Leptin, Obesity, and Obstructive Sleep Apnea

The United States has the notable distinction of having the highest concentration of obese individuals in the world, with a staggering 55% of the adult population being overweight. The body mass index (BMI; weight in kilograms divided by the square of height in meters) is widely used to distinguish between obese and nonobese adults. Overweight is defined as a BMI measure of 25.0 to 29.9 and obesity as a BMI measure of 30.0 or greater. Excess weight is a major health hazard, with the risk of death from all causes, cardiovascular disease, and cancer increasing throughout the range of moderate and severe overweight for both men and women in all age groups. In recent years, body circumference indexes (e.g., waist circumference, waist-to-height circumference ratio, waist-to-hip circumference ratio) have been advocated because they can identify adults with a central (android) pattern of obesity, who are at higher risk of obesity-related health problems, independent of the BMI.

Excess body fat has several effects on the respiratory system—most notably, a decline in the respiratory reserve volume and an increase in the FEV₁/FVC ratio. The vital capacity (VC), total lung capacity (TLC), and functional residual volume (FRV) are generally maintained in otherwise normal individuals with mild-to-moderate obesity but are reduced by up to 30% in morbidly obese patients. The work of breathing (WOB) is increased by abnormal chest elasticity, increased chest wall resistance, increased airway resistance (Raw), abnormal diaphragmatic position, and upper airway resistance, as well as by the need to eliminate a higher daily production of carbon dioxide. Severely obese patients are often hypoxemic, with a widened alveolar-arterial oxygen gradient, caused primarily by ventilation-perfusion (V/Q) mismatching. In addition, obesity is a major risk factor for the development pulmonary thromboembolism.

The obstructive sleep apnea (OSA) syndrome OSA is a disabling condition characterized by excessive daytime sleepiness, disruptive snoring, repeated episodes of upper airway obstruction during sleep, and nocturnal hypoxemia. OSA occurs in 4 to 9% of middle-aged men and in 1 to 2% of middle-aged women. Obesity is a major risk factor for OSA, occurring in up to 50% of obese men. The etiology of obesity is heterogeneous, with several factors having the potential to cause a positive energy balance over long periods. These factors include a high-fat diet, a low level of habitual physical activity, a low resting metabolic rate for a given body mass and body composition, a high respiratory quotient in the fasting state (i.e., a tendency to oxidize more carbohydrates than lipids under standardized conditions), and perhaps high insulin sensitivity. Interest in the pathophysiology of obesity has recently intensified with the discovery of leptin, the anti-obesity hormone. Leptin, a protein of 167-amino acids, has a structure similar to that of cytokines. The hormone is produced predominantly in white adipose tissue. Leptin levels increase exponentially with increasing fat mass. Leptin circulates in the plasma in a free-form state or bound to leptin-binding proteins. Leptin acts by binding to specific receptors in the hypothalamus to alter the expression of several neuropeptides that regulate neuroendocrine function, energy intake, and expenditure. Leptin inhibits the synthesis of hypothalamic neuropeptide Y (NPY), a potent stimulator of food intake. In addition, downregulation of NPY results in increased sympathetic nervous system outflow and energy expenditure. Furthermore, increasing leptin levels activate the thyroid, growth hormone, and gonadal axes and suppress the pituitary-adrenal axis. Leptin also has an effect on peripheral tissues. Leptin directly inhibits intracellular lipid by reducing fatty-acid and triglyceride synthesis and, concomitantly, by increasing lipid oxidation. This effect on lipid metabolism may be mediated by an inhibitory effect of leptin on acetyl-CoA carboxylase activity, the rate-limiting enzyme in fatty-acid synthesis.

Most obese subjects have high circulating leptin levels, indicating that, in most circumstances, obesity is a leptin-resistant state. Much like type II diabetes, it is possible that receptor or post-receptor defects could be responsible for leptin resistance in obese subjects. Treatment with subcutaneous leptin re-
roduces weight in all mammalian species tested.\textsuperscript{22} Leptin-induced weight loss is completely specific for loss of adipose tissue, whereas food restriction results in loss of both adipose tissue and lean body mass.\textsuperscript{22} Furthermore, in animal studies leptin selectively decreases visceral adiposity.\textsuperscript{23} Despite the demonstration of leptin resistance in most obese humans, subcutaneous recombinant leptin induces a significant dose-dependent reduction in fat mass and weight loss in these subjects.\textsuperscript{24} Mutant obese C57BL/6-J-Lepob mice, which lack circulating leptin, exhibit respiratory depression and elevated PaCO\textsubscript{2}.\textsuperscript{25,26} An infusion of leptin into these animals markedly increases minute ventilation (VE) across all sleep/wake states and improves lung mechanics.\textsuperscript{25,26} These studies suggest that both obesity and OSA may be due to leptin resistance. In this issue of \textit{CHEST} (see page 580), Ip and colleagues have demonstrated that obese subjects with OSA have significantly higher levels of leptin when compared with weight-matched BMI controls. Interestingly, subjects treated with nasal continuous positive airway pressure (nCPAP) for 6 months demonstrated significant reductions in circulating leptin levels. This supports the findings of Chin and colleagues who, in addition to demonstrating a fall of leptin levels with nCPAP, demonstrated significant reductions in visceral fat accumulation.\textsuperscript{27} This raises the intriguing possibility that treatment of OSA with nCPAP may reverse the leptin receptor abnormality found in this disorder. This would suggest that nCPAP, as well as exogenous leptin agonists or agents that restore leptin receptor sensitivity, may have roles in reversing the primary pathophysiologic abnormalities of the obesity-OSA syndrome.

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Nasal Dilation, Sleep, and What Is Hypopnea?

The role of nasal resistance in the occurrence of snoring and obstructive sleep apnea hypopnea syndrome (OSAHS) has been a matter of speculation for years. In 1988, it was reported in a study of 16 patients that the use of a plastic internal nasal dilator (Nozovent; Prevancure; Frölunda, Sweden) improved airflow by approximately 25%. It was speculated that such a device could decrease the volume of snoring and the degree of OSAHS severity.

In the following years, the inventor of the device and his teams of investigators published five studies supporting that contention. Four of the studies reported purely or mostly subjective data, a fifth study reported objective data regarding the effect of the device on OSAHS. Unfortunately, all of these studies shared design weaknesses that left their findings far from conclusive. Still, the studies suggested that the dilation of the nasal valve could be beneficial for snorers and those with OSAHS, and other investigators were sparked to examine those possibilities.

Studies have clearly verified that the placement of the Nozovent device increases the cross-sectional area of the nasal valve (the nasal valve is the narrowest segment of the nasal cavity, found at the junction of the upper and lower lateral nasal cartilages) and lowers nasal resistance. Most awake patients perceive improved nasal airflow that is similar to the effect of a topical decongestant. Still, the sleep-related findings of the initial investigators had not been verified. In 1992, two Canadian studies using the Nozovent device appeared that included nocturnal polysomnographic data. While the details of these data were minimal in one of the studies, both of these investigators verified the aforementioned increase in nasal patency, but could not demonstrate any change in apneas or hemoglobin saturation associated with use of the nasal dilator. Only one of the studies looked at snoring and it reported no change. The original investigators had reported that people who use Nozovent felt an improvement in sleep quality. One of these Canadian studies indicated about a 20% decrease in nocturnal arousals that they believed might account for that perception of an improvement in sleep quality.

In this issue of CHEST, Schönhofer et al (see page 587) examined the effect of the Nozovent device on 26 consecutive subjects with OSAHS. Their study included a more rigorous objective investigation of the effect of the Nozovent device with nocturnal polysomnographic conditions that were well defined using a standard montage that included inductive plethysmography. Their subjective outpatient snoring data were based on a standard 5-point system, and perceived excessive daytime somnolence was estimated by the Epworth Sleepiness Scale (ESS). Mild to severe OSAHS patients were represented.

The study found no improvement in apnea frequency, snoring, oxygen saturation, or sleep parameters. A minimal improvement in the ESS score was noted; in 25 patients, no change or only a mild decrease in snoring was estimated by the bed partner.

This totals three independent investigations that have been unable to verify the findings of the original investigative teams. These independent studies appear to be better designed, with this most recent being very well done. We must strongly consider the possibility that the original reports may be incorrect. It may be that only a few patients derive significant objective benefit from the Nozovent device. So far, no way to identify those few patients has been found.

During the review process, the authors’ use of the traditional definition of hypopnea was questioned (a ≥ 50% reduction in the amplitude of oronasal airflow from baseline lasting at least 10 s, associated with a decrease in O2 saturation of ≥ 4%). It is true that thermal sensors detect apnea well, but exhalations of 50 to 500 mL (hypopneas) might not exhibit enough variance in temperature to accurately indicate a decrease in volume. The decision to add a decrease in O2 saturation to the definition has helped ensure that hypoventilation has actually occurred. However, if that definition were applied in the clinical practice of sleep medicine, scores of patients might be sent home without treatment for what is obvious OSAHS.

It may be time to reevaluate the “standard” definition of hypopnea. Certainly O2 desaturation is a helpful adjunct when interpreting a reduction of the thermal oronasal airflow tracing, but the consideration of the following occurrences may also be helpful: (1) associated arousal, (2) concurrent crescendo snoring (in the snore-sensor graphic output channel), (3) associated decreases from baseline...