AHA Scientific Statement

Obesity and Cardiovascular Disease: Pathophysiology, Evaluation, and Effect of Weight Loss

An Update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease From the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism

Paul Poirier, MD, PhD, FCRPC; Thomas D. Giles MD; George A. Bray, MD; Yuling Hong, MD, PhD; Judith S. Stern, ScD; F. Xavier Pi-Sunyer, MD, MPH; Robert H. Eckel, MD

***Abstract*— Obesity is becoming a global epidemic in both children and adults. It is associated with numerous comorbidities such as cardiovascular diseases (CVD), type 2 diabetes, hypertension, certain cancers, and sleep apnea/sleep-disordered breathing. In fact, obesity is an independent risk factor for CVD, and CVD risks have also been documented in obese children. Obesity is associated with an increased risk of morbidity and mortality as well as reduced life expectancy. Health service use and medical costs associated with obesity and related diseases have risen dramatically and are expected to continue to rise. Besides an altered metabolic profile, a variety of adaptations/alterations in cardiac structure and function occur in the individual as adipose tissue accumulates in excess amounts, even in the absence of comorbidities. Hence, obesity may affect the heart through its influence on known risk factors such as dyslipidemia, hypertension, glucose intolerance, inflammatory markers, obstructive sleep apnea/hypoventilation, and the prothrombotic state, in addition to as-yet-unrecognized mechanisms. On the whole, overweight and obesity predispose to or are associated with numerous cardiac complications such as coronary heart disease, heart failure, and sudden death because of their impact on the cardiovascular system. The pathophysiology of these entities that are linked to obesity will be discussed. However, the cardiovascular clinical evaluation of obese patients may be limited because of the morphology of the individual. In this statement, we review the available evidence of the impact of obesity on CVD with emphasis on the evaluation of cardiac structure and function in obese patients and the effect of weight loss on the cardiovascular system. (*Circulation*. 2006;113:898-918.)**

Key Words: AHA Scientific Statements ■ obesity ■ cardiovascular diseases ■ heart diseases ■ diagnosis

Obesity is becoming a global epidemic,[1,2] and in the past 10 years in the United States, dramatic increases in obesity have occurred in both children and adults.[3–5] Historically, the Metropolitan Life Insurance Company data that express body fatness as percent ideal body weight have been used,[6] but currently overweight and obesity are classified by body mass index (BMI). BMI (weight in kilograms/height^2 in meters) is frequently used as a surrogate measure of fatness in children and adults. In adults, overweight is defined as a BMI of 25.0 to 29.9 kg/m^2; obesity is defined as a BMI $\geq$30.0 kg/m^2. Table 1 shows the classification developed by a National Heart, Lung, and Blood Institute task force, along with the associated disease risk with increasing BMI.[7] Through the use of the BMI, the epidemic of obesity that began in the 1980s has been tracked through the end of the century.[4,8] The original alarm was sounded in 1994 by the National Center for Health Statistics when they reported their data from the first 3 years of the National Health and Nutrition Examination Survey (NHANES).[9] The authors observed that from 1988–1994 (NHANES III) to NHANES 1999–2000, the prevalence of overweight in adults increased from 55.9% to 64.5%. During that same period, the prevalence of obesity increased from 22.9% to 30.5%.[4,5,10] This sudden, unanticipated jump in the prevalence of obesity led the American Heart Association (AHA) to call for action to curb the consequences of this epidemic.[11,12] More recently,

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TABLE 1. Classification of Overweight and Obesity by Percentage of Body Fat, Body Mass Index, Waist Circumference, and Associated Diseases Risk

		Disease Risk* Relative to Normal Weight and Waist Circumference	
	Body Mass Index, kg/m^2	Men, ≤102 cm; Women, ≤88 cm	Men, >102 cm; Women, >88 cm
Underweight	<18.5	...	...
Normal	18.5–24.9	...	...
Overweight	25.0–29.9	Increased	High
Obesity, class			
I	30.0–34.9	High	Very high
II	35.0–39.9	Very high	Very high
III (extreme obesity)	≥40	Extremely high	Extremely high

*Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.
From the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report: National Institutes of Health.[7]

the AHA has addressed and reviewed a variety of weight loss approaches for the management and treatment of obesity.[13] Beyond an unfavorable risk factor profile, overweight and obesity also affect heart structure and function. Moreover, the cardiovascular clinical evaluation of obese patients may be limited because of the morphology of the individual. This statement reviews the available evidence of the impact of obesity on cardiovascular disease (CVD), with emphasis on the evaluation of cardiac structure and function in obese patients and the effect of weight loss on the cardiovascular system.

Obesity as a Metabolic/Genetic CVD Risk Factor

Over the past 2 decades, an explosive increase in the number of people with the metabolic syndrome (MetS) has taken place all around the globe. To better characterize the syndrome, several definitions of the MetS have been published, and the issue of the definition of the MetS has been reviewed lately.[14] However, the uncertainty about its pathogenesis has brought some doubt with regard to whether the MetS is a syndrome or an independent CVD risk factor.[15] Nevertheless, MetS may be associated with the global epidemic of obesity and diabetes—reported in Zimmet et al as "diabesity."[16] Given the elevated risk of not only diabetes but also CVD from the MetS,[17] strategies to stop the emerging global epidemic of obesity are urgently needed.[16] The MetS can present in a variety of ways aligned to the various components that constitute the syndrome.[18] Of note, abdominal obesity is a risk factor for CVD worldwide.[19,20] The estimated years of life lost as the result of obesity differ among races and between genders, but it was estimated that the optimal BMI for adults age 18 to 85 years is 23 to 25 for whites and 23 to 30 for blacks.[21] The MetS is associated with an increased risk of both diabetes[17] and CVD.[22–25] In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study involving European men and women, nondiabetic persons with the MetS had an increased risk of death from all causes as well as from CVD.[26] The overall hazard ratios for all-cause and CVD mortality in persons with the MetS as compared with persons without it were 1.44 and 2.26 in men and 1.38 and 2.78 in women after adjustment for age, blood cholesterol levels, and smoking. In 2 other European prospective studies,[22,23] the presence of the MetS predicted increased CVD and coronary heart disease (CHD) mortality rates. Again, this is not unexpected, given that the MetS comprises established CVD risk factors. It was suggested that the life-shortening effect of obesity could rise as the obese who are now at younger ages carry their elevated risk of death into middle and older ages.[27]

The epidemic of obesity is occurring on genetic backgrounds that have not changed, but it is nonetheless clear that genetics plays an important role in the development of obesity.[28] From the time of the early twin and adoption studies >10 years ago, large groups of individuals have been evaluated for genetic defects related to the development of obesity.[29,30] These genetic defects can be divided into 2 groups: the rare genes that produce significant obesity, and a group of more common genes that underlie the propensity to develop obesity—the so-called "susceptibility" genes.[28] Within a permissive environment, the more common genetic factors involved in obesity regulate the distribution of body fat, the metabolic rate and its response to exercise and diet, and the control of feeding and food preferences.[31,32] Recent research has identified >41 sites on the genome as possible links to the development of obesity in a favorable environment.[28] It is important to assess the gene–environment obesity relation because the prevalence of obesity, especially in children, is likely to continue to rise.

Obesity and Associated Comorbidities

Obesity is associated with numerous comorbidities such as CVD, type 2 diabetes, hypertension, certain cancers, and sleep apnea. In fact, obesity is an independent risk factor for CVD,[33,34] and CVD risks have been documented in obese children.[8,35] Indeed, a relationship exists between BMI in adolescence and all-cause mortality.[3] After a follow-up of 31.5 years, with those with a BMI between the 25th and 75th percentiles used as control subjects, it was reported that a BMI above the 95th percentile in adolescence predicted adult

mortality rates in both male (80% increment) and female (≈100% increment) patients. A 30% increase in all-cause mortality was also seen in female and male subjects when baseline BMI was between the 85th and 95th percentiles.[3] Another study, after 55 years of follow-up, reported an excess mortality rate among male but not female subjects who were overweight (BMI >75th percentile in the US reference population) in adolescence as compared with those who were lean (BMI 25th to 49th percentiles). The observed increased risk of death was independent of adult BMI.[36] Thus, obesity is associated with an increased risk of morbidity and mortality and is associated with reduced life expectancy.[21,27,37–41]

Besides an altered metabolic profile, a variety of adaptations/alterations in cardiac structure and function occur in the individual as adipose tissue accumulates in excess amounts,[42] even in the absence of comorbidities. Hence, obesity may affect the heart through its influence on known risk factors such as dyslipidemia, hypertension, glucose intolerance, inflammatory markers, obstructive sleep apnea/hypoventilation, and the prothrombotic state, as well as through yet-unrecognized mechanisms. As a whole, overweight/obesity predisposes or is associated with numerous cardiac complications such as CHD, heart failure, and sudden death through its impact on the cardiovascular system. The pathophysiology of these entities linked to obesity will be discussed in the following sections.

Cardiovascular Impact of Increased Adipose Tissue Mass

Adipose Tissue Circulation

It has long been recognized that an extensive capillary network surrounds adipose tissue.[43] Adipocytes are located close to vessels with the highest permeability, the lowest hydrostatic pressure, and the shortest distance for transport of molecules to and from the adipocytes.[44,45] Resting blood flow is usually 2 to 3 mL/min per 100 g of adipose tissue[46,47] and can increase ≈10-fold. This increment is still lower (≈20 mL/min per 100 g) than that seen in skeletal muscle (50 to 75 mL/min per 100 g).[48] Adipose tissue blood flow increases after meal intake,[49] but this modulation varies and may be decreased in patients with the features of the obesity-related MetS.[50,51]

Also, adipose tissue comprises a substantial proportion of total body weight. Therefore, a large quantity of fluid is present in the interstitial space of adipose tissue, as the interstitial space is ≈10% of the tissue wet weight.[52] Excess fluid in this compartment may have important repercussions in obese individuals with heart failure if this extra volume is redistributed into the circulation; however, modulation of blood flow through adipose tissue typically prevents this from occurring. This is because blood flow in adipose tissue is regulated by β_1-receptors that mediate vasodilation, in contrast to those of skeletal muscle, which are mainly β_2.[45] As a consequence of this decrease in blood flow in adipose tissue, the fluid present in the interstitial compartment is not readily accessible. Although cardiac output increases with total fat mass, the perfusion per unit of adipose tissue actually decreases with increasing obesity, that is, from 2.36 mL/min per 100 g to 1.53 mL/min per 100 g of adipose tissue (≈35%) in patients who have 15% to 26% body fat compared with those with >36% body fat.[47] Accordingly, the increase in systemic blood flow encountered in obesity cannot be explained solely by increased requirements caused by adipose tissue perfusion because the enlarged vascular bed of adipose tissue is less vascularized than other tissue. Probably, the concomitant increase in lean body mass in these individuals accounts for some of the increased cardiac output.[53] Indeed, it has been reported that stroke volume, cardiac output, and left ventricular mass may be more related to fat-free mass than to fat mass.[53,54]

The adipose tissue is not simply a passive storehouse for fat but an endocrine organ that is capable of synthesizing and releasing into the bloodstream an important variety of peptides and nonpeptide compounds that may play a role in cardiovascular homeostasis. Although this is not an extensive enumeration, adipose tissue is a significant source of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor-1, resistin, lipoprotein lipase, acylation stimulating protein, cholesteryl-ester transfer protein, retinal binding protein, estrogens (through P450 aromatase activity), leptin, angiotensinogen, adiponectin, insulin-like growth factor-I (IGF-I), insulin-binding protein 3 (IGFBP3), and monobutyrin.[55–59] Of clinical consideration, circulating concentrations of plasminogen activator inhibitor-1, angiotensin II, C-reactive protein (CRP), fibrinogen, and TNF-α are all related to BMI.[60,61] It has been estimated that in vivo, ≈30% of the total circulating concentrations of IL-6 originate from adipose tissue.[60,62] This is of importance because IL-6 modulates CRP production in the liver, and CRP may be a marker of a chronic inflammatory state that can trigger acute coronary syndrome.[63]

Hemodynamic Repercussion of Obesity

Obesity produces an increment in total blood volume and cardiac output that is caused in part by the increased metabolic demand induced by excess body weight.[64,65] Thus, at any given level of activity, the cardiac workload is greater for obese subjects.[66,67] Obese subjects have higher cardiac output and a lower total peripheral resistance than do lean individuals. The increased cardiac output is attributable mostly to increased stroke volume because heart rate increases little if at all.[68,69] Also, in obesity, the Frank-Starling curve is shifted to the left because of incremental increases in left ventricular filling pressure and volume, which over time may produce chamber dilation. Ventricular chamber dilation may then lead to increased wall stress, which predisposes to an increase in myocardial mass and ultimately to left ventricular hypertrophy, characteristically of the eccentric type.[70,71] Left atrial enlargement may also occur in normotensive obese individuals but typically in the setting of increased left ventricular mass. Left atrial enlargement may not be mediated solely through left ventricular diastolic dysfunction impairment but may simply reflect a physiological adaptation to the expanded blood volume.[72] As a consequence, left atrial dilation may mediate the excess risk of atrial fibrillation associated with obesity.[73] However, left ventricular hypertrophy (LVH) in long-standing obesity and/or the effects of concomitant hy-

pertension may also be contributing factors to left atrial enlargement.

Weight loss through diet and exercise is recommended in the management of obesity,[13] but it is important to recognize that obesity is associated with persistence of elevated cardiac filling pressures during exercise.[74,75] Increased cardiac output during exercise is typically accompanied by an increase in left ventricular filling pressure, often exceeding 20 mm Hg. Therefore, the average left ventricular filling pressure is often within the upper limits of normal at rest but increases disproportionately with increased venous return during exercise.[68] This is consistent with a high-pressure system, and, accordingly, obese patients may demonstrate higher right heart filling pressures, systolic pressure, cardiac output, and pulmonary vascular resistance index.[65] The latter may reflect intrinsic pulmonary disease, abnormal left ventricular function, or undiagnosed causes of pulmonary hypertension such as sleep apnea/hypoventilation or recurrent pulmonary thromboembolism. With increased venous return, small increments of central blood volume are associated with a significant increase in left ventricular end-diastolic pressure. A decrease in central blood volume accompanies weight reduction, and, when present, relief of edema and dyspnea may accompany this improvement.[68]

Effects on Ventricular Function

Eccentric LVH, which is commonly present in morbidly obese patients (BMI≥40 kg/m^2), is often associated with left ventricular diastolic dysfunction. Moreover, as with left ventricular mass, longer durations of obesity are associated with poorer left ventricular systolic function and greater impairment of left ventricular diastolic function.[76] Because of the presence of nonspecific symptoms, the evaluation of the presence of left ventricular diastolic dysfunction is clinically important in obese subjects.[34,77–79] Age and cardiac hypertrophy of the concentric[80,81] or, more commonly, the eccentric type[82,83] predispose to left ventricular systolic dysfunction. Although postmortem studies have demonstrated a relationship between heart weight and body weight,[80,84] obese patients without concomitant comorbidities may be afflicted only by diastolic dysfunction and hyperkinetic systole without LVH when indexed by fat-free mass.[83] In humans and most animal models, the development of obesity leads not only to increased fat depots in classic adipose tissue locations but also to significant lipid deposits in other organs. With fat gain, lipid deposition can impair tissue and organ function in 2 possible ways: (1) The size of fat pads around key organs may increase substantially, modifying organ function either by simple physical compression or because periorgan fat cells may secrete various locally acting molecules, and (2) lipid accumulation can occur in nonadipose cells and may lead to cell dysfunction or cell death, a phenomenon known as lipotoxicity.[85–87] Abnormal cellular adaptations may unfavorably affect the cardiac muscle, which is one of the several mechanisms leading to cardiomyopathy.

Cardiomyopathy of Obesity (Adipositas Cordis)

Obesity cardiomyopathy was recognized as early as 1818.[88] The case described by Cheyne[88] is of historic interest, not only because it is a carefully recorded documentation of a fatty heart but because it was the first reported case of Cheyne-Stokes respiration. Subsequently, other reports of excessive epicardial fat and fatty infiltration of the myocardium in the hearts of obese subjects were published that related the anatomic change to cardiac dysfunction.[84,89] Initially, the fatty heart probably is not an infiltrative process but is a metaplastic phenomenon.[90] Metaplasia is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.[91] It may represent an adaptative substitution of cells that are sensitive to stress by cell types better able to withstand the adverse environment. Cords of cells can gradually accumulate fat between muscle fibers or cause myocyte degeneration, resulting in cardiac conduction defects.[92,93] These cords of fat cells may also emanate from epicardial fat.[90] When the right ventricle is involved, the sinus node musculature, the atrioventricular node, the right bundle branch,[92] and, ultimately, the entire myocardium of the atrioventricular region might be replaced by fat.[93] Occasionally, a pattern of restrictive cardiomyopathy develops.[94,95] In this situation, small irregular aggregates and bands of adipose tissue separate myocardial cells, a potential result of pressure-induced atrophy from the intervening fat.[94] An alternative explanation could be, as discussed previously, the lipotoxicity of the myocardium induced by free fatty acids, which can cause apoptosis of lipid-laden cells such as cardiomyocytes.[96]

Thus, through different mechanisms (increased total blood volume, increased cardiac output, LVH, left ventricular diastolic dysfunction, adipositas cordis), obesity may predispose to heart failure. Because dyspnea with exertion and lower-extremity edema are often nonspecific signs of heart disease in obesity,[67,77,97] it may be difficult to clinically assess an obese individual because of several limitations inherent to the subject's morphology.

Clinical and Laboratory Assessment of Obese Individuals

History and Physical Examination

The physical examination and ECG often underestimate the presence and extent of cardiac dysfunction in obese patients. Cardiovascular manifestations likely occur on a continuum from the overweight to the morbidly obese individuals because symptoms and signs of obesity cardiomyopathy occur mainly in patients with a relative weight ≥175% or a BMI ≥40 kg/m^2.[64] On physical examination, jugular venous distention and hepatojugular reflux may not be seen, and heart sounds are usually distant. However, dorsal hand veins, if visible, can estimate central venous pressure. The hand is lowered beneath the sternal angle until the dorsal veins are distended. The arm is then gradually and passively raised while the dorsal veins are observed. Normally, the dorsal hand veins empty at the level of the sternal angle when the patient's trunk is 30° to 45° above the horizontal. Although this bedside technique remains a crude evaluation with several limitations, persistent distention is recorded as the vertical distance above the angle of Louis.[98] In the very obese patient, symptoms of heart disease may remain nonspecific,

TABLE 2. ECG Changes That May Occur in Obese Individuals

↑ Heart rate
↑ PR interval
↑ QRS interval
↑ or ↓ QRS voltage
↑ QT_c interval
↑ QT dispersion
↑ SAECG (late potentials)
ST-T abnormalities
ST depression
Left-axis deviation
Flattening of the T wave (inferolateral leads)
Left atrial abnormalities
False-positive criteria for inferior myocardial infarction

but the clinician should carefully search for the presence of cor pulmonale. In the majority of individuals, the splitting of the S_2 is most often heard at the second or third left interspace parasternally, but in obese patients, the split S_2 is either inaudible or very poorly defined in the second interspace and is often best heard at the first left interspace.[99] An electronic stethoscope may be helpful. This is of importance because pulmonary artery systolic pressure has been reported to be above the suggested normal limit (≤30 mm Hg) in 51% of obese patients,[100] and for each increase in BMI, the pulmonary artery systolic pressure is increased by ≈0.1 to 0.4 mm Hg.[100]

Electrocardiogram

Like physical evaluation, the ECG is influenced by morphological changes induced by obesity, such as (1) displacement of the heart by an elevated diaphragm in the supine position, (2) increased cardiac workload with associated cardiac hypertrophy, (3) increased distance between the heart and the recording electrodes induced by the accumulation of adipose tissue in the subcutaneous tissue of the chest wall (and possibly increased epicardial fat), and (4) the potential associated chronic lung disease secondary to the sleep apnea/hypoventilation syndrome.

Several changes in the ECG occur with increasing obesity (Table 2). In addition to low QRS voltage and leftward trend in the axis, other frequent alterations seen are nonspecific flattening of the T wave in the inferolateral leads (attributed to the horizontal displacement of the heart) and voltage criteria for left atrial abnormality.[101–103] More frequent ST-segment depression is seen in overweight patients with CHD.[104] Weight loss induces a rightward shift of the QRS axis,[105,106] but conduction intervals (duration of the P wave, QRS complex, and the PQ interval) are not affected by weight loss.[106] An increased incidence of false-positive criteria for inferior myocardial infarction has been reported in both obese individuals and in women in the final trimester of pregnancy. This is presumably because of diaphragmatic elevation.[107]

Left ventricular hypertrophy is strongly associated with cardiac morbidity and mortality.[108] Multiple ECG criteria for LVH are present more regularly in morbidly obese than in lean individuals but less frequently than might be expected on the basis of the high prevalence of echocardiographic LVH in such patients.[101] Therefore, LVH is probably underdiagnosed by usual electrocardiographic criteria in morbidly obese individuals. A low frequency of LVH by voltage criteria in morbid obesity is encountered where LVH was demonstrated in two thirds of the obese subjects by echocardiography.[101,109,110] As left ventricular mass increases, electrical forces usually become more posteriorly oriented, and the S wave in lead V_3 may be the most representative voltage for evaluating posterior forces. With LVH, the heart is oriented more horizontally in the mediastinum, which may explain the usefulness of the R wave in AVL. In obesity, the heart is shifted horizontally, presumably from the restricted diaphragmatic expansion caused by the abdominal pannus. Thus, it was proposed that for men at all ages, LVH is present by QRS voltage alone when the amplitudes of the R wave in lead AVL and the S wave in lead V_3 are >35 mm. For women at all ages, the same criteria were set at >25 mm.[111] When ECG voltage criteria were compared with left ventricular mass estimated by echocardiography, a sensitivity of 49%, specificity of 93%, and overall accuracy of 76% were revealed. These percentages are higher than most widely used criteria (Romhilt-Estes point score and Sokolow-Lyon voltage). Therefore, Sokolow-Lyon voltage should be replaced by the Cornell voltage criteria, which appear to be less influenced by the presence of obesity.[112]

Although ECG parameters in obese patients should be expected to change after weight loss, the impact of weight loss in obese patients on the QRS voltage is not consistent; studies report a decrease,[113–115] no change,[116] or an increase in the QRS amplitude.[102,105,106] With weight loss, a decreased amount of fat mass may counterbalance a true decrease in left ventricular mass, and a low QRS voltage could be secondary to myocardial atrophy.[115,117,118] Thus, these opposite vectors may negate the resultant QRS amplitudes.

Echocardiography

In times past, the cardiac status of obese individuals was difficult to assess, and obesity-induced cardiac abnormalities were found only after death.[80,84,88,90,103,119–123] Even since the development of echocardiography, transthoracic echocardiography can be technically difficult in obese patients.[124,125] Differentiation between subepicardial adipose tissue and pericardial effusion is often difficult in obese patients.[125,126] Epicardial adipose tissue is known to be a common cause of false-positive effusion (pseudopericardial effusion), and this adipose tissue depot may cause an underestimation of the amount of pericardial fluid.[121,127] Adipose tissue can also be found within the heart—for example, in the interatrial septum. From necropsy descriptions, the definition of the lipomatous hypertrophy of the interatrial septum corresponds to a maximal transverse dimension of interatrial fat >20 mm.[128,129] Although numerous indices of left ventricular diastolic filling are derived from echocardiography or cardiac Doppler evaluation, the increased intravascular volume in obesity may mask the Doppler-derived abnormalities of diastolic filling. Pulmonary venous Doppler evaluation may be used, but if not technically accessible, transmitral Doppler

image may properly evaluate the presence of left ventricular diastolic dysfunction.[130,131] Tissue Doppler has also been used to document diastolic dysfunction in obesity.[132] To evaluate left ventricular mass in obese subjects, it has been suggested that indexing left ventricular mass according to height$^{2.13}$ or height$^{2.7}$ may be more appropriate than normalization for body surface area, or even for height.[133,134] Another potential way to normalize the left ventricular mass is with lean body mass.[135,136] Interestingly, after indexing by lean body mass, there were no gender differences on left ventricular mass, and the relative effects of adiposity and blood pressure on left ventricular mass were of similar magnitude.[136] This finding was underscored recently by the results of the Strong Heart Study cohort, which showed that stroke volume and cardiac output are more strongly related to fat-free mass than other variables in both normal-weight and overweight individuals.[53]

Thus, obesity is associated with changes in the ECG that may affect the diagnosis of LVH or even CAD. Undoubtedly, the adiposity status has an impact on the heart size and function, but the optimal indexing criteria to define LVH after an echocardiographic study in obese individuals remain to be refined and confirmed. The next section will discuss comorbidities associated with obesity, with emphasis on the pathophysiology and the effect of weight loss.

Vascular Disease

Venous Insufficiency

A common finding in massive obesity is pedal edema, which may be partly a consequence of elevated ventricular filling pressure despite elevation in cardiac output.[137,138] However, in patients with circadian venous edemas, high-volume lymphatic overload (dynamic insufficiency), as well as increased intravascular volume associated with the decreased mobility encountered in obese individuals (reducing the pumping function of calf and leg muscles), may result in reflux of blood in the leg veins because of venous valvular incompetence. As for other causes of leg edema, the risk of the severe and sustained lower-extremity venous stasis disease seen in severe obesity is pretibial ulceration and cellulitis. In the absence of right heart failure, surgically induced weight loss is effective in correcting the venous stasis disease in a large majority of patients.[139]

Venous Thrombosis and Pulmonary Embolus

The incidence of venous thromboembolism in the upper tertile of BMI was 2.42 times that in the lowest BMI tertile,[140] and waist circumference >100 cm in men was also related to venous thromboembolism.[141] Obesity also has been associated with an increased risk of pulmonary embolism in women,[142] but this is less clear for men.[141] Also, in an autopsy study, morbid obesity was an independent risk factor for death from pulmonary embolism after the exclusion of established clinical, environmental, and molecular risk factors.[143,144]

Endothelial Function

Obesity is associated with abnormal endothelial function.[145] It is often inferred that the reduction in endothelial function is the result of a decrease in nitric oxide (NO). Decreased NO in obesity may be related to an increase in oxidative stress[146] or may result from proinflammatory cytokines. In the Framingham Heart Study, BMI was highly associated with systemic oxidative stress, as determined by creatinine-indexed urinary 8-epi-$PGF_{2\alpha}$ levels.[147] A decrease in the function of NO would result in vasoconstriction and an increase in vascular resistance that may predispose to CVD risk factors such as hypertension.

Hypertension

The majority of patients with high blood pressure are overweight.[148] Hypertension is about 6 times more frequent in obese subjects than in lean men and women.[148] Not only is hypertension more frequent in obese subjects than in normal-weight control subjects, but also weight gain in young people is a potent risk factor for subsequent development of hypertension. A 10-kg higher body weight is associated with a 3.0-mm Hg higher systolic and a 2.3-mm Hg higher diastolic blood pressure. These increases translate into an estimated 12% increased risk for CHD and 24% increased risk for stroke.[7] However, results from NHANES III reported more specific estimates for the prevalence of high blood pressure per age group and BMI group.[149] Among men, the prevalence of high blood pressure increased progressively with increasing BMI, from 15% at a BMI of <25 kg/m^2 to 42% at a BMI of ≥ 30 kg/m^2. Women showed a pattern similar to that of men; prevalence of hypertension being 15% at a BMI of <25 kg/m^2 to 38% at a BMI of ≥ 30 kg/m^2.[149] The trend of higher prevalence of high blood pressure with increasing BMI was similar for white, black, and Mexican Americans of both genders, and the age-adjusted rates were highest among blacks at every level of BMI.[149] It is well recognized that technical difficulties exist in the indirect measurement of blood pressure in the obese patient that may result in an overestimation of the level of blood pressure.[150–152] Nevertheless, obesity is strongly associated with higher-than-optimal blood pressure.[153,154] This increase in blood pressure is greatest when the obesity is of abdominal distribution.[151,155–158] Factors to be considered in linking obesity to an increase in blood pressure are related to changes in cardiac output and peripheral vascular resistance, because $BP = CO \times SVR$, where BP is blood pressure, CO is cardiac output, and SVR is systemic vascular resistance. These factors include (1) direct effects of obesity on hemodynamics and (2) mechanisms linking obesity and an increase in peripheral vascular resistance: endothelial dysfunction, insulin resistance, sympathetic nervous system, substances released from adipocytes (IL-6, TNF-α, and so forth), and sleep apnea.

Obesity per se is associated with alterations in hemodynamics.[159] An increase in oxygen demand produced by excess adipose tissue ($\approx$1.5 mL/kg per minute) requires an increase in cardiac output. Also, a parallel increase occurs in blood volume. Thus, obese individuals have an increase in blood volume, stroke volume, and cardiac output. This high-output state is associated with a reduction in peripheral vascular resistance in individuals with a normal blood pressure, as would be predicted from the Poiseuille formula: $R = \Delta P/$

$F=(8/\pi)\times(\eta)\times(l/r^4)$, where R is resistance, $8/\pi$ is a numerical factor, η is blood viscosity, and l/r^4 is a geometric factor that includes vessel characteristics. Because of the marked influence of the geometric factor (to the fourth power) in the equation, resistance is decreased. However, obese persons with a greater-than-optimal increase in blood pressure (ie, hypertension) have a peripheral vascular resistance that is either inappropriately "normal" or increased. Therefore, although an increase in cardiac output may add to the increase in blood pressure, in the obese individual, an abnormal increase in blood pressure is primarily dependent on an increase in peripheral vascular resistance.

Factors Leading to an Increase in Peripheral Vascular Resistance in Obesity Associated With Hypertension

The MetS (cardiovascular dysmetabolic syndrome; metabolic syndrome X) links hypertension with an increase in visceral fat.[157,160–162] Insulin resistance has been proposed as a common mechanism linking the other components of the MetS, but racial differences exist in the relation between blood pressure and insulin resistance.[163–165] Years ago, in the MetS, the prevalence of hypertension (blood pressure >130/85 mm Hg) was reported to be 80.1% for men and 40.7% for women.[166] More recently, racial differences between genders in terms of MetS-associated high blood pressure were reported. Indeed, high blood pressure prevalence may vary from 3.9% in women to 17.1% in men age 20 to 34 years to 70.3% in women and 80.7% in men age ≥65 years.[165] Obviously, if lower levels of blood pressure were considered optimal, the percentage of individuals with hypertension would be almost universal for men.[167]

One potential link between insulin resistance and an increase in blood pressure is the sympathetic nervous system.[166] Overactivity of the sympathetic nervous system is supported by data from the Normotensive Aging Study showing that urinary norepinephrine increases with BMI, abdominal girth, and insulin-glucose levels.[166] The role of insulin, however, is not supported by observations that patients with insulinomas are not hypertensive[168] and that chronic intrarenal hyperinsulinemia does not cause hypertension.[169] It was recently suggested that the documented association between obesity, fasting insulin, insulin sensitivity, and blood pressure may be explained by phenomena related to the concomitant variation in the amount of abdominal fat, as estimated by waist circumference.[157]

The association of obesity with a "systemic inflammatory state" may provide one other mechanism for an increase in blood pressure. A strong correlation exists between obesity and IL-6 and CRP levels.[170] IL-6 is a proinflammatory cytokine that, among many other things, stimulates the production of CRP from the liver. Thus, obesity is somewhat similar to a low-grade systemic inflammation. Low-grade inflammation may play a role in increasing blood pressure.[171] Increases in systolic and diastolic blood pressures, pulse pressure, and mean arterial pressure were significantly associated with levels of IL-6, whereas systolic blood pressure, pulse pressure, and mean arterial pressure were associated with levels of soluble intercellular adhesion molecule-1. Elevated plasma IL-6 levels were significantly associated with systolic and diastolic blood pressures in women, whereas in men, IL-6 was associated with fasting insulin and fasting insulin resistance index.[171] Regardless of the mechanisms involved, weight loss in obese individuals is associated with a decrease in blood pressure. In 50% or more of individuals, the average decrease in blood pressure is 1 to 4 mm Hg systolic and 1 to 2 mm Hg diastolic per kilogram of weight reduction as normalization of blood pressure.[172–174] Of note, after the weight loss has ceased, the persistent effect of weight loss on blood pressure may not always be encountered.[175,176]

The physician who evaluates a referred patient for hypertension should be very concerned about obese patients who admit habitual snoring, nocturnal gasping or choking, witnessed episodes of apnea, and daytime sleepiness and should consider sleep-disordered breathing.[177–179]

Sleep Apnea

Numerous respiratory complications are associated with obesity. Obese individuals have an increased demand for ventilation and breathing workload, respiratory muscle inefficiency, decreased functional reserve capacity and expiratory reserve volume, and closure of peripheral lung units. These often result in a ventilation–perfusion mismatch, especially in the supine position. Obesity is a classic cause of alveolar hypoventilation. Historically, the obesity-hypoventilation syndrome has been described as the "pickwickian" syndrome, and obstructive apnea was observed first in patients with severe obesity. Accordingly, obesity could represent a major cause of respiratory insufficiency and pulmonary hypertension in patients with obstructive sleep apnea. Sleep apnea is defined as repeated episodes of obstructive apnea and hypopnea during sleep, together with daytime sleepiness or altered cardiopulmonary function.[180] The prevalence of sleep-disordered breathing and sleep disturbances rises dramatically in obese subjects,[181] and obesity is by far the most important modifiable risk factor for sleep-disordered breathing.[178,179] It is estimated that 40 million Americans have sleep disorders and that the vast majority of these patients remain undiagnosed.[178,179] Despite careful screening by history and physical examination, sleep apnea is revealed only by polysomnography in a significant number of patients.[182] Although some clinical presenting features could be useful as screening tools to diagnose sleep apnea, a high index of suspicion is needed by clinicians because the diagnostic accuracy may be low.[183] The association of sleep-disordered breathing and sleep apnea with hypertension was studied in 6132 subjects over 40 years of age.[184] Mean systolic and diastolic blood pressure and prevalence of hypertension increased significantly with increasing severity of sleep-disordered breathing. It was considered that obesity might be a confounding factor, given the strong association of obesity with sleep apnea. However, sleep apnea might be one of the intermediary mechanisms by which overweight is causally related to hypertension. Interestingly, sleep apnea is associated with increased levels of CRP. Thus, obesity may influence many processes that are linked—for example, sleep apnea, hypertension, and atherosclerosis.[185] Although a link exists be-

tween sleep apnea and systemic hypertension, the association of obesity with both disorders confounds the relation.

It is important to remember, however, that the clinical and electrocardiographic signs of cor pulmonale appear later than those of pulmonary hypertension assessed by right heart catheterization. From a cardiology viewpoint, patients with sleep apnea have an increased risk of diurnal hypertension, nocturnal dysrhythmias, pulmonary hypertension, right and left ventricular failure, myocardial infarction, and stroke, as well as increased mortality rates.[186] Numerous treatments are available for sleep apnea, but weight loss in obese patients should always be advocated.[180]

Pulmonary Hypertension

The prevalence of pulmonary hypertension in subjects with obstructive sleep apnea is 15% to 20%, and pulmonary hypertension is rarely observed in the absence of daytime hypoxemia.[187,188] According to Kessler et al,[187] the gravity of pulmonary hypertension is generally mild to moderate (pulmonary artery pressure ranging between 20 and 35 mm Hg) and does not necessitate specific treatment. Similarly, this degree of pulmonary hypertension is often observed in patients with chronic obstructive pulmonary disease. Interestingly, in the latter population, a high prevalence of MetS was recently reported.[189] Pulmonary hypertension may be associated with morbid obesity, particularly during exercise, and may be associated with hemodynamic evidence of pulmonary arteriolar hypertrophy.[190,191] Obesity is also associated with sleep apnea and alveolar hypoventilation,[192] alveolar hypoxia being the most potent stimulus for pulmonary vasoconstriction.

Stroke

Numerous studies have reported an association between BMI and waist-to-hip ratio and stroke.[193–201] Indeed, obesity is listed as a potential modifiable risk factor for stroke, but the independence of this relationship from cholesterol, hypertension, and diabetes was only recently identified.[202] In the Physician's Health Study prospective cohort of 21 414 men, overweight men (25 to 29.9 kg/m^2) had a significant multiple-adjusted relative risk for total stroke of 1.32, for ischemic stroke of 1.35, and for hemorrhagic stroke of 1.25 as compared with men with BMI $<$25 kg/m^2. Obese men ($>$30 kg/m^2) had significant multiple-adjusted relative higher risks (1.91, 1.87, and 1.92, respectively) as compared with men with a BMI $<$25 kg/m^2.[202] Each 1-unit increase in BMI was associated with a multiple-adjusted increase of 4% in the risk of ischemic stroke and 6% for hemorrhagic stroke. However, stroke severity for ischemic stroke was not associated with BMI.[202] The increase of stroke in obesity may be predicted by the prothrombotic/proinflammatory state that so often accompanies excessive adipose tissue accumulation.[203,204]

Coronary Artery Disease

Pathogenesis

Atherosclerosis begins in childhood (5 to 10 years) as deposits of cholesterol esters in monocyte-derived macrophage foam cells in the intima of large muscular arteries (fatty streaks).[205,206] Important early events in the development of atherosclerosis are endothelial cell dysfunction in the epicardial vessels, resistance vessels, or both, and inflammation of the vessel wall. In the setting of the insulin resistance of obesity, coronary endothelial dysfunction is seen at the level of the resistance vessels. However, in older individuals, the effect of adiposity and body fat distribution on endothelial dysfunction may be less important than in young subjects.[207] Individuals at high risk for CHD can be identified through the measurement of carotid intimal-medial thickness (IMT), a marker of generalized atherosclerosis. Despite its limitations,[208,209] carotid IMT among adults is associated with obesity and other CHD risk factors and cardiovascular events.[210–213] Carotid IMT at age 35 years has been correlated with BMI measured throughout life, and childhood levels of BMI are associated with carotid IMT only among obese adults.[214] This emphasizes the adverse, cumulative effects of childhood obesity that persist into adulthood.

As individuals age, the atherosclerotic lesion becomes more complex. Of importance, the distinction of the lipid-filled "vulnerable" plaque from the fibrous "stable" lesion becomes important for the development of acute coronary syndromes.[215,216] In adults, obesity is often associated with advanced atherosclerosis. Indeed, postmortem examination of arteries from individuals 15 to 34 years of age (Determinants of Atherosclerosis in Youth [PDAY] study) who died from accidental injuries, homicides, or suicides revealed that the extent of fatty streaks and advanced lesions (fibrous plaques and plaques with calcification or ulceration) in the right coronary artery (RCA) and in the abdominal aorta were associated with obesity and with the size of the abdominal panniculus.[217–220] Obesity in young men, as crudely defined by the BMI, was associated with both fatty streaks and raised lesions in the RCA. Black subjects had more extensive fatty streaks than did white subjects in all arterial segments examined, and men did have more extensive raised lesions in the RCA than did women.[221] Importantly, when BMI and abdominal panniculus thickness were simultaneously considered in men, a BMI $\geq$30 kg/m^2 was associated with raised lesions in the RCA only among individuals with a large panniculus thickness ($\geq$17 mm), which reinforces the concept that central fat distribution is more important than total fat as a risk factor for atherosclerosis.[221] Moreover, this association between adiposity and RCA lesions remained significant after adjustment for other risk factors, eg, non-HDL and HDL cholesterol concentrations, hypertension, smoking, and glycohemoglobin.[222] In fact, these covariates accounted for only 15% of lesion volume in these young obese subjects. This has been reinforced in a younger cohort of men in whom the maximal density of macrophages per square millimeter in the lesions was associated with visceral obesity.[223] Of note, raised lesions in coronary arteries observed in young women lagged behind those seen in young men by 10 to 20 years.[19,20,222,224] The preferential deposition of fat centrally after the menopause may explain in part why the risk for CHD events increases 10 to 20 years later in women than men.[19,20,225] Overall, the data from the PDAY study provide convincing evidence that obesity in adolescents and young adults accelerates the progression of atherosclerosis decades before the appearance of clinical manifestations.

Prospective studies that have reported follow-up data over >2 decades, such as Framingham Heart Study, the Manitoba Study, and the Harvard School of Public Health Nurses Study, have documented that obesity is an independent predictor of clinical CHD.[37,226–228] On the other hand, in patients with known CVD or after acute myocardial infarction, overall obesity as assessed by BMI is inversely related to mortality.[229,230] Abdominal obesity appears to be an independent predictor of all-cause mortality in men and perhaps also in women. In the Trandolapril Cardiac Evaluation (TRACE) register, the mortality rate was increased 23% as compared with patients who were not abdominally obese. Excluding diabetes and hypertension from the multivariate analysis did not change the findings. This implies that the impact of obesity on all-cause mortality is mediated by mechanisms other than hypertension and diabetes.[230]

Assessment of Coronary Artery Disease With Imaging Techniques

Assessing CHD with imaging techniques is important in obese patients. As discussed earlier, because baseline ECG may be influenced by the presence of obesity (false-positive for inferior myocardial infarction, microvoltage, nonspecific ST-T changes) and because obese patients may have impaired maximal exercise testing capacity (dyspnea, orthopedic limitations, left ventricular diastolic dysfunction), other modalities may be of interest in the evaluation of CHD in this population. Although attenuation correction has been developed for single-photon-emission computed tomography, attenuation artifacts, most commonly resulting from attenuation by the diaphragm or the breast, frequently can be seen in obesity. However, evaluation of significant clinical CHD may be adequately assessed in obese subjects through the use of nuclear cardiology imaging.[231–233] Because of impaired exercise tolerance through mechanical and physiological limitations of stress testing,[67] a dipyridamole thallium^{201} or technetium^{99m} perfusion scan may be used instead of exercise testing in very obese patients for evaluating the presence of ischemic heart disease. The specificity of single-photon-emission computed tomography may be slightly greater with technetium^{99m} rather than thallium,[201] in part because of its higher energy (140 versus 70 keV), but both isotopes continue to pose a problem of interpretation if accurate attenuation correction and gating are not performed. Although differences in tracer distribution may be seen, prolonged transmission scanning (5 versus 10 seconds per view) with thallium^{201} is not mandatory for accurate clinical interpretation in obese as compared with lean patients after correction for the attenuation factor caused by obesity,[234] and triple-head simultaneous emission transmission tomography with technetium^{99m} is also accurate in obesity.[235] Nevertheless, in severe obesity, a higher incidence of false-positive noninvasive functional tests for the detection of CHD is seen.[235,236]

Transesophageal echocardiography may be of diagnostic use in the evaluation of the presence of CHD in severely obese individuals. Transesophageal dobutamine stress echocardiography combines the advantages of pharmacological stress testing with superior-quality cardiac imaging, has been reported to be safe, and appears to be a good alternative to cardiac catheterization for assessing the presence of CHD and ischemic threshold in morbidly obese patients.[237] Obese individuals may have limitations because the examination table for nuclear medicine or catheterization usually does not accommodate very obese subjects. If cardiac catheterization is contemplated, femoral access may not be ideal, not only because of the volume of adipose tissue but also because of the presence of intertrigo. Nevertheless, the use of femoral closure devices may help decrease bleeding complications. Alternatively, the percutaneous radial approach has numerous advantages in the very obese patient because the frequency of complications with the use of this technique is very low.[236,238]

Coronary Artery Disease Revascularization Procedure in Obesity

Among the 9405 patients who were evaluated from 1986 to 1997 at the Duke University cardiac catheterization laboratory, the prevalence of obesity increased from 20% to 33%.[239] Characteristics of the obese patients in the catheterization laboratory are younger age and more comorbidities but more single-vessel disease at baseline.[239,240] Obesity was also associated with more clinical events over the post–30-day period after cardiac catheterization, with higher cumulative inpatient medical costs and significant differences in unadjusted survival rates at 10 years.[239] Prospective evidence shows that abdominal obesity is associated, after only a 4-year follow-up, with accelerated progression of carotid atherosclerosis in men independent of overall obesity and other risk factors.[241] This association between abdominal obesity and carotid atherosclerosis was found to be particularly evident when accompanied by serum apolipoprotein B ≥1.01 g/L and an increased prevalence of small dense LDL.[241] Also, abnormal glucose tolerance may be an important determinant for long-term prognosis after coronary angioplasty,[242] which may be dependent on the features of the MetS.[243] After coronary artery bypass, the components of the insulin resistance syndrome are associated with angiographic progression of atherosclerosis in nongrafted coronary arteries.[244] Therefore, abnormalities of glucose metabolism with features of the MetS could modulate the extent of atherosclerosis within the coronary artery tree and modulate acute coronary syndrome events.[245,246]

Cardiac surgeons often perceive obesity as a risk factor for perioperative adverse outcomes after coronary artery bypass grafting (CABG). Obese patients have been shown to have a higher incidence of postoperative thromboembolic disease in noncardiac surgery, and their high risk of thromboembolic disease may necessitate an aggressive approach to deep venous thrombosis prophylaxis.[247] In contrast to common beliefs, obesity is not associated with increased mortality rates or postoperative cerebrovascular accidents after CABG.[248,249] However, an increased incidence of sternal and superficial wound infection, saphenous vein harvest site infection, and atrial dysrhythmias was seen.[250–252] Curiously, despite numerous alterations in respiratory physiology in obese patients, such as increased breathing workload, respiratory muscle inefficiency, decreased functional reserve capacity and expiratory reserve volume, and closure of peripheral lung units, pulmonary complications are comparable to

those seen in nonobese patients after CABG.[250,251] This discrepancy may reflect different treatment attitudes on the part of the staff in the late postoperative period, with more vigorous pulmonary toilet performed or more vigilance in enforcing postoperative use of incentive spirometry and early ambulation in patients undergoing cardiac surgery. However, this may not apply to severely obese patients (BMI >35 kg/m^2), who were more likely to have prolonged mechanical ventilation and longer postoperative stay.[252] Indeed, a study in the immediate postoperative period, including >24 000 patients, reported infrequent major unanticipated problems with ventilation in the postanesthesia period, but when obesity was complicated by diabetes, renal dysfunction, and age >60 years in men, problems with ventilation ensued.[253]

Congestive Heart Failure

Congestive heart failure (CHF) is the only common cardiovascular condition that is increasing in incidence, prevalence, and mortality rates. Although several new therapies have been introduced for the treatment of CHF, the overall 5-year mortality rate for CHF is presently estimated at 50%. An elevated BMI predisposes to CHF by promoting hypertension, diabetes, and CHD, and excess obesity is associated with an increased risk of development of CHF.[225,254–257] It is estimated that the risk of CHF increases 5% for men and 7% for women for each increment of 1 U of BMI with the existence of a continuous gradient without evidence of a threshold.[255] Once the patient presents with CHF, the presence of obesity may not adversely affect the patient's outcome.[258–260] Indeed, among patients with CHF, subjects with higher BMI are at decreased risk for death and hospitalization as compared with patients with a "healthy" BMI.[258,260–264] Current guidelines for the management of heart failure provide conflicting directions for the prognosis and management of BMI. American College of Cardiology (ACC)/AHA heart failure clinical practice guidelines for adults do not directly address the issue of BMI.[265] The European Society of Cardiology recommends weight loss for overweight and obese patients with heart failure even though this recommendation is not supported by data from clinical trials.[266] An analysis from 7767 patients with stable heart failure enrolled in the Digitalis Investigation Group Trial (DIG) reported that higher BMI was associated with lower mortality risk.[267] One must keep in mind that the analysis considers only BMI at the time of enrollment, whereas changes in BMI over time are not available. Thus, the findings do not address the impact of weight loss or weight gain during the study period (37 months). In contrast, preoperative obesity (>140% ideal body weight) may increase morbidity and mortality rates after heart transplantation.[268]

The interrelation between sleep disorders and CVD is a topic of growing interest.[269] The frequency with which obstructive sleep apnea causes left-sided CHF and the mechanisms by which this occurs are not clear. Pulmonary hypertension and right heart disease are expected in obese patients with long-standing and moderately severe hypoxemia, which could be potentiated through CHF. In addition, patients with CHF and/or sleep disorders are at increased risk of fatal arrhythmias, and it is important to consider that obesity may modulate this increased risk.

Arrhythmias

The statement "Sudden death is more common in those who are naturally fat than in the lean" is attributed to Hippocrates.[34] Weight-stable obese subjects have an increased risk of arrhythmias and sudden death, even in the absence of cardiac dysfunction,[69,270] and the risk of sudden cardiac death with increasing weight is seen in both genders.[226] In the Framingham Study, the annual sudden cardiac mortality rate in obese men and women was estimated to be about 40 times higher than the rate of unexplained cardiac arrest in a matched nonobese population.[226,270] Specifically, in severely obese men, a 6- and 12-fold excess mortality rate was reported in the age group 35 to 44 and 25 to 34 years, respectively.[39]

Prolonged QT_c interval was observed in ≈30% of subjects with impaired glucose tolerance in a report emanating from the NHANES III cohort,[271] and a positive association existed between BMI and QT_c.[272] Although not consistent,[104,273,274] the relation between fatness and the QT_c interval remains even after adjustment of absolute QT intervals for heart rate with different formulas (Bazett, Framingham, Fridericia) and by multiple regression analysis.[272] Hence, a prolonged QT interval is observed in a relatively high percentage of obese subjects, and the association between abnormal QT_c and BMI is most evident in the severely obese.[116,272] Of clinical importance, ≈8% of patients present with a QT_c >0.44 seconds and ≈2% with a QT_c >0.46 seconds.[275] Interestingly, prolongation of QT_c interval is associated with visceral obesity in healthy premenopausal women (assessed by computerized tomography), independent of obesity and other risk factors.[276] Although the QT_c may not be extremely increased (≈440 ms) in the obese population,[273,275] it is important to emphasize that screening for prolonged QT in obesity may have stringent criteria because a prolongation of QT_c of >420 ms may be predictive of increased mortality rates in a healthy population followed up for 15 years.[277] Although abnormal QT_c has been shown in other insulin-resistant states often associated with obesity, such as hypertension and diabetes,[271] no available report describes specific ECG abnormalities in lipodystrophy. Although QT dispersion has been reported to be increased in obesity without improvement after weight loss, visceral obesity may be a better discriminate to evaluate the impact of weight loss on QT dispersion.[278] Of interest, QT dispersion may be comparable to age- and sex-matched control subjects when obese subjects did not have the comorbidities often associated with obesity.[279] In a model in which the QT_c interval was the dependent variable and changes in waist-to-hip ratio, BMI, plasma free fatty acids, epinephrine, norepinephrine, and glucose levels were the independent variables, it was reported that the mathematical model explained ≈70% of the variance in the QT_c interval changes.[278] When visceral obesity or insulin levels increase, sympathovagal balance may be the best explanation for changes in QT_c and QT dispersion.[280]

The occurrence of small high-frequency ECG potentials (1 to 20 μV) seen at the end of the QRS complex and into the ST segment is also associated with increased risk for ventric-

ular arrhythmias and sudden cardiac death.[281] The occurrence of late potentials using signal-averaged electrocardiography in a group of obese individuals without clinical heart disease was evaluated.[282] The prevalence and number of abnormalities increased with increasing BMI. In patients with a BMI of 31 to 40 kg/m^2, 35% of subjects had abnormal late potentials, whereas in the subgroups with a BMI of 41 to 50 kg/m^2 and a BMI >50 kg/m^2, 86% and 100% of subjects had abnormalities, respectively.[282] Importantly, these abnormalities were found in obese patients with and without hypertension or diabetes. The presence of late potentials may be facilitated by pathological myocardial changes associated with obesity (myocyte hypertrophy, focal myocardial disarray, fibrosis, fat and mononuclear cell infiltration).

The clinical significance of obesity-associated QT prolongation and the mechanisms involved remain speculative. It is interesting to note, however, that elevated free fatty acids may affect cardiac repolarization. This may in part be secondary to increased plasma catecholamines.[278,283] Clinically, a correlation between the levels of long-chain saturated fatty acids and the occurrence of ventricular arrhythmias in patients with myocardial infarction was reported in a univariate analysis.[284] Moreover, high glucose concentrations may promote increased vasomotor tone and ventricular instability by reducing NO availability.[285,286] Moreover, because extremely obese patients often have a dilated cardiomyopathy, fatal arrhythmias may be the most frequent cause of death.[69,82] Nevertheless, all these abnormalities do not infer a cause–effect relationship with regard to the increased risk of arrhythmias and sudden death with increasing weight.

The autonomic nervous system is an important contributor to the regulation of both the cardiovascular system and energy expenditure, and it is assumed to play a role in the pathophysiology of obesity and related complications.[34,287] Obesity and the cardiac autonomic nervous system are intrinsically related. A 10% increase in body weight is associated with a decline in parasympathetic tone accompanied by a rise in mean heart rate, and, conversely, heart rate declines during weight reduction.[288] Fluctuation of heart rate around mean heart rate provides valuable information on the activity of the cardiac autonomic nervous system, which is called heart rate variability (HRV). It was demonstrated that a 10% weight loss in severely obese patients is associated with significant improvement in autonomic nervous system cardiac modulation.[289] This translates into decreased heart rate and an increased HRV mainly through an increment in cardiac parasympathetic modulation. This is of importance because higher heart rate is associated with increased mortality rates,[290,291] and decreased HRV is associated with increased cardiac mortality, independent of ejection fraction.[292]

Weight Loss

Cardiopulmonary Impact of Weight Reduction Therapy

Intentional weight loss in obese patients can improve or prevent many of the obesity-related risk factors for CHD.[13,293] It is important for cardiovascular healthcare professionals to understand the clinical effects of weight loss and be able to implement appropriate weight-management strategies in obese patients. Current therapies available for weight management that cause weight loss by inducing a negative energy balance include dietary intervention, physical activity, pharmacotherapy, and surgery. Behavior modification to enhance dietary and activity compliance is an important component of all of these treatments. Diverse modalities had been addressed lately by the AHA.[13] At present, the therapeutic intervention used does not appear to be relevant to the benefit of weight reduction on the cardiovascular system, with a few exceptions to be noted below.

TABLE 3. Benefits of Weight Reduction on the Cardiovascular System

↓ Blood volume
↓ Stroke volume
↓ Cardiac output
↓ Pulmonary capillary wedge pressure
↓ Left ventricular mass
Improvement of left ventricular diastolic dysfunction
Improvement of left ventricular systolic dysfunction
↓ Resting oxygen consumption
↓ Systemic arterial pressure
↓ Filling pressures of the right and the left side of the heart
↓ or no change in systemic arterial resistance
↓ Resting heart rate
↓ QT_c interval
↑ HRV

HRV indicates heart rate variability.

Surgically induced weight loss produces a decrease in resting oxygen consumption and cardiac output that is proportional to the magnitude of weight loss.[74,294] Stroke volume falls in parallel to the decrease in blood volume and heart volume. Systemic arterial pressure declines, but systemic arterial resistance changes little if at all. Left ventricular stroke work diminishes. Pulmonary capillary wedge pressure tends to decrease but may still remain higher in relation to cardiac output as compared with normal-weight subjects. Left ventricular dysfunction may persist most strikingly during exercise.[74] At any given cardiac output, all right heart pressures tend to be higher than in normal-weight subjects,[74] with relative increases in left ventricular end-diastolic pressure.[68] Table 3 enumerates the beneficial effects of weight loss on the cardiovascular system.

Even if weight loss produces a reduction in left ventricular mass, only 14% to 25% of the reduction in left ventricular mass can be explained solely by the change in body weight.[295,296] Perhaps the most important variable in weight loss–induced reduction of left ventricular mass is the reduction in blood pressure and associated neurohormones. Sympathetic mechanisms have been implicated in the development of LVH,[108] and weight reduction in obese subjects reduces the indices of sympathetic activity such as plasma norepinephrine levels and urinary norepinephrine excretion. The renin-angiotensin system may also be involved in the

pathogenesis of LVH, and weight reduction may decrease plasma renin activity and aldosterone levels.[297] The improvement in hyperinsulinemia also may be related to the reduction in left ventricular mass in hypertensive obese subjects because insulin resistance is an important independent contributing factor to left ventricular mass in normotensive nondiabetic obese subjects.[298] The exact mechanism explaining the association between LVH and insulin resistance in not known, but one can speculate that hyperinsulinemia plays a role as a growth factor. A reduction in angiotensin-converting enzyme activity after weight reduction could also be important.[299]

Risks of Weight Loss

Weight loss through different modalities, for example, starvation,[113,115] liquid protein diets,[117,118] very-low-calorie diets, and even obesity surgery,[81] has been associated with prolongation of the QT_c interval. The prolongation of the QT_c interval is independent of the biological and nutritional value of the constituent protein or the addition of mineral and trace supplements in the diet.[117] Most importantly, liquid protein diets that have been associated with potentially life-threatening arrhythmias were only suspected after a 24-hour Holter recording.[300] Ventricular tachycardia (torsade de pointes) and fibrillation, refractory to lidocaine, propranolol, phenytoin, mexiletine, disopyramide, and procainamide, have all been documented in subjects who died under observation.[113,117,118,301] These diets are still in use today. Accordingly, more care is now taken to ensure micronutrient supplementation and to monitor for adverse effects.

Fenfluramine and dexfenfluramine, which reduce appetite by enhancing serotonin at nerve terminals in the hypothalamus, were removed from the marketplace in the United States in 1997 after reports of cardiac valve disorders,[302] particularly aortic and mitral insufficiency. Valve involvement in these patients was histopathologically similar to that noted in the carcinoid syndrome or ergotamine-induced valve disease.[303,304] The development of valvulopathy correlated strongly with duration of exposure.[305] An increased risk of primary pulmonary hypertension also was documented.[306–309] Of interest, no cases were reported of cardiac valve abnormalities associated with the use of phentermine alone,[310] and regression of valvular disease after cessation of fenfluramine or dexfenfluramine has been described.[311–313] The most frequent troubling abnormality is aortic regurgitation, which is usually mild[311,314–316] if it occurs at all.[317] This finding appeared to be more significant in patients who took fenfluramine and dexfenfluramine for longer than 3 months.[314]

Sibutramine hydrochloride and orlistat are the latest drugs available on the market for the treatment of obesity and have been shown to be effective in the treatment of obesity and associated comorbidities.[318,319] Sibutramine hydrochloride, a centrally acting drug[320] that is approved for long-term use, has not been associated with valve abnormalities.[321,322] However, increases in blood pressure and heart rate may occur with the use of this drug,[322,323] and, like phentermine, sibutramine should not be used in patients with untreated hypertension, CHD, CHF, arrhythmias, or stroke.[320] The effects of the endocannabinoid receptor antagonists in the treatment of obesity on heart structure and function are not known.

Obesity and the Future of Healthcare Services

Health service use and medical costs associated with obesity and related diseases have increased and will increase dramatically.[324] Abdominal obesity as assessed by waist circumference (independent of ethnicity, gender, smoking status, and age) is associated with increased total healthcare expenditures, especially with the costs of inpatient care. Waist circumference may be a better predictor of healthcare costs than the widely used BMI.[325] Although CVD and diabetes mellitus medication costs have been shown to be lower in surgically treated obese patients, other medication costs, related to the surgery side effects, may increase.[326,327] However, it was shown that the initial costs of bariatric surgery on healthcare costs might be amortized over 3.5 years. After 5 years, average cumulative costs per 1000 operated patients were $19.5 million (Canadian), versus $25.3 million for control subjects.[328] Notwithstanding, increased physical activity early in life may become the cost-effective nonpharmacological avenue to combat obesity.[329] Because of the increased metabolic demand induced by excess body weight,[67] at any given level of activity, the cardiac workload is greater for obese subjects. Nevertheless, this recommendation needs to be heeded with advice from an experienced clinician in exercise therapeutics.

It is very important to inform patients about the results to be expected to avoid unrealistic weight loss expectations. The primary target should not be body weight normalization, but rather some weight loss, which can lead to substantial improvements in risk factors.[330] Aside from enhanced metabolic profile, weight loss favorably affects the cardiovascular system through diverse mechanisms. Of interest, even if weight loss is minimal, obese individuals with a good level of cardiorespiratory fitness show a reduced risk for cardiovascular mortality as compared with lean, poorly fit subjects.[331] Although no prospective trials have convincingly shown changes in mortality rate with weight loss in obese patients, it has been reported that individuals who attempted intentionally to lose weight present significantly lower all-cause mortality, independent of weight change.[332–334] Nonetheless, intentional weight loss (from 33.5 to 27.7 kg/m^2) was associated with a 25% reduction in mortality rates in overweight patients with diabetes.[334]

Conclusions

Obesity is a chronic metabolic disorder associated with CVD and increased morbidity and mortality rates. It is apparent that a variety of adaptations/alterations in cardiac structure and function occur as excessive adipose tissue accumulates, even in the absence of systemic hypertension or underlying organic heart disease. To meet increased metabolic needs, circulating blood volume, plasma volume, and cardiac output all increase. The increase in blood volume in turn increases venous return to the right and the left ventricles, eventually producing dilation of these cardiac cavities, increasing wall tension. This leads to LVH, which is accompanied by a decrease in diastolic chamber compliance, eventually resulting in an increase in left ventricular filling pressure and left ventricular enlargement. As long as LVH adapts to left ventricular chamber enlargement, systolic function is preserved. When

LVH fails to keep pace with progressive left ventricular dilation, wall tension increases even more and systolic dysfunction may ensue. Systemic hypertension, pulmonary hypertension (left ventricular failure, chronic hypoxia), and CHD all occur with disproportionately high frequency in obese individuals and may cause or contribute to alterations in cardiac structure and function. The risk of sudden cardiac death is also increased in obesity.

Although no prospective studies to date demonstrate that intentional weight loss increases survival, strong evidence indicates that weight loss in overweight and obese individuals reduces risk factors for diabetes and CVD. We hope that within the next decade, new information may be provided that weight reduction is beneficial for hard CVD outcomes—that is, CHD events, CHD death, CHF, stroke, and total mortality. Until then, we hope that a favorable result will ensue through the clinical approach. The problem of overweight/obesity has been identified as one of the major CVD risk factors since 1998, and, although we understand to some extent the pathophysiological link between overweight/obesity and many forms of CVD, a number of remaining scientific questions need to be addressed for us to have a more complete understanding of the relationship between overweight/obesity and CVD. The AHA writing group recommends the following important areas for further research:

1. A better understanding of how genes and gene–environment interaction lead to the CVD related to overweight/obesity;
2. Identification of the optimal biomarkers and nonmetabolic markers for predicting overweight/obesity and major CVD comorbidities, including subclinical CVD;
3. A better understanding of ethnic/racial differences in the development and progression of CVD in overweight/obesity;
4. Evaluation of the strategies, efficacy, and side effects of obesity treatment with lifestyle/behavioral intervention and drug therapy and its impact on CVD;
5. Identification of genetic determinants or biomarkers that predict which obese individuals are at highest risk for heart failure;
6. Fundamental studies attempting to understand the basis for heart failure in the obese and insulin-resistant individual; and
7. Policy research on the impact of overweight/obesity on future health care in people with or without CVD.

Author Disclosures

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Paul Poirier	Quebec Heart and Lungs Institute, Laval Hospital Research Center, Canada	Bristol-Myers Squibb; GlaxoSmithKline; Abbott	None	Bristol-Myers Squibb; Pfizer; Merck; Aventis; GlaxoSmithKline; AstraZeneca; Fournier Pharma; Novartis	None	None	None
Thomas D. Giles	Louisiana State University Health Science Center	None	None	Novartis; BMS/Sanofi; A/Z; CV Therapeutics; Sankyo/Forest	None	Novartis; BMS/Sanofi; A/Z; CV Therapeutics; Sankyo/Forest	None
George A. Bray	Pennington Biomedical Research Center, Baton Rouge, La	None	None	None	None	Takeda; Pharmaceutical; Johnson&Johnson	None
Yuling Hong	American Heart Association	None	None	None	None	None	None
Judith S. Stern	University of California at Davis	None	None	None	None	Masterfoods Nutrition Advisory Board; WeightWatchers Medical Advisory Board; Salt Institute Medical Advisory Board.	None
Xavier Pi-Sunyer	Columbia University	Novartis; Abbott; Merck; AstraZeneca; Sanofi	None	None	None	Lilly; Sanofi; Weight Watchers; Amylin; Novo; Abbott; Pfizer	None
Robert H. Eckel	University of Colorado Health Sciences Center	None	None	None	None	Merck Pharmaceuticals	None

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Reviewer Disclosures

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Martin A. Alpert	St. John's Mercy Medical Center	None	None	Bristol Myers Squibb; Sanofi-Aventis; Pfizer	None	None	None
Steven Heymsfield	Merck	None	None	None	None	None	None
Dan Kelly	Washington University School of Medicine	None	None	None	None	Pfizer	None
Julia Steinberger	University of Minnesota	None	None	None	None	Am Phytotherapy Research Lab, Inc.	None

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Paul Poirier, Thomas D. Giles, George A. Bray, Yuling Hong, Judith S. Stern, F. Xavier Pi-Sunyer and Robert H. Eckel

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