inary results in CABG patients [abstract]. Anesthesiology 1998; 89:A543
10 deBoisblanc BP, McClarity E, Lord K. Oxygen consumption in the intensive care unit: indirect calorimetry is the way to go, but where? Crit Care Med 1998; 26:1153–1154
33 Marik PE. Sublingual capnography: a clinical validation study. Chest 2001; 120:923–927
37 Connors AF, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 1996; 276:889–897

A Waist Is a Terrible Thing to Mind

Central Obesity, the Metabolic Syndrome, and Sleep Apnea Hypopnea Syndrome

In this issue of CHEST (see page 829), Schäfer and colleagues report on a consecutive sample of men who had been referred for suspected sleep apnea-hypopnea syndrome (SAHS) and were subjected to overnight polysomnography, anthropomorphic measurements reflecting obesity and body fat distribution, and blood testing for various cardiovascular risk factors as well as the measurement of serum leptin levels. They found significant associations between
apnea-hypopnea index (AHI) and the following: body weight, body mass index (BMI), the sum of fat skin folds, and the percentage of body fat; levels of fasting blood glucose, uric acid, and fibrinogen; and leptin levels. The correlation of AHI with leptin levels disappeared when it was corrected for collinearities with indexes of obesity. The authors found no correlation between AHI and hypertension, smoking, age, and dyslipidemia. These data comprise the latest contribution to an expanding literature relating sleep-disordered breathing with the so-called metabolic syndrome, a constellation of obesity and metabolic abnormalities that are associated with increased cardiovascular morbidity. This increasing body of evidence suggests that the metabolic syndrome may be a “final common pathway” linking SAHS with vascular disease.

While many investigators have observed that insulin resistance (either impaired glucose tolerance or unambiguous type II diabetes mellitus) resulting in hyperinsulinemia, abdominal (central) obesity, atherogenic dyslipidemias, essential hypertension, and microalbuminuria frequently coincide in individual patients, it was not until 1988 that Reaven proposed that the co-existence of some of these disorders was not by chance but rather comprised what he termed “syndrome X.” He was even able to hypothesize a direction of causality, citing data that suggested the following: (1) that obesity, sedentary lifestyle, and genetic propensity can cause insulin resistance; (2) that insulin resistance results in hyperinsulinemia; (3) that hyperinsulinemia can provoke catecholamine excess and renal retention of salt and water, either or both of which can raise BP; (4) that hyperinsulinemia results in elevated hepatic very low-density lipoprotein (VLDL) triglyceride secretion and inversely correlates with high-density lipoprotein (HDL) cholesterol concentrations; and (5) impaired glucose tolerance, hypertension, and elevated VLDL triglyceride/reduced HDL cholesterol are all associated with increased atherogenesis and cardiovascular risk. Kaplan later suggested another mechanism by which hyperinsulinemia could provoke hypertension, by means of a direct effect on vascular smooth muscle. Since the name syndrome X had already been claimed 20 years earlier (describing patients with cardiac ischemia but angiographically normal coronary arteries), a variety of alternative appellations subsequently were brought forward, including the rather tame insulin resistance syndrome. More dramatic were “the deadly quartet” and “CHAOS” (Coronary artery disease, Hypertension, Adult-onset diabetes, Obesity, and Stroke). In 1998, an expert panel of the World Health Organization finally agreed on the term metabolic syndrome, and that name and the syndrome definition that they developed seem to have stuck. The published definition requires glucose intolerance and/or insulin resistance plus two or more of the following conditions: hypertension; elevated plasma triglycerides and/or reduced HDL cholesterol; central obesity; and microalbuminuria. Hyperuricemia or gout, increased low-density lipoprotein cholesterol or the prevalence of small, dense low-density lipoprotein particles, disorders of fibrinolysis, and activation of inflammatory mechanisms also have been identified as probable or possible components of the metabolic syndrome, but some remain controversial.

Teleologic considerations have given rise to the hypothesis that the metabolic syndrome is a remnant of evolutionary development under the pressures of a “feast-or-famine” existence. The theory holds that one or more “thrifty” genes emerged that act to conserve energy during times of famine. Examples of this include reducing thermogenesis or inhibiting pregnancy and lactation. The genotype also should enable the maximal storage of energy during times of plenty in the form of adipose tissue rather than glycogen since this type of energy storage provides more sustenance during periods of starvation. The thrifty genes thus afford a survival advantage when the food supply is highly variable. However, this theory holds that the survival advantages of the genotype become liabilities when energy supplies are abundant and remain so. The metabolic syndrome results, and survival is impaired. Several putative mediators have been identified in support of this theory. One of them is leptin, which is a 167-amino acid protein produced by adipocytes and a variety of other tissues. Leptin has been shown to suppress hypothalamic neuropeptide Y in mice, and, since neuropeptide Y stimulates appetite and thermogenesis, it is involved in a useful negative feedback mechanism. The ob gene has been identified as encoding for leptin, and the db gene as encoding for a hypothalamic leptin receptor in mice, and similar genes have been located in humans. Interestingly, mice that are heterozygous for defective ob or db genes live longer when fasted than do normal mice, thus demonstrating the kind of survival advantage necessary for a thrifty gene. Other possible mediators of the thrifty genotype are insulin receptor substrates (particularly insulin receptor substrate-1), phosphoinositide 3-kinase, hormone-sensitive lipase, endothelial lipoprotein lipase, mitochondrial uncoupling proteins, tumor necrosis factor (TNF)-α, glycogen synthase, and others.

As would befit the evolutionary pressure of a feast-or-famine existence lasting millennia as opposed to the constant abundance of (at most) the last few hundred years, metabolic syndrome is quite common. Most estimates place the prevalence of
The metabolic syndrome in nonobese individuals at 10%, and in obese subjects at > 50%. Moreover, research in certain isolated populations with now-steady food supplies suggests that the higher mortality and lower fertility of individuals with glucose intolerance has been selecting for individuals with the thrifty gene, as is demonstrated by a decline in the incidence of glucose intolerance. Not all is rosy in the land of the thrifty gene hypothesis, however. Several populations have been identified that are inordinately discordant for components of the syndrome. For instance, Pima Native Americans exhibit a very high prevalence of obesity and glucose intolerance, but a relatively low rate of dyslipidemia and hypertension. In addition, a factor analysis of data from the Cardiovascular Health Study suggested that body mass, glucose intolerance, dyslipidemia, and hypertension are independent, though overlapping, domains. The validity and objectivity of this analytic technique has been questioned, however.

The specific role of central obesity in patients with the metabolic syndrome also remains to be explained. The differentiation of obesity into two identifiable patterns dates back > 50 years, when Vague defined “android” and “gynoid” types based on measurements of skin-fold thickness at various body locations and drew some interesting correlations with disease prevalence. Modern medicine currently uses the terms central and peripheral for these patterns (apple and pear may be used by those botanically inclined) and waist-to-hip girth ratio (WHR), CT imaging, and MRI scans have been added to the diagnostic armamentarium. Central and peripheral obesity differ in the type of adipose tissue that accumulates. The more metabolically active brown adipocytes accumulate in central locations, while white adipocytes are found peripherally. In addition, many studies have confirmed the existence of a tighter correlation of central obesity with insulin resistance, dyslipidemia, hypertension, and atherosclerotic heart disease than for obesity without regard to pattern. A variety of theories have been proposed to explain this, including the increased production of various mediators by brown adipocytes (candidates include leptin and TNF-α), or increased lipolysis in abdominal adipocytes leading to excess free-fatty-acid transport to the liver. The mediators may reduce peripheral insulin sensitivity, or the free fatty acids may decrease hepatic insulin uptake, degradation, and sensitivity as well as affect peripheral insulin sensitivity. Of possible relevance is the fact that leptin levels decline after suction lipectomy of subcutaneous abdominal fat deposits.

The importance of the metabolic syndrome lies in its association with cardiovascular morbidity as well as other possible end-organ effects, such as nonalcoholic steatohepatitis. Although each of the components of the metabolic syndrome individually have been identified as risk factors for cardiovascular disease, an individual with three or more components is at particularly high risk. For instance, Wilson et al have reported a prospective analysis of the Framingham Offspring Study looking for cardiovascular events in 2,406 men and 2,569 women between the ages of 18 to 74 years. Gender-specific quintiles for baseline values of HDL cholesterol, triglycerides, total cholesterol, BMI, systolic BP, and glucose (as a surrogate for insulin resistance) were computed, and the lowest quintile for HDL cholesterol and highest quintiles for the other variables were used to compute the risk. Clusters of three or more risk factors occurred in 17% of the subjects. Fully 20% of the cardiovascular events in men and 48% of the events in women could be attributed solely to the clustering of three or more factors.

The metabolic syndrome has not escaped the interest of the sleep medicine community, and the article by Schäfer and coworkers in this issue of CHEST is but the latest in a series of reports. Early reports by Davies et al and Stoojs et al documented an increased prevalence of insulin resistance in small groups of subjects with SAHS, but differences in BMI accounted for the entire relationship. Similarly, Levinson and colleagues published a small study in 1994 that failed to detect a relationship between central obesity using WHR and severity of SAHS, although patients did tend to have higher WHR when compared to normative values. Strohl et al were able to demonstrate an association between hyperinsulinemia (as well as BP) and AHI independent of BMI in 386 men referred for polysomnography, and more recently, two relatively large prospective studies demonstrated a relationship between SAHS severity and insulin resistance that was independent of BMI. Ip and colleagues studied 270 consecutive nondiabetic patients (73% men) who had been referred for evaluation of suspected SAHS and found such a quantitative relationship for both AHI and minimum oxyhemoglobin saturation with insulin resistance. Central obesity (ie, the WHR) also was correlated with SAHS severity. Not unexpectedly, given the previous discussion, hypertension was significantly related to insulin resistance in their subjects. Punjabi and associates recruited 150 men with no history of diabetes, cardiac disease, or pulmonary disease and subjected them to polysomnography, oral glucose tolerance testing, and measurement of fasting insulin and lipid levels. They found a surprisingly high prevalence of SAHS, ranging from 40 to 60% depending on the value of AHI score used to define a case. Impaired glucose tolerance and insulin resistance were associated with
SAHS severity, as represented by both AHI and the degree of oxyhemoglobin desaturation. The WHR bore no relationship to the degree of SAHS, but HDL cholesterol level decreased with increasing AHI.

Several studies have previously examined plasma leptin levels, with or without indexes of the metabolic syndrome, in patients with SAHS. Vgontzas and colleagues27 demonstrated initially elevated leptin levels, with or without indexes of the metabolic syndrome. Their data also failed to connect the dots between SAHS and the metabolic syndrome.

Lee K. Brown, MD, FCCP
Albuquerque, NM

Dr. Brown is Medical Director, New Mexico Center for Sleep Medicine, Lovelace Health Systems, and The Division of Pulmonary, Allergy, and Critical Care, Department of Internal Medicine, University of New Mexico School of Medicine.

Correspondence to: Lee K. Brown MD, FCCP, Medical Director, New Mexico Center for Sleep Medicine, Lovelace Health Systems, 4700 Jefferson Blvd NE, Suite 800, Albuquerque, NM 87109; e-mail: lkbrown@alum.mit.edu

REFERENCES

15 vague J. The degree of masculine differentiation of obesity: a factor determining predisposition to diabetes, atherosclero-