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Review Article

Respiratory Complications of Obesity

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ABSTRACT

Obesity, well known as a cardiovascular risk factor, can also lead to significant respiratory complications. The respiratory changes associated with obesity extend from a simple change in respiratory function, with no effect on gas exchange, to the more serious condition of hypercapnic respiratory failure, characteristic of obesity hypoventilation syndrome. More recently, it has been reported that there is an increased prevalence of asthma which is probably multifactorial in origin, but in which inflammation may play an important role. Hypoventilation in the obese subject is the result of complex interactions that involve changes in the ventilatory mechanics and anomalies in breathing control. Two other conditions (COPD and sleep apnea-hypopnea syndrome [SAHS]), often present in obese patients, can trigger or aggravate it. The prevalence of hypoventilation in the obese is under-estimated and the diagnosis is usually established during an exacerbation, or when the patient is studied due to suspicion of SAHS. Ventilatory management of these patients, ventilatory management of these patients includes either CPAP or NIV. The choice of one or another will depend on the underlying clinical condition and whether or not there is another comorbidity. Both NIV and CPAP have demonstrated their effectiveness, not only in the control of gas exchange, but also in improving the quality of life and survival of these patients.

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Complicaciones respiratorias de la obesidad

RESUMEN

La obesidad, bien conocida como factor de riesgo cardiovascular, puede asimismo comportar una importante afectación respiratoria. Las alteraciones respiratorias relacionadas con la obesidad abarcan desde la simple alteración de la función ventilatoria, sin consecuencias sobre el intercambio gaseoso, hasta la situación más grave, la insuficiencia respiratoria hipercápnica característica del síndrome de obesidad hipoventilación. Más recientemente se ha señalado la presencia de un incremento de prevalencia de asma de probable etiología multifactorial pero en el que puede desempeñar un papel importante la inflamación. La hipoventilación en el sujeto obeso es el resultado de complejas interacciones que implican a las alteraciones de la mecánica ventilatoria y a anomalías del control ventilatorio. Otras dos entidades (enfermedad pulmonar obstructiva crónica y síndrome de apnea hipopnea del sueño [SAHS]), frecuentemente presentes en los pacientes obesos, pueden potenciarla o agravarla. La prevalencia de hipoventilación en el obeso se encuentra subestimada y es frecuente que el diagnóstico sólo se establezca con motivo de una exacerbación o cuando el paciente es estudiado por sospecha de SAHS. El manejo ventilatorio de estos pacientes, mediante CPAP o ventilación no invasiva (VNI), dependerá de la situación clínica subyacente y de la presencia o no de otra comorbilidad. Tanto la VNI como la CPAP han mostrado su eficacia no sólo en el control de las alteraciones gasométricas, sino también en la mejora de la calidad de vida y en la supervivencia de los pacientes.

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"It is very injurious to health to take in more food than the constitution will bear, when, at the same time one uses no exercise to carry off this excess."
Hippocrates, 400 B.C.

Introduction

Even though obesity is recognized in our times as a pressing problem, its beginning goes back to the origin of the species and it is found on the threshold of survival itself. In fact, one of the basic principles of survival is dictated by the need to eat, store energy and remain as inactive as possible in order to conserve it. Probably because of this, the story of the fight against obesity is a story of failure. We perfectly understand that its causes and therapeutic management are in theory extremely simple: no scientific innovation or academic knowledge is necessary for its treatment. In spite of this, obesity is clearly increasing and is currently on the verge of becoming a growing public health-care problem, motivated by the high number of subjects that present obesity as well as by the comorbidities that accompany it. While the role of obesity as a cardiovascular risk factor is well known, it receives much less attention as a cause for respiratory disease.

Epidemiology of Obesity

Obesity is classified in terms of severity based on the body mass index (BMI) measured in kg/m², as moderate (BMI 30-35), severe (BMI 35-40) and massive or morbid (BMI > 40 kg/m²). A BMI between 25 and 29.9 kg/m² is considered overweight. Obesity is today a major problem of public health in the world. Recent data indicate that 25-30% of the occidental population in developed countries present obesity. In France, data from the ObEpi study demonstrated an increase of the prevalence of obesity in the population over the age of 15, increasing from 8.2% in 1997 to 14.5% in 2009. Proportionally, the prevalence of massive obesity increased, going from 0.3% in 1997 to 1.3% in 2009.^{1,2} Recently-published data from Spain, obtained from the National Health Survey (*Encuesta Nacional de Salud*) show a similar increase.³ Obesity is a major cause of morbidity and, for example, in the year 2000 in the United States it was either the direct or indirect cause of approximately 400,000 deaths and represented 7% of health-care costs.^{4,5}

Obesity and Respiratory Disease

A couple of decades ago, the respiratory complications associated with obesity started to occupy an important place in medical publications. However, fictional literature anticipated science: in 1836, Charles Dickens presented his pamphlets *The Posthumous Papers of the Pickwick Club*,⁶ which is, without doubt, the best characterization of an obese individual with undoubtable respiratory problems:

"... and on the box sat a fat and red-faced boy, in a state of somnolence... the fat boy rose, opened his eyes, swallowed a huge piece of pie he had been in the act of masticating when he fell asleep... Joe-dams the boy he's gone to sleep again!"
The Posthumous Papers of the Pickwick Club,
(Charles Dickens, 1836).

More than 150 years passed before Bickelmann et al⁷ found a physiopathological explanation for the phenotype of Joe, that "fat, red-faced boy" when they discovered the presence of apnea and alveolar hypoventilation in this type of individuals. They suggested for this clinical group of symptoms the name of "Pickwick syndrome" in paying homage to this great writer. Since then, the knowledge and understanding of the physiopathology of respiratory implications in obesity have been developing.

Obesity and Lung Function

Obesity results in a decrease in thoracic distensibility, especially of the chest wall as a consequence of the restriction imposed on the expansion of the ribcage and diaphragm. Although also present, the fall in lung distensibility is less important and has a double mechanism: an increase in pulmonary blood volume and alveolar collapse as a consequence of the closure of the small airway, particularly at the lung bases.⁸

Maximal mouth pressures are generally normal, but they may be reduced in cases of morbid obesity. This is similar in the case of the resistance of the respiratory muscles, which is only altered in cases of massive obesity.⁹ As a consequence of this group of anomalies, the ventilatory effort increases. Thus, in patients with BMI > 40 VO₂ at rest, it can reach up to 16% of total VO₂, while it rarely exceeds 3% in non-obese subjects.¹⁰

The alterations in ventilatory mechanics are seen in the lung volume studies:

Effects on Static Volumes

The most frequent functional anomaly in obese subjects is the decrease in expiratory reserve volume (ERV) with conservation of the residual volume, which is more marked in dorsal decubitus and results in a reduction in the functional residual capacity.⁸ It has been demonstrated that this decrease in ERV has an exponential correlation with the increase in BMI.¹¹ Total lung capacity (TLC) is generally conserved, except in morbid obesity where it may drop up to 20%. Like BMI, these anomalies are more important in subjects with android or centripetal obesity than in those with gynecoid obesity.¹² A reduction in TLC under 80% should lead to contemplating an associated respiratory disorder. Weight loss is generally accompanied by normalization of lung capacity volumes.^{13,14}

Effects on Variable Volume and Flow

While vital capacity (VC) is generally conserved, forced expiratory volume in one second (FEV₁) can be mildly lower in patients with severe obesity, although in general the FEV₁/VC ratio is normal in the absence of associated disease. However, maximum expiratory flow 25-75% can be significantly reduced, particularly in male subjects with severe obesity, reflecting obstruction of the small airway especially in the lung bases.¹⁵

Diffusion Test in Obesity

The test for diffusing capacity for carbon monoxide is generally normal or shows a slight increase, consequence of the increase in pulmonary blood volume.¹⁶

Obesity and Ventilatory Behavior during Exercise

In comparison with normal subjects who are not overweight, obese individuals present, for the same level of exercise, greater VO₂ and greater minute ventilation at the expense of an increase in respiratory frequency, in such a way that tidal volume decreases ("fast and superficial breathing").^{17,18} Likewise, there is evidence of a reduction of the anaerobic threshold and maximum VO₂,^{17,19} which in subjects with massive obesity can reach levels equivalent to those of a subject with severe ventricular dysfunction.²⁰

Gas Exchange in Obesity

It is frequently observed that arterial blood gases (ABG) are altered in obese subjects and said normality is proportional to BMI. Two main physiopathological mechanisms can explain these anomalies of the gas exchange: ventilation-perfusion imbalance, responsible

for isolated hypoxemia, and alveolar hypoventilation, responsible for the so-called "obesity hypoventilation syndrome" (OHS).

Mechanisms Involved in Hypoxemia

Isolated hypoxemia is the most frequent anomaly of the gas exchange in obesity and can be found in up to 30% of patients. This hypoxemia, which is generally mild, frequently presents only in decubitus or is aggravated by this position due to the consequent increase in the ventilation-perfusion imbalance.^{7,8} This anomaly admits a double mechanism that is both capillary and alveolar: in addition to the increase in regional blood flow in the bases (consequence of the hypovolemia that is characteristic of obesity) that increases the pulmonary blood flow and favors capillary recruitment, there are also underventilated alveolar areas as a consequence of the collapse of the small airway. Hypoxemia is more frequent and more severe in the cases of massive obesity (BMI > 40) and seems to correlate with the reduction of the ERV.²¹

Mechanisms of Hypoventilation in Obese Subjects: Can't Breathe or Won't Breathe?

Alveolar hypoventilation is present in approximately 10% of obese subjects.⁴ Compared with simple obese subjects with no respiratory complications, hypercapnic subjects are characterized by less distensibility in the overall respiratory system, less ERV, and TLC, and an abnormal ventilatory pattern (increase in respiratory frequency, decrease in tidal volume, while Ti/T_{tot} remains unchanged), less strength and resistance of the respiratory muscles, and a ventilatory response to hypercapnia that is markedly depressed or at least inappropriate.^{8,9} Therefore, it is not surprising that the ventilatory effort and the energy output of the ventilation are higher in these patients, which may lead to a greater predisposition to fatigue of the respiratory muscles.¹⁰

Hypoventilation in the obese is multifactorial and includes a diversity of mechanisms that are frequently intricate²²⁻²⁴ (table 1). However, the exact mechanism is not known and remains unclear why some obese patients hypoventilate while the great majority do not. Two fundamental hypotheses have been proposed. The first, "hypothesis of mechanical overload", postulates that hypoventilation is secondary to the mechanical limitation resulting from the decrease in thoracopulmonary distensibility.¹⁰ This theory that the obese "cannot breathe" presents two fundamental limitations. In the first place, there is a poor correlation between BMI and the degree of hypoventilation. On the other hand, there is also no correlation between BMI and thoracic distensibility.

The second theory, "hypothesis of the ventilatory center hyporeactivity", postulates the incapacity of the respiratory center to respond physiologically to an increase in $PaCO_2$. It has been seen that, although these subjects present a higher baseline ventilatory impulse, the response of the $P_{O.1}$ (which reflects the activity of the respiratory center) and the ventilation when given an increase of $PaCO_2$ is lower or at least inappropriate.^{25,26} Reduced activity on diaphragm EMG to hypercapnic stimulus has also been observed.²⁷ However, these alterations are not found in all obese subjects with hypoventilation, which suggests the existence of at least two different phenotypes.^{8,28} It has been postulated that the alteration of the ventilation control obeys to genetic mechanisms, but this is not clear as studies carried out with the family members of patients with OHS show normal respiratory center behavior.²⁹ On the other hand, it cannot be ruled out that the alterations in ventilation control were not the cause but instead the consequence of hypoxemia and/or chronic hypercapnia,³⁰ and even that it was an adaptive response to the mechanical overload in order to avoid excessive respiratory effort.²¹ For these authors, the obese "won't breathe".

Table 1

Physiopathological mechanisms that are potentially involved in the genesis of respiratory failure in the obese

Hypoxemic respiratory failure
Increase in the PAO_2/PaO_2 gradient secondary to the V/Q imbalance (particularly in the lung bases) as a consequence of:
– Hypervolemic and hyperdynamic status (hyperperfusion)
– Airway closure and alveolar collapse
Hypercapnic respiratory failure
Altered or inappropriate ventilatory control
Decrease in thoracopulmonary compliance
Inappropriate compensation of the ventilatory load
Increase in resistance of the UA and inspiratory load threshold
Diminished response to the elastic and resistive loading
Increased ventilatory effort and oxygen cost of breathing
Diminished respiratory muscle strength and resistance
Excito-contraction uncoupling
Respiratory muscle fatigue (peripheral and/or central)
Diaphragm dysfunction secondary to:
– Increase in adipose tissue deposits
– Mechanical disadvantage (inadequate longitude-tension ratio)
Modification of the ventilatory pattern (fast and superficial breathing)
Increased resistance of the respiratory system
Increased VCO_2
Coexisting conditions
SAHS or increased UA resistance syndrome
COPD
Aggravating conditions
Supine position
REM sleep

Comorbidity and Hypoventilation

Two other entities (COPD and sleep apnea) that are frequently present in obese patients can promote or worsen alveolar hypoventilation. As in morbid obesity, COPD increases ventilatory effort, modifies respiratory mechanics and reduces the efficiency of the respiratory muscles. Consequently, the coexistence of COPD can contribute to hypercapnia in obese subjects. In these patients, in general, the magnitude of the increase in $PaCO_2$ is inversely proportional to the degree of reduction of the FEV_1 . As for sleep apnea syndrome, this merits separate commentary.

Obesity and Asthma

As the prevalence of asthma and obesity has increased in recent years, numerous publications have examined the possibility of an epidemiological connection between the two disorders. Cross-sectional cohort studies done in children and adolescents as well as in adults have revealed a significant association between obesity and asthma, showing a relative risk of 1.4 to 2.2 for asthma in obese subjects, with a marked dose-effect ratio as the prevalence of asthma increases in proportion to BMI.³¹⁻³⁴ However, what cannot be deduced is a cause-effect relationship as the majority of said studies could not show that obesity precedes the development of the bronchial activity. Various longitudinal studies have confirmed these results, finding a relative risk of asthma of 1.6 to 2.7 in the obese population.^{32,35-38} Important published meta-analyses that analyzed both types of studies^{39,40} confirmed this tendency and showed a more marked association in women than in men. However, as the majority of these studies define the presence of asthma based on self-described symptoms and not on a diagnosis defined by strict clinical-immunophysiological criteria, it is not clear today whether obesity really implies a higher risk for asthma, or if it simply produces physiological modifications that can mimic its symptoms.⁴¹

Different factors could explain this asociación.⁴² As we have already mentioned, obesity induces alterations in ventilatory mechanics, such as the decrease in lung volumes and the reduction

of the diameter of the small airway,¹¹ both of which are conditions capable of generating a tendency towards bronchoconstriction and bronchial hyperreactivity and, in absence of these, generating an increase in the sensation of dyspnea. In the same manner, other conditions that frequently complicate obesity, such as gastroesophageal reflux and sleep respiratory disorders, represent confounding factors. Another of the hypotheses is based on the inflammatory context that accompanies obesity. It has been well-documented that adipose tissue has immune functions and that obesity is accompanied by a state of systemic inflammation.⁴³ Excessive adipose tissue produces cytokines, some of which (TNF- α , IL 6, IL10, exotoxin) have been implicated in the inflammatory response in the airway of asthma patients.⁴⁴ Two substances in particular, specifically produced by adipose tissue, seem to have greater importance. The first, leptin, which has a similar structure to IL-6, plays a fundamental role in the inflammation in these subjects by regulating the levels of other cytokines and the proliferation and activation of T lymphocytes and monocytes.⁴⁵ It has been associated with an increase in bronchial inflammation in animal models, increased levels of other cytokines and immunoglobulin E, as well as the bronchial hyperreactivity to certain allergens.⁴⁶ The second, adiponectin, seems to have opposing effects but it has the particularity of being the only adipose hormone whose levels are lower in obese patients, which suggests a potential role in the genesis of asthma in these patients.⁴⁷

A third potential mechanism refers to an increase in bronchial hyperreactivity in obese subjects. However, in this aspect, the results published are contradictory and the majority of studies refute this hypothesis.⁴⁸⁻⁵⁰

Last of all, two additional hypotheses have been proposed to explain this association: the first postulates a potential activation of common genes that codify the predisposition to both diseases. In favor of this hypothesis, specific regions of the genome have been identified that are related with asthma as well as obesity (e.g. chromosomes 5q, 6 and 12 q⁴²). The second favors an eventual hormonal influence, which would explain the aforementioned increase of this association in the female population.⁴²

In summary, there are robust epidemiological data that confirm the connection between obesity and asthma. However, this relationship seems complex and multifactorial, while the exact mechanism or mechanisms to explain it still have not been clarified.

Sleep Apnea, Obesity and Hypoventilation

Sleep apnea-hypopnea syndrome (SAHS) is characterized by reiterated episodes of complete or partial obstruction of the upper airway (UA) during sleep, causing its fragmentation and associated daytime sleepiness.⁵¹ It is a frequent condition that affects 3-4% of the adult population,⁵² and obesity is its main risk factor. Two-thirds of SAHS patients are obese.⁵³ On the other hand, more than half of the morbidly obese population present SAHS.⁵⁴ One explanation is that obese subjects, particularly those with trunk obesity, present an increase in adipose tissue deposits in the soft palate, the tongue and the posterior and lateral wall of the oropharynx. This increase reduces the pharyngeal area, increases the extraluminal pressure and modifies the collapsibility of the UA. In addition, with the alteration of the elastic characteristics of the lung secondary to the reduction of the lung volume, the tendency towards collapse increases.⁵⁵ Last of all, some frequent comorbidities in these patients, such as diabetes, can cause a neuropathy of the pharyngeal dilating muscles favoring the appearance of apnea.⁵⁵ Closing a vicious circle, recent hypotheses also suggest a potential contribution of SAHS in the perpetuation of obesity in these patients. The mechanisms involved could be diverse. First of all, daytime sleepiness can translate into reduced daytime activity with the consequent reduction in

metabolic consumption. In this sense, Basta et al⁵⁶ recently demonstrated that there is a close correlation between the apnea-hypopnea index (AHI) and the degree of daytime activity. An alteration in the glucidic metabolism has also been demonstrated and that even the reduction of delta sleep on one hand and the repeated episodes of sympathetic activation as a consequence of apnea on the other hand can produce a state of insulin resistance. This mechanism would explain the greater propensity towards diabetes of these subjects.^{57,58} This leads one to believe that the correction of sleep apnea may have a beneficial effect on weight loss in these patients, but this has not been demonstrated.⁵³

Differences between Obesity Hypoventilation Syndrome and Obstructive Sleep Apnea-Hypopnea Syndrome

Obesity hypoventilation syndrome OHS is commonly defined as the combination of obesity (BMI > 30 kg/m²) and daytime hypercapnia (PaCO₂ > 45 mmHg).³⁰ It is postulated that OHS is no more than an advanced evolutionary stage of SAHS. However, the exact relationship between these two conditions, and in particular the contribution of SAHS to the appearance of hypercapnia, is not clear. There is even controversy in the definition of OHS in such a way that some authors suggest that SAHS should form part of the definition of OHS, while others consider them separate entities.^{59,60}

The former base their reasoning on the similarities between both conditions. In the first place, 90% of hypercapnic obese subjects present SAHS,^{23,24} while 11 to 15% of the obese patients with SAHS present hypercapnia, which rises to 23-27% when the BMI is > 40.²³ SAHS as well as obesity are considered chronic inflammatory states associated with increased cardiovascular risk.⁵⁵ On the other hand, like BMI, SAHS is more frequent in obese hypercapnic patients than in the non-hypercapnic ones. Lastly, hypercapnia is more frequent in patients with SAHS than in normal controls paired for age and sex, and also in obese SAHS patients compared with non-obese ones.⁵⁴

The appearance of hypercapnia in SAHS could be explained as a consequence of an inadequate post-apnea ventilatory response. This would reflect the incapacity of the respiratory muscles to deal with the greater load due to the increased UA resistance.^{61,62} A significant increase in the resistance of the UA and in the ventilatory effort have been demonstrated in the decubitus position in hypercapnic SAHS patients compared with non-hypercapnic ones, which becomes even more significant in the presence of obesity.^{63,64} In fact, it has been observed that the value of PaCO₂ in hypercapnic subjects with SAHS is directly proportional to the ratio between the duration of apnea and the interapnea period ("apnea/interapnea ratio") and inversely proportional to the magnitude of the post-apnea ventilatory response.^{61,62} Hypercapnia would be a consequence of an imbalance between the hypoventilation generated by the apnea and the compensatory hyperventilation. On the other hand, this reduction of the post-apnea ventilatory response may not be the consequence of a dysfunction of the respiratory muscles, but may instead represent an adaptation directed at preserving the quality of sleep, avoiding the micro-awakenings motivated by the inspiratory overexertion, therefore the OHS would correspond with an "advanced degree" of SAHS. In agreement with this hypothesis, a recently-published study demonstrated, in a group of patients with diagnosis of "pure" OHS (in whom polysomnography (PSG) had initially eliminated the diagnosis of SAHS), the appearance of obstructive apnea after the correction of the alveolar hypoventilation.⁶⁵ The hypothesis of the authors is that the non-invasive ventilation (NIV), in restituting the sensitivity of the respiratory center to CO₂, could unmask the primitive mechanism of the hypoventilation, this being SAHS.

Other authors reject this identity between SAHS and OHS. Their argument is that OHS is defined by the presence of hypercapnia in an obese subject after the exclusion of other causes of respiratory insufficiency, included among them SAHS, given that this conditions

can *per se* determine hypercapnia.⁶⁰ This leads them to postulate the hypothesis of two independent mechanisms (but at the same time interdependent) for the production of hypercapnia in these subjects: one dependent on obesity and another on apnea.

In summary, in obese subjects the development of hypercapnia depends on the relative balance between severity of the obstructive events of the UA and the importance of the non-apneic hypoventilation. In this manner, these patients could be divided into two subgroups: those with coexistence of SAHS and those without SAHS. Thus, it seems more logical not to include SAHS within the entity of OHS and to restrict this appellation to subjects in whom the only mechanism responsible for hypoventilation is obesity itself and to those in whom hypercapnia persists after correcting sleep apnea using regular CPAP treatment.⁶⁰ It has been proposed to modify the denomination of OHS, coining the following terms: obesity-linked hypoventilation (OLH),⁶⁰ sleep hypoventilation syndrome (SHS)³⁰ or OHS without SAHS.⁶⁶ This entity would be defined in two situations: a) presence of hypercapnia in an obese subject without SAHS or COPD ("pure" OLH, "pure" SHS or OHS without SAHS); and b) persistence of hypercapnia in obese patients with SAHS despite treatment with CPAP, (OLH combined with SAHS, SHS combined with SAHS or OHS with SAHS).

The Role of Leptin: A Hormonal Explanation for Hypoventilation?

As has already been mentioned, the ultimate cause for why some obese individuals develop hypoventilation and others do not is still unclear. In recent years, studies have analyzed the possible role of leptin, a hormone produced mainly by adipose tissue. Leptin, whose receptors are found mainly in the hypothalamus, is involved in several physiological actions.^{67,68} Nevertheless, its main action seems to be found in the regulation of body weight. It has been observed that its levels in plasma correlate with the adipose mass⁶⁹ and would function as a negative counterregulatory system, activating specific receptors that lower appetite and increase the energetic output.⁶⁷ Recent research also suggests a role of leptin in ventilatory control. Experiments in mice with a genetic deficit of leptin showed a marked alteration in ventilatory control with development of respiratory insufficiency.⁷⁰ This dysfunction of the ventilatory control worsens during sleep and particularly during the REM period. In addition, these animals present a modification in the characteristics of myosin, which makes the diaphragm less resistant to fatigue.⁷¹ These modifications do not appear in the animals without congenital deficit of leptin and in whom obesity is induced artificially. Moreover, they revert after the administration of leptin.

It has been postulated that leptin would play a similar role in the genesis of OHS in males in such a manner that if, physiologically, high levels of this hormone in obese subjects stimulated the respiratory centers in response to the increase in the ventilatory load, a deficit of leptin could be the key in the development of OHS. However, the deficit of leptin in obese humans is extremely rare, and, on the contrary, high circulating levels of said hormones have been verified. Thus, it could be suggested that hypoventilation would result in said subjects from a state of resistance to leptin.⁷² Given that leptin exerts its ventilatory action through hypothalamic receptors, it has been speculated that said "leptin-resistance" could be due to an anomaly in the transport of leptin to the CNS or to an alteration at the level of the central receptor.⁷³ In favor of the first hypothesis, it has been demonstrated that leptin CSF/plasma ratios fall as BMI rises,⁷⁴ which would advocate a saturation of the transport system to high levels of circulating leptin.

Some data of the literature support the role of leptin in the control of the ventilation of obese patients. It has been seen that the level of leptin better predicts the presence of OHS than BMI,⁷⁵ regardless of the existence or absence of apnea during sleep.

Furthermore, in these patients, NIV treatment corrects the high levels of leptin, postulating that, in correcting hypoventilation, the need would be reduced for high levels of leptin to fight against the greater ventilatory load.⁷⁶

Much greater is the evidence relating leptin with SAHS. It has been demonstrated that intermittent hypoxemia is a powerful stimulant for the release of leptin, regardless of the level of obesity.⁷⁷ This may explain why, with the same body weight, SAHS patients have higher levels of leptin than individuals without SAHS,⁷⁸ likewise for the correlation found between the levels of leptin and the severity of SAHS measured in terms of the apnea-hypopnea index.⁷⁹

Closing a circle, the high levels of leptin will favor the centripetal distribution of body fat, with its characteristic increase in fat deposits in the neck and in the airway region. This would favor the appearance of UA obstruction during sleep.⁷⁹ In fact, CPAP treatment, in addition to reducing the levels of leptin in SAHS patients,⁸⁰ also diminished the level of body fat in said patients.⁸¹ Lastly, in patients with SAHS, levels of leptin have been observed to be significantly higher in hypercapnic than in non-hypercapnic patients, and this is regardless of BMI.⁸² These findings could suggest that the anomalies in the metabolism of leptin would constitute the union nexus between the two most relevant respiratory complications in obesity: SAHS and OHS, which in both cases are related to conditions associated with leptin resistance (fig. 1).

In brief, it can be said that there are hypothetically two types of obese subjects with risk for developing respiratory anomalies: the rare cases of patients with "true" leptin deficit (with low levels in plasma and CNS) and those, much more frequent, with high levels of leptin in plasma but proportionally low in CSF. This hypothesis once again establishes an important nexus between SAHS and OHS but, at the same time, it opens a fascinating pathway: the possible role of the analogous potential of leptin capable of crossing the hematoencephalic barrier in the management of the respiratory consequences of obesity.

Sleep and Breathing in Obese Subjects

Sleep constitutes the quintessential period of fragility of the respiratory system and it aggravates the two mechanisms responsible for respiratory insufficiency in obese subjects. Supine decubitus increases the V/Q alteration, worsening hypoxemia. As for hypoventilation, all its potential trigger mechanisms reach their maximum expression at night. The ventilatory control depends on three mechanisms: the first, with a bulbar location and automatic in nature, causes the maintained continuity of the ventilation and ensures homeostatic adaptations. The second, with a suprapontine location, corresponds with conscious, voluntary control. In addition to this, there is the ventilatory stimulus of wakefulness itself, depending on the activation of the ascending reticular activator system. These last two mechanisms are abolished during sleep. Consequently, ventilatory control in this period is exclusively due to the automatic control mechanisms dependent on the metabolic afferences (in particular pCO₂) and on the stretch receptors. In addition, as mentioned beforehand, the respiratory center presents an inappropriate response to CO₂ in an important percentage of these patients.^{25,26} To this, we must add the potential appearance during sleep of apnea and hypopnea episodes and the increase in the ventilatory load as a consequence of the decubitus position, both situations capable of favoring the development of hypercapnia.

When PSG is done on an obese subject, 5 different types of ventilatory disorders can be identified^{28,83} (table 2): obstructive episodes of the UA, apnea and central hypopnea, central hypoventilation (also called "sleep hypoventilation"), "obstructive" hypoventilation and, last of all, episodes of hypoxemia secondary to V/Q imbalance. These anomalies can be revealed by nighttime

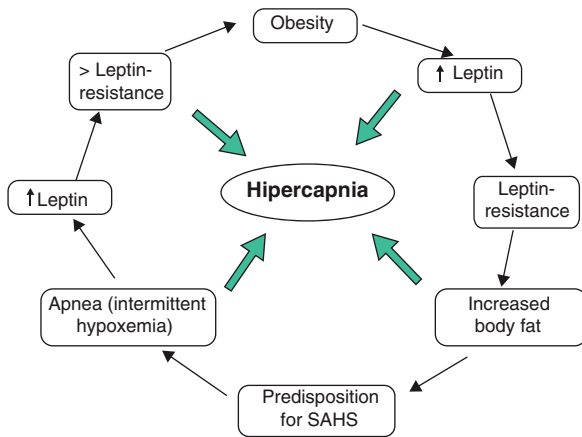


Figure 1. Leptin and hypoventilation in obese subjects. Probable physiopathological interactions.

oximetry, seen as peaks of desaturation in the first two cases, and as continuous desaturation in the remainder. With continuous desaturation, the parallel development of hypercapnia differentiates between both types of hypoventilation of worsened hypoxemia due to V/Q alteration. The episodes of central hypoventilation are the consequence of a decrease in the ventilatory impulse induced by sleep, especially in REM phase.²⁸ This stage is characterized by generalized muscular hypotonia, but with preservation of the diaphragm activity. As has been mentioned before, there is evidence that muscle strength and resistance of the diaphragm are lower in obese subjects, which favors the appearance of hypercapnia. As for obstructive hypoventilation, this corresponds to sustained periods of reduced ventilation due to partial obstruction of the UA.⁸³ Both types of hypoventilation can be differentiated by ventilatory polygraphy with the analysis of the flow curve: while central hypoventilation is characterized by a reduction in the flow amplitude, conserving a rounded aspect ("non-limited" flow) accompanied by a proportional decrease, in phase, of the amplitude of the thoracoabdominal bands, obstructive hypoventilation is characterized by an aspect of inspiratory flow limitation ("on plateau" aspect) accompanied, in general, by a phase contrast in the thoracoabdominal bands. The identification of the two patterns has therapeutic value as, while central hypoventilation requires ventilatory support, in the case of the obstructive pattern it may be enough to increase the levels of continuous positive airway pressure (CPAP) (or positive expiratory pressure (PEP) in the case that the patient is under bi-level pressure ventilation).⁸³

It should be kept in mind that somnolence can be present in the absence of sleep respiratory disorders in up to 35% of obese subjects, which underlines the probable role of obesity *per se* in the genesis of daytime sleepiness disorders present in this population.^{28,54}

Diagnosis of Respiratory Insufficiency in Obese Subjects

The clinical manifestations of hypoventilation depend on numerous factors: the degree of obesity, the presence of comorbidity like COPD and SAHS and, of course, on the degree of hypoventilation.

In spite of the characteristic nature of a large obese person with hypoventilation, improper diagnosis is frequent. In a cohort study at a general hospital, 31% of patients with BMI > 35 hospitalized for different reasons, presented hypoventilation that went unnoticed and almost half of the patients with a BMI > 50 presented daily hypercapnia.⁸⁴

In general, the diagnosis of hypoventilation in obese subjects is frequently suspected in two situations: in the course of an

Table 2

Classification of the ventilatory disorders during sleep in obese subjects

Obstructive apnea and/or hypopnea
Central apnea
Continuous desaturation in oxygen
With nocturnal hypercapnia
Central hypoventilation ("sleep hypoventilation")
"Obstructive" hypoventilation
Without nocturnal hypercapnia
Worsened V/Q imbalance

For details, refer to the text.

exacerbation or during the study of a possible SAHS. As for the exacerbation, it is considered OHS in an obese patient who, in presence of a banal respiratory infection, develops a disproportionate situation of respiratory insufficiency. The diagnostic confirmation requires arterial blood gas, complete functional exploration and PSG. With regards to the second situation, OHS can go left unnoticed if arterial blood gas is not studied, although it may be suspected given the appearance of lower O₂ saturation. This is also true if "normal" SaO₂ does not eliminate the possibility of nocturnal hypoventilation, particularly in patients without subjacent bronchopulmonary pathology.⁸⁵

As for early detection, in the absence of daytime hypercapnia, an excessively high baseline can be evidence of a nocturnal hypoventilation, especially if there is also SAHS.²⁴

Treatment of Respiratory Complications in Obese Subjects

Weight loss is the first therapeutic measure in the management of obese patients. A loss of 5 to 10% of body weight can improve lung function tests. Ventilatory mechanics, PaO₂ and PaCO₂ in the presence of SAHS can dramatically reduce AHI.^{13,55} In the case of asthma, weight loss has a relevant effect on the reduction of dyspnea, the number of asthma attacks and the improvement in the quality of life in these patients, while improving the obstruction of the small airway.⁸⁶ It has been estimated that between 15 and 38% of the cases of adult asthma could be prevented with obesity-control measures.⁸⁷ However, weight loss by means of dietary measures is usually difficult to achieve. Bariatric surgery can change the respiratory prognosis in these patients. Recent data indicate that it is associated with a significant long-term improvement in lung volumes, arterial gases, polycythemia, pulmonary hypertension⁸⁸ and asthma control.⁸⁹ It also contributes to a partial or total improvement of SAHS.⁹⁰

Bariatric surgery carries far from negligible risk of perioperative morbidity and mortality in OHS patients,⁹¹ and it is recommended to initiate non-invasive ventilatory assistance before surgery, which should be maintained after extubation in order to reduce the perioperative complications. One must also keep in mind the recurrence of obesity between 3 and 7 years after surgery.⁹²

Treatment of Respiratory Insufficiency

Regardless of the measures aimed at weight control, the therapeutic management of these patients makes it necessary to use ventilatory support techniques. Its objective is to correct at the same time the sleep respiratory disorders and daytime hypercapnia, but also the residual hypoxemia that usually persists after the correction of alveolar hypoventilation. The initial therapeutic management of these patients depends on the clinical situation of the patient and on the PSG results.

In the case of acute respiratory insufficiency, and with the exception of situations of immediate vital risk (shock, severe encephalopathy, multiorgan failure), NIV should be considered as a

first-line treatment in the management of the ventilatory failure in these patients.⁶³

Currently, the respirators most commonly used for the ventilatory management of these patients are barometric, while the support pressure mode + PEP, or ventilation with "bi-level" positive pressure, is the mode most often used. There is frequently an initial requirement for the addition of supplementary oxygen in order to maintain adequate SaO₂. The management of these patients can be done in a respiratory critical care unit, in an intermediate care unit or in a hospital ward, depending on the severity of the symptoms, the possibilities of the health-care center and the experience and skills of the medical team in managing NIV.^{93,94} Once the clinical condition is established, these patients will be treated under the most adequate ventilatory mode based on the results of the EFR and PSG.⁹⁵

In the case of hypercapnic patients diagnosed in stable situation (absence of acidosis), the election of the initial ventilatory mode depends on two factors: co-existence or absence of SAHS and on the severity of hypercapnia. If PaCO₂ is < 50 mmHg and PSG confirms the diagnosis of SAHS, most authors agree on starting with CPAP treatment. In addition to correcting apnea, the therapy can restore daytime normocapnia. However, in a significant number of patients, hypercapnia persists despite an adequate CPAP treatment. In said cases, it should be assumed that hypercapnia responds to a mechanism other than SAHS, which is obesity *per se* that perpetuates hypoventilation. Said patients require support that is able to increase ventilation instead of simple stabilization of the UA, and in said case it is logical to propose the addition of inspiratory assistance, meaning change to NIV.⁹⁶

In patients with PaCO₂ > 50 mmHg, the initial therapy should be oriented towards NIV. Once eucapnia is reached, however, it is recommendable to perform diagnostic PSG and, if there is treatable SAHS, to initiate CPAP. It has been demonstrated that more than one-third of patients initially treated with NIV can be transferred to CPAP with good long-term control.^{97,98}

Despite this proposed treatment algorithm, predicting which patients will respond to CPAP and which will need ventilatory assistance is frequently difficult. In some series, predictive factors for insufficient response to CPAP have been identified, including: the presence of high BMI, a more severe restrictive syndrome, a greater degree of nocturnal hypoxemia and higher levels of PaCO₂.⁹⁸⁻¹⁰⁰ This shows the multifactorial character of hypercapnia and reflects the relative contribution of the different physiopathological mechanisms.

In patients in whom PSG does not show significant SAHS, NIV is the first-choice therapeutic treatment. In these cases, hypercapnia should be considered secondary to obesity *per se*, but additional causes (e.g. COPD) should be investigated.

There is a small subgroup of patients in whom NIV with pressure support is not able to correct hypoventilation. This situation can require the use of volumetric respirators. Lastly, in exceptional situations in which NIV is ineffective, tracheotomy may be required.

The compliance with therapy and the personalized choice of the ventilator parameters, based on the particular physiopathology of each case, condition the success of NIV in these patients.

As for the optimization of NIV, it should be based on the knowledge of the physiopathological mechanisms and requires adequate monitoring, including at least recordings of nocturnal SaO₂ under ventilation coupled with the control of nocturnal PtcCO₂,¹⁰¹ and periodic arterial blood gas. Ideally, PG or PSG should be done under ventilation.¹⁰² Such monitoring will determine the PEP levels necessary for correcting apnea, the adequate support pressure in order to reach normocapnia and, if there is persistent hypoxemia with a mechanism other than hypoventilation, the need for oxygen therapy. In figure 2, an algorithm is proposed for the ventilatory management of these patients.

A fundamental aspect that should be considered is related to the mechanisms by which NIV, as well as on numerous occasions CPAP, applied at night are able to correct daytime hypoventilation of obese patients. Some authors, although not all, indicate that the correction of nocturnal ventilatory anomalies in these patients can normalize the sensitivity of the chemoreceptor to CO₂.^{28,103,104} On the other hand, the improvement in lung volumes, thoracopulmonary compliance and the efficacy of the respiratory muscles can be adjuvant mechanisms and it is well-known that CPAP as well as NIV can reduce inspiratory effort in these patients.^{103,105}

In addition to the improvement in blood gas, it is fundamental to improve the quality of sleep, already altered in these patients. In this regard, the data are not conclusive because at least one study by Chouri-Pontarolo et al²⁸ revealed that although NIV reduces the number of micro-awakenings related with respiratory events, the number of non-respiratory micro-awakenings increased.

Treatment of Asthma

Published data indicate that obesity is associated with more severe forms of asthma and that the presence of obesity can modify the response to treatment in asthma patients.¹⁰⁶ This can be explained by the different tissue bioavailabilities of different medications in these patients. Another hypothesis is that some of the cytokines produced by the adiposities produce a relative state of corticosteroid resistance.¹⁰⁷ Obese subjects require a more intensive treatment of asthma and more frequently require emergency department services.⁴¹ A recent study showed that a BMI > 31 compared with one of 22-25 increased the use of bronchodilators in 94%.¹⁰⁸

To summarize, although the base treatment of asthma in these patients does not vary, its management is more difficult and can require greater doses of anti-inflammatory drugs for an adequate control.

Respiratory Complications in Obesity: the Challenge

Today, the diagnosis and treatment of respiratory complications in obese subjects represent a new challenge for health-care systems. A national survey in Spain published in 2000 reported that 15% of patients on NIV were in the long term diagnosed with OHS.¹⁰⁹ Furthermore, several epidemiological studies that were recently published corroborate that hypoventilation in obese patients and COPD are the two most frequent indications for prescription of NIV, both in acute as well as in stable state.^{96,110-112}

Several factors explain this behavior:

- The marked increase in the prevalence of obesity.
- The greater understanding of obesity as a cause of respiratory disease.
- The physiopathology of hypercapnia related to obesity, which entails factors susceptible to being controlled with NIV.
- The efficacy of NIV in the control of the gasometric alterations of obese subjects.

Various studies have confirmed that NIV as well as CPAP over the long-term reduce the number of hospitalizations while improving clinical symptoms, quality of life and survival in acute state as well as at 5-years in this population.^{84,96,97,112,113} Therefore, maintaining long-term ventilatory support in these patients is essential in most cases in order to maintain normocapnia and clinical stability.

As the progressive increase of obesity in the western world has reached the point where it may be considered an epidemic, it is necessary to continue the research directed at clarifying the pathogeny of respiratory insufficiency in obese patients and foresee the health-care resources necessary to ensure the correct attention of these patients, including NIV.

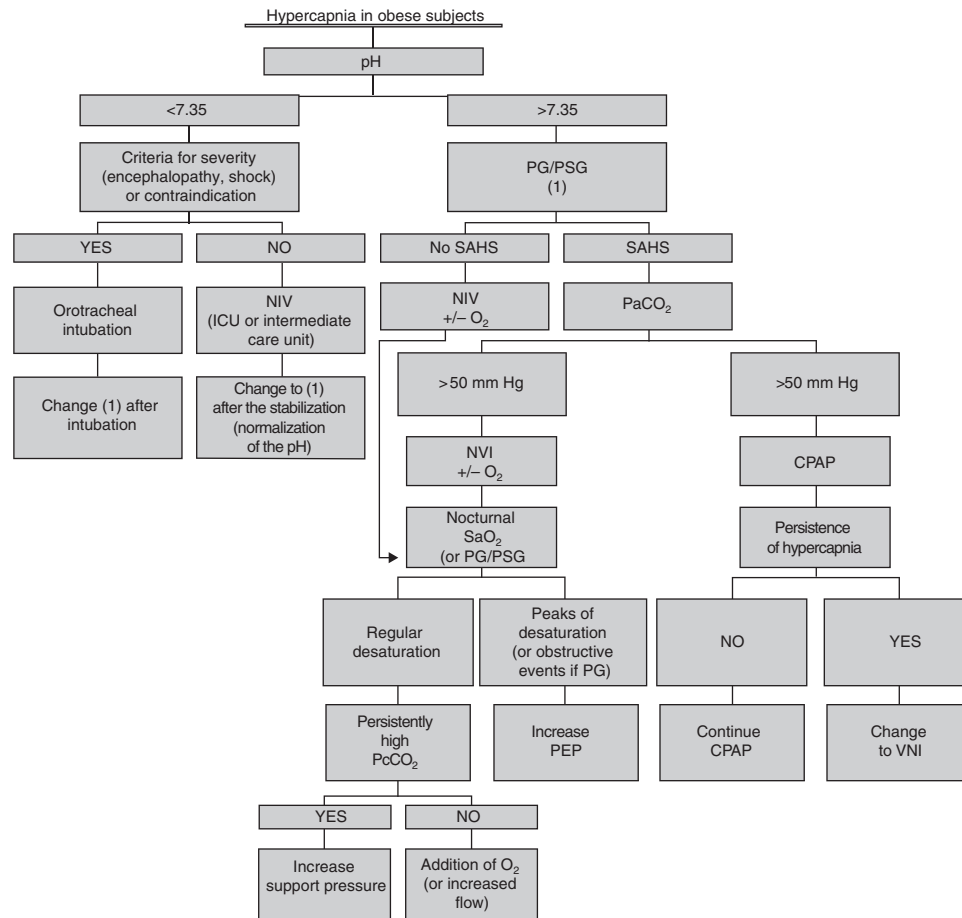


Figure 2. Management algorithm for hypercapnia in obese patients. CPAP: continuous positive airway pressure; NIV: non-invasive ventilation; OLH: obesity-linked hypoventilation; PSG: polysomnography; SAHS: sleep apnea-hypopnea syndrome; SRBD: sleep-related breathing disorder. Modified from Rabec et al,¹⁴ with permission.

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