmia during sleep. This progressed to bradycardia with a heart rate of less than 30 during apneas in 6 patients. There was abrupt reversal with onset of ventilation with recurrent cycles of 1 to 1.5 minutes each. Prolonged sinus pauses ranging from 2.5 to 6.3 seconds accompanied the apnea and bradycardia in six patients whereas second degree A-V block was noted in two. Complex premature ventricular contractions were

noted more frequently during sleep, and in two patients self-limited runs of ventricular tachycardia accompanied the sinus bradycardia during sleep.

Eight patients underwent tracheostomy resulting in normalization of sleep patterns and cessation of obstructive apneas. There was abolition of all bradyarrhythmias, second degree A-V block and ventricular tachycardia, and the complex premature ventricular contractions were less frequent. The obstructive apneas and abnormal rhythms recurred when the tracheostomy site was temporarily occluded establishing a cause and effect relationship. Although obstructive apnea was prevented by tracheostomy, episodes of central apnea accompanied by 2.5 to 6.5 seconds of asystole occurred in two patients (74, 75). These finds have established a characteristic rhythm disorder and led to speculation of their possible role in the sudden infant death syndrome (76-80).

Pulmonary Emboli - Although the obesity hypoventilation syndrome is known to be associated with polycythemia and venous stasis, the incidence of clinically significant pulmonary embolizations remains unknown. Case reports have appeared in the literature since the early 1950's suggesting that somnolent obese patients have an increased risk (81-83).

Increased In-Hospital Mortality - The overall prognosis of untreated patients who develop the obesity hypoventilation syndrome is not known. However, one series followed 10 patients during 11 episodes of ventilatory failure. In-hospital mortality was 70

percent. Three deaths were related to hypoventilation despite ventilatory therapy. Three patients died of pulmonary emboli and one of acute renal failure (84). This series supports the clinical impression that hospitalized patients with obesity hypoventilation syndrome present a myriad of abnormalities and have a markedly increased morbidity and mortality.

TREATMENT OF OBESITY HYPOVENTILATION SYNDROME

The medical modalities that are available for treatment of patients with the obesity hypoventilation syndrome are summarized in Table 21.

Table 21

Obesity Hypoventilation Syndrome
Medical Management

Weight reduction
Nasopharyngeal airway
Respiratory stimulants
Anticoagulation
Cardiac monitoring and antiarrhythmic agents

Weight reduction reverses all of the clinical and many of the physiologic manifestations of the Pickwickian syndrome (4). Reduction of the mechanical resistive load results in a decreased work of breathing and increased efficiency of the respiratory muscles. Lung volumes increase and closing volume decreases resulting in improvement in ventilation-perfusion mismatch and therefore hypoxemia. In some patients there is a return in responsiveness of the respiratory center to carbon dioxide. There is also a suggestion that weight reduction alone will convert patients

with symptomatic to asymptomatic sleep apnea. Orr has shown that patients with equally severe upper airway obstruction in terms of absolute numbers and mean duration could be separated into symptomatic and asymptomatic groups. The only significantly different variable was weight (85). Although somnolence improves it is not entirely relieved in all patients with weight reduction (34). These patients are then similar to the excessive daytime sleepiness classification of the nonobese with sleep apnea (86).

Nasopharyngeal Airway - After removal of endotracheal tubes following ventilatory support Walsh noted that patients with obesity hypoventilation syndrome frequently resumed periodic apnea (34). Insertion of a soft latex nasopharyngeal tube ablated the obstructive apneic episodes. Since that time it has been recognized that surgical tracheostomy may be avoided if patients tolerate this intervention during weight loss.

Respiratory Center Stimulants - Progesterone -- Increased minute ventilation and reduction of alveolar carbon dioxide have been observed in pregnancy and during the luteal changes of menstruation, and administration of progesterone to normal men produces similar changes (87-91). These observations resulted in the first report of the use of progesterone in the obesity hypoventilation syndrome. Lyons and Huang treated 8 such patients who had periodic respirations with 100 mgm of intramuscular progesterone daily and demonstrated a 30 percent increase in alveolar ventilation. Carbon dioxide response curves were likewise restored to normal. Hypoventilation recurred one month after progesterone was

discontinued (58). These findings have been confirmed by Sutton and Zwillick who treated 10 male out-patients with obesity hypoventilation syndrome with 20 mgm of sublingual medroxyprogesterone acetate every 8 hours. Results of ventilatory parameters monitored at 4 to 9 months of progesterone and after withdrawal and reinstitution of therapy are presented in Figures 11, 12, and 13.

Figure 11

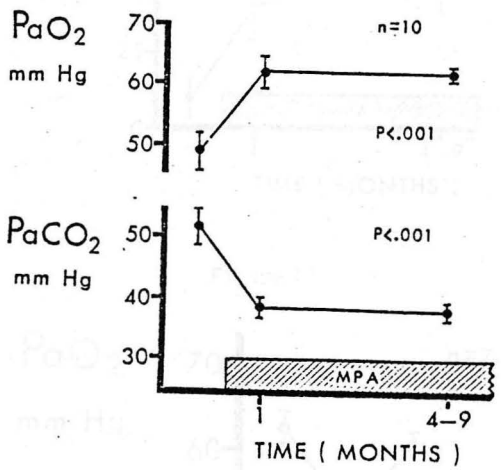


Figure 12

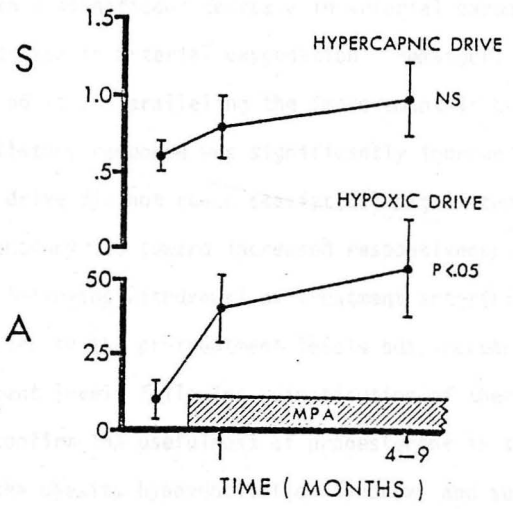
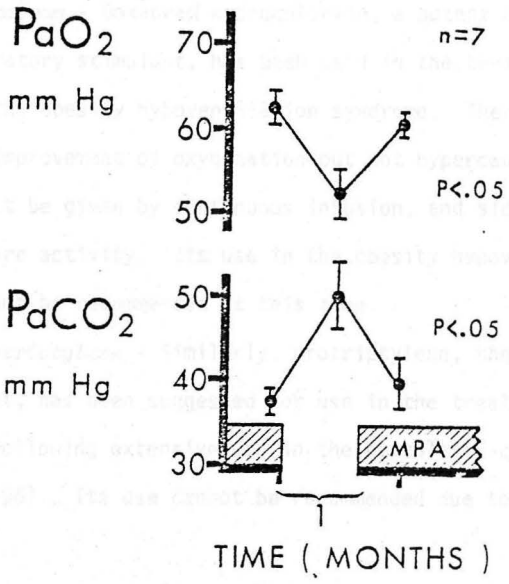


Figure 13



Since there was no significant weight change, these findings confirm that progesterone results in improvement of alveolar ventilation with a significant decrease in arterial carbon dioxide tension and increase in arterial oxygenation. Hematocrits fell from a mean of 56 to 50 paralleling the improvement in hypoxemia. Hypoxemic ventilatory response was significantly improved; changes in hypercapnic drive did not reach statistical significance, although the tendency was toward increased responsiveness.

One month following withdrawal of treatment arterial blood gases had reverted to the pretreatment levels but increased to previous treatment levels following reinstitution of therapy (92). These results confirm the usefulness of progesterone in the management of the obesity hypoventilation syndrome and support the importance of the respiratory center defect that has been demonstrated in these patients (93).

Doxapram - Doxapram hydrochloride, a potent centrally acting respiratory stimulant, has been used in the treatment of one case of the obesity hypoventilation syndrome. There was a tendency to improvement of oxygenation but not hypercapnia (94). This drug must be given by continuous infusion, and side effects include seizure activity. Its use in the obesity hypoventilation syndrome cannot be recommended at this time.

Protriptylene - Similarly, protriptylene, the tricyclic antidepressant, has been suggested for use in the treatment of sleep apnea following extensive use in the narcolepsy-cataplexy syndrome (95-96). Its use cannot be recommended due to its

deleterious effects on myocardial conductivity and contractility in patients already demonstrated to have significant cardiac arrhythmias (97).

Cardiac Monitoring - The prevalence of cardiac arrhythmias during sleep in patients with the sleep apnea syndrome has led to a recommendation for nocturnal Holter type ECG monitoring (74). A seizure and urinary incontinence has been confirmed in one patient during a 10 second asystole (54). Oral atropine in a dose of 1.2 to 2.4 mgm has been shown to abolish sinus bradycardia, A-V block and sinus pauses in patients with the obesity hypoventilation syndrome. There is no apparent effect on sleep pattern or airway obstruction (74). Atropine should be considered an adjunct to respiratory stimulant therapy in patients who demonstrate nocturnal bradyarrhythmias.

Anticoagulation - Because of the documented in-hospital mortality, and the apparent increased risk of pulmonary emoblism, low dose heparin anticoagulation is recommended in hospitalized obesity hypoventilation syndrome patients, particularly when diuresis is attempted.

Surgical Tracheostomy - Tracheostomy has been shown to improve daytime somnolence as well as respiratory and cardiac dysrhythmias in patients with predominantly obstructive apnea. Motta has also documented a reduction in systemic and mean pulmonary artery pressure. This was accompanied by a significant increase in arterial $P_{a_{O_2}}$ recorded during central apneic episodes (98).

Recommendation for tracheostomy should be limited to patients with purely obstructive apnea with severe cardiac and hemodynamic

changes that do not respond to treatment with progesterone. The probable respiratory center defect in patients with the sleep apnea syndrome and the demonstration of conversion to central apnea following tracheostomy warrant further investigation.

Surgical Tracheostomy and Diaphragm Pacing - Electrophrenic respirations or diaphragmatic pacing was first used as a long term treatment in patients with central hypoventilation. The left phrenic nerve was stimulated 8 hours per night. This technique resulted in an increase in tidal volume, improved regional ventilation in the paced lung and a decrease in systemic hypertension (99).

Gee has performed tracheostomies on 13 patients with well documented obstructive apnea. Nine patients then showed hypoventilation during sleep, which he assumed to be central in origin. Therefore, diaphragmatic pacing was instituted, but periodic obstructive sleep apnea was induced in three patients. Pacing induced upper airway obstruction despite tracheostomy was seen in two cases whose airways were not obstructed following tracheostomy. During spontaneous breathing asleep these patients had repeated prolonged periods of central apnea (100-101). These findings suggest that diaphragmatic pacing should not be recommended in patients with obesity hypoventilation syndrome and sleep apnea.

SUMMARY AND CONCLUSIONS

The respiratory complications of simple obesity are due to well documented mechanical abnormalities of the respiratory system. These result in dyspnea, rapid shallow respiration and hypoxemia.

The obesity hypoventilation syndrome has a more complex etiology. There is now considerable evidence to indicate that dysrhythmic sleep with apnea is the most significant factor in pathogenesis of this syndrome. The syndrome's overwhelming male predominance is likely related to abnormal sleep patterns demonstrated by nonobese men, coupled with a possible genetic predisposition toward abnormalities of the respiratory center.

Although unproven, a respiratory center defect may account for the initiation of the commonly observed upper airway obstruction.

Weight reduction and progesterone therapy are the initial treatments of choice. Tracheostomy should be avoided except in severely hypoxemic patients with uncontrollable bradyarrhythmias unresponsive to progesterone. Diaphragmatic pacing should be avoided.

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