

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/height² 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/m²; obesity is defined as a BMI \geq 30.0 kg/m². 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,

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on September 26, 2005. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0278. To purchase additional reprints: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 410-528-4121, fax 410-528-4264, or e-mail kramsay@lww.com. To make photocopies for personal or educational use, call the Copyright Clearance Center, 978-750-8400.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit <http://www.americanheart.org/presenter.jhtml?identifier=3023366>.

© 2006 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.106.171016

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

	Body Mass Index, kg/m ²	Disease Risk* Relative to Normal Weight and Waist Circumference	
		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 diabetes¹⁷ 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 ($\approx 100\%$ 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 $\approx 10\%$ 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 ($\approx 35\%$) 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, $\approx 30\%$ 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 ($\text{BMI} \geq 40 \text{ kg/m}^2$), 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 Cheyne⁸⁸ 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 adaptive 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 $\geq 175\%$ or a $\text{BMI} \geq 40 \text{ kg/m}^2$.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 S₂ is most often heard at the second or third left interspace parasternally, but in obese patients, the split S₂ 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 V₃ 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 V₃ 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 stress¹⁴⁶ 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_{2α} 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/m² to 42% at a BMI of ≥30 kg/m². Women showed a pattern similar to that of men; prevalence of hypertension being 15% at a BMI of <25 kg/m² to 38% at a BMI of ≥30 kg/m².¹⁴⁹ 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 (≈ 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: $R = \Delta P /$

$F=(8/\pi)\times(\eta)\times(1/r^4)$, where R is resistance, $8/\pi$ is a numerical factor, η is blood viscosity, and $1/r^4$ 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 hypertensive¹⁶⁸ 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/m²) 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/m². Obese men (>30 kg/m²) had significant multiple-adjusted relative higher risks (1.91, 1.87, and 1.92, respectively) as compared with men with a BMI <25 kg/m².²⁰² 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 ≥ 30 kg/m² was associated with raised lesions in the RCA only among individuals with a large panniculus thickness (≥ 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 thallium²⁰¹ 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 thallium²⁰¹ 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/m²), 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/m², 35% of subjects had abnormal late potentials, whereas in the subgroups with a BMI of 41 to 50 kg/m² and a BMI >50 kg/m², 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

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.

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.

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 is 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 drug³²⁰ 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/m²) 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

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
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

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
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

This table represents the relationships of reviewer that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire which all reviewers are required to complete and submit.

References

- Eckel RH, York DA, Rosser S, Hubbard V, Caterson I, St Jeor ST, Hayman LL, Mullis RM, Blair SN; American Heart Association. Prevention Conference VII: obesity, a worldwide epidemic related to heart disease and stroke: executive summary. *Circulation*. 2004;110:2968–2975.
- World Health Organization. Obesity: Preventing and managing the global epidemic. [WHO Technical report series No. 894]. 2000. Geneva. World Health Organization.
- Engeland A, Bjorge T, Sogaard AJ, Tverdal A. Body mass index in adolescence in relation to total mortality: 32-year follow-up of 227,000 Norwegian boys and girls. *Am J Epidemiol*. 2003;157:517–523.
- Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA*. 2002;288:1723–1727.
- Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. *Int J Obes Relat Metab Disord*. 1998;22:39–47.
- Himes JH, Bouchard C. Do the new Metropolitan Life Insurance weight-height tables correctly assess body frame and body fat relationships? *Am J Public Health*. 1985;75:1076–1079.
- Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report: National Institutes of Health. *Obes Res*. 1998;Suppl 2:51S–209S.
- Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. *JAMA*. 2002;288:1728–1732.
- Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults: the National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA*. 1994;272:205–211.
- Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991–1998. *JAMA*. 1999;282:1519–1522.
- Eckel RH. Obesity and heart disease: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation*. 1997;96:3248–3250.
- Eckel RH, Krauss RM. American Heart Association call to action: obesity as a major risk factor for coronary heart disease: AHA Nutrition Committee. *Circulation*. 1998;97:2099–2100.
- Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, Hong Y, Eckel RH; American Heart Association Council on Nutrition, Physical Activity, and Metabolism. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation*. 2004;110:2952–2967.
- Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415–1428.
- Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2005;28:2289–2304.
- Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001;414:782–787.
- Grundy SM, Hansen B, Smith SC Jr, Cleeman JI, Kahn RA; American Heart Association; National Heart, Lung, and Blood Institute; American Diabetes Association. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. *Circulation*. 2004;109:551–556.
- Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004;109:433–438.
- Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.
- Yusuf S, Vaz M, Pais P. Tackling the challenge of cardiovascular disease burden in developing countries. *Am Heart J*. 2004;148:1–4.
- Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA*. 2003;289:187–193.
- Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24:683–689.
- Lakka HM, Laaksonen DE, Lakka TA, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288:2709–2716.
- Girman CJ, Rhodes T, Mercuri M, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Am J Cardiol*. 2004;93:136–141.
- Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*. 2004;110:1245–1250.
- Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K; DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med*. 2004;164:1066–1076.
- Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, Hayflick L, Butler RN, Allison DB, Ludwig DS. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med*. 2005;352:1138–1145.
- Snyder EE, Walts B, Perusse L, Chagnon YC, Weisnagel SJ, Rankinen T, Bouchard C. The human obesity gene map: the 2003 update. *Obes Res*. 2004;12:369–439.
- Stunkard AJ, Foch TT, Hrubec Z. A twin study of human obesity. *JAMA*. 1986;256:51–54.
- Stunkard AJ, Sorensen TI, Hanis C, Teasdale TW, Chakraborty R, Schull WJ, Schulsinger F. An adoption study of human obesity. *N Engl J Med*. 1986;314:193–198.
- Vohl MC, Sladek R, Robitaille J, Gurd S, Marceau P, Richard D, Hudson TJ, Tchernof A. A survey of genes differentially expressed in

- subcutaneous and visceral adipose tissue in men. *Obes Res.* 2004;12:1217–1222.
32. Bouchard L, Drapeau V, Provencher V, Lemieux S, Chagnon Y, Rice T, Rao DC, Vohl MC, Tremblay A, Bouchard C, Perusse L. Neuromedin beta: a strong candidate gene linking eating behaviors and susceptibility to obesity. *Am J Clin Nutr.* 2004;80:1478–1486.
 33. Poirier P, Eckel RH. Obesity and cardiovascular disease. *Curr Ath-eroscler Rep.* 2002;4:448–453.
 34. Poirier P, Eckel RH. The heart and obesity. In: Fuster V, Alexander RW, King S, O'Rourke RA, Roberts R, Wellens HJJ, editors. *Hurst's The Heart.* New York: McGraw-Hill Companies, 2000;2289–2303.
 35. Teixeira PJ, Sardinha LB, Going SB, Lohman TG. Total and regional fat and serum cardiovascular disease risk factors in lean and obese children and adolescents. *Obes Res.* 2001;9:432–442.
 36. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents: a follow-up of the Harvard Growth Study of 1922 to 1935. *N Engl J Med.* 1992;327:1350–1355.
 37. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med.* 2002;162:1867–1872.
 38. Eckel RH, Barouch WW, Ershow AG. Report of the National Heart, Lung, and Blood Institute–National Institute of Diabetes and Digestive and Kidney Diseases Working Group on the pathophysiology of obesity-associated cardiovascular disease. *Circulation.* 2002;105:2923–2928.
 39. Drenick EJ, Bale GS, Seltzer F, Johnson DG. Excessive mortality and causes of death in morbidly obese men. *JAMA.* 1980;243:443–445.
 40. Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L; NEDCOM, the Netherlands Epidemiology and Demography Compression of Morbidity Research Group. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Ann Intern Med.* 2003;138:24–32.
 41. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med.* 2004;351:2694–2703.
 42. Poirier P, Martin J, Marceau P, Biron S, Marceau S. Impact of bariatric surgery on cardiac structure, function and clinical manifestations in morbid obesity. *Expert Rev Cardiovasc Ther.* 2004;2:193–201.
 43. Christian HA. Some newer aspects of the pathology of fat and fatty infiltration. *Bull Johns Hopkins Hosp.* 1905;16:1–6.
 44. Crandall DL, Hausman GJ, Kral JG. A review of the microcirculation of adipose tissue: anatomic, metabolic, and angiogenic perspectives. *Microcirculation.* 1997;4:211–232.
 45. Rosell S, Belfrage E. Blood circulation in adipose tissue. *Physiol Rev.* 1979;59:1078–1104.
 46. Larsen OA, Lassen NA, Quaade F. Blood flow through human adipose tissue determined with radioactive xenon. *Acta Physiol Scand.* 1966;66:337–345.
 47. Lesser GT, Deutsch S. Measurement of adipose tissue blood flow and perfusion in man by uptake of ⁸⁵Kr. *J Appl Physiol.* 1967;23:621–630.
 48. Oberg B, Rosell S. Sympathetic control of consecutive vascular sections in canine subcutaneous adipose tissue. *Acta Physiol Scand.* 1967;71:47–56.
 49. Karpe F, Fielding BA, Ilic V, Humphreys SM, Frayn KN. Monitoring adipose tissue blood flow in man: a comparison between the (133)xenon washout method and microdialysis. *Int J Obes Relat Metab Disord.* 2002;26:1–5.
 50. Karpe F, Fielding BA, Ilic V, Macdonald IA, Summers LK, Frayn KN. Impaired postprandial adipose tissue blood flow response is related to aspects of insulin sensitivity. *Diabetes.* 2002;51:2467–2473.
 51. Summers LK, Samra JS, Humphreys SM, Morris RJ, Frayn KN. Subcutaneous abdominal adipose tissue blood flow: variation within and between subjects and relationship to obesity. *Clin Sci (Lond).* 1996;91:679–683.
 52. Linde B, Chisolm G. The interstitial space of adipose tissue as determined by single injection and equilibration techniques. *Acta Physiol Scand.* 1975;95:383–390.
 53. Collis T, Devereux RB, Roman MJ, de Simone G, Yeh J, Howard BV, Fabsitz RR, Welty TK. Relations of stroke volume and cardiac output to body composition: the strong heart study. *Circulation.* 2001;103:820–825.
 54. Bella JN, Devereux RB, Roman MJ, O'Grady MJ, Welty TK, Lee ET, Fabsitz RR, Howard BV. Relations of left ventricular mass to fat-free and adipose body mass: the strong heart study: the Strong Heart Study Investigators. *Circulation.* 1998;98:2538–2544.
 55. Kern PA, Saghizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB. The expression of tumor necrosis factor in human adipose tissue: regulation by obesity, weight loss, and relationship to lipoprotein lipase. *J Clin Invest.* 1995;95:2111–2119.
 56. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor- α in human obesity and insulin resistance. *J Clin Invest.* 1995;95:2409–2415.
 57. Lundgren CH, Brown SL, Nordt TK, Sobel BE, Fujii S. Elaboration of type-I plasminogen activator inhibitor from adipocytes: a potential pathogenetic link between obesity and cardiovascular disease. *Circulation.* 1996;93:106–110.
 58. Stepan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. *Nature.* 2001;409:307–312.
 59. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocr Rev.* 2000;21:697–738.
 60. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol.* 1999;19:972–978.
 61. Cigolini M, Targher G, Bergamo AI, Tonoli M, Agostino G, De Sandre G. Visceral fat accumulation and its relation to plasma hemostatic factors in healthy men. *Arterioscler Thromb Vasc Biol.* 1996;16:368–374.
 62. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, Klein S, Coppack SW. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor- α , in vivo. *J Clin Endocrinol Metab.* 1997;82:4196–4200.
 63. Ridker PM. Novel risk factors and markers for coronary disease. *Adv Intern Med.* 2000;45:391–418.
 64. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. *Am J Med Sci.* 2001;321:225–236.
 65. Kasper EK, Hruban RH, Baughman KL. Cardiomyopathy of obesity: a clinicopathologic evaluation of 43 obese patients with heart failure. *Am J Cardiol.* 1992;70:921–924.
 66. Mattsson E, Larsson UE, Rossner S. Is walking for exercise too exhausting for obese women? *Int J Obes Relat Metab Disord.* 1997;21:380–386.
 67. Poirier P, Despres JP. Exercise in weight management of obesity. *Cardiol Clin.* 2001;19:459–470.
 68. Kaltman AJ, Goldring RM. Role of circulatory congestion in the cardiorespiratory failure of obesity. *Am J Med.* 1976;60:645–653.
 69. Messerli FH, Nunez BD, Ventura HO, Snyder DW. Overweight and sudden death: increased ventricular ectopy in cardiopathy of obesity. *Arch Intern Med.* 1987;147:1725–1728.
 70. Messerli FH. Cardiopathy of obesity: a not-so-Victorian disease. *N Engl J Med.* 1986;314:378–380.
 71. Ku CS, Lin SL, Wang DJ, Chang SK, Lee WJ. Left ventricular filling in young normotensive obese adults. *Am J Cardiol.* 1994;73:613–615.
 72. Sasson Z, Rasooly Y, Gupta R, Rasooly I. Left atrial enlargement in healthy obese: prevalence and relation to left ventricular mass and diastolic function. *Can J Cardiol.* 1996;12:257–263.
 73. Wang TJ, Parise H, Levy D, D'Agostino RB Sr, Wolf PA, Vasan RS, Benjamin EJ. Obesity and the risk of new-onset atrial fibrillation. *JAMA.* 2004;292:2471–2477.
 74. Backman L, Freyschuss U, Hallberg D, Melcher A. Reversibility of cardiovascular changes in extreme obesity: effects of weight reduction through jejunioileostomy. *Acta Med Scand.* 1979;205:367–373.
 75. Alexander JK, Peterson KL. Cardiovascular effects of weight reduction. *Circulation.* 1972;45:310–318.
 76. Alpert MA, Lambert CR, Panayiotou H, Terry BE, Cohen MV, Massey CV, Hashimi MW, Mukerji V. Relation of duration of morbid obesity to left ventricular mass, systolic function, and diastolic filling, and effect of weight loss. *Am J Cardiol.* 1995;76:1194–1197.
 77. Karason K, Lindroos AK, Stenlof K, Sjostrom L. Relief of cardiorespiratory symptoms and increased physical activity after surgically induced weight loss: results from the Swedish Obese Subjects Study. *Arch Intern Med.* 2000;160:1797–1802.
 78. Alpert MA, Lambert CR, Terry BE, Cohen MV, Mulekar M, Massey CV, Hashimi MW, Panayiotou H, Mukerji V. Effect of weight loss on left ventricular diastolic filling in morbid obesity. *Am J Cardiol.* 1995;76:1198–1201.

79. Chakko S, Mayor M, Allison MD, Kessler KM, Materson BJ, Myerburg RJ. Abnormal left ventricular diastolic filling in eccentric left ventricular hypertrophy of obesity. *Am J Cardiol.* 1991;68:95–98.
80. Amad KH, Brennan JC, Alexander JK. The cardiac pathology of chronic exogenous obesity. *Circulation.* 1965;32:740–745.
81. Drenick EJ, Fislis JS. Sudden cardiac arrest in morbidly obese surgical patients unexplained after autopsy. *Am J Surg.* 1988;155:720–726.
82. Messerli FH, Sundgaard-Riise K, Reisin ED, Dreslinski GR, Ventura HO, Oigman W, Frohlich ED, Dunn FG. Dimorphic cardiac adaptation to obesity and arterial hypertension. *Ann Intern Med.* 1983;99:757–761.
83. Iacobellis G, Ribaldo MC, Leto G, Zappaterreno A, Vecchi E, Di Mario U, Leonetti F. Influence of excess fat on cardiac morphology and function: study in uncomplicated obesity. *Obes Res.* 2002;10:767–773.
84. Smith HL, Willius FA. Adiposity of the heart: a clinical and pathologic study of one hundred and thirty-six obese patients. *Arch Intern Med.* 1933;52:911–931.
85. Morabito D, Vallotton MB, Lang U. Obesity is associated with impaired ventricular protein kinase C-MAP kinase signaling and altered ANP mRNA expression in the heart of adult Zucker rats. *J Investig Med.* 2001;49:310–318.
86. van de WG, Zaninetti D, Lang U, Vallotton MB, Jeanrenaud B. Identification of a major defect in insulin-resistant tissues of genetically obese (fa/fa) rats. Impaired protein kinase C. *Diabetes.* 1987;36:310–314.
87. Montani JP, Carroll JF, Dwyer TM, Antic V, Yang Z, Dulloo AG. Ectopic fat storage in heart, blood vessels and kidneys in the pathogenesis of cardiovascular diseases. *Int J Obes Relat Metab Disord.* 2004;28(suppl 4):S58–S65.
88. Cheyne J. A case of apoplexy in which the fleshy part of the heart was converted into fat. *Dublin Hosp Rep.* 1818;2:216–223.
89. Roberts WC, Roberts JD. The floating heart or the heart too fat to sink: analysis of 55 necropsy patients. *Am J Cardiol.* 1983;52:1286–1289.
90. Carpenter HM. Myocardial fat infiltration. *Am Heart J.* 1962;63:491–496.
91. Lugo M, Putong PB. Metaplasia: an overview. *Arch Pathol Lab Med.* 1984;108:185–189.
92. Balsaver AM, Morales AR, Whitehouse FW. Fat infiltration of myocardium as a cause of cardiac conduction defect. *Am J Cardiol.* 1967;19:261–265.
93. Spain DM, Cathcart RT. Heart block caused by fat infiltration of the inter-ventricular septum (cor adiposum). *Am Heart J.* 1946;32:659–664.
94. Dervan JP, Ilcercil A, Kane PB, Anagnostopoulos C. Fatty infiltration: another restrictive cardiomyopathic pattern. *Cathet Cardiovasc Diagn.* 1991;22:184–189.
95. De Scheerder I, Cuvelier C, Verhaaren R, De Buyzere M, De Backer G, Clement D. Restrictive cardiomyopathy caused by adipositas cordis. *Eur Heart J.* 1987;8:661–663.
96. Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, Orci L, Unger RH. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A.* 2000;97:1784–1789.
97. Poirier P, Alpert MA. Heart disease. In: Eckel RH, editor. *Obesity: Mechanisms and Clinical Management.* Philadelphia: Williams & Wilkins, 2003;181–201.
98. Mackenzie J. *The Study of the Pulse, Arterial, Venous and Hepatic, and Movements of the Heart.* Edinburgh: 1902.
99. Nelson WP, North RL. Splitting of the second heart sound in adults forty years and older. *Am J Med Sci.* 1967;254:805–807.
100. Weyman AE, Davidoff R, Gardin J, Ryan T, St John Sutton M, Weissman NJ. Echocardiographic evaluation of pulmonary artery pressure with clinical correlates in predominantly obese adults. *J Am Soc Echocardiogr.* 2002;15:454–462.
101. Alpert MA, Terry BE, Cohen MV, Fan TM, Painter JA, Massey CV. The electrocardiogram in morbid obesity. *Am J Cardiol.* 2000;85:908–910.
102. Eisenstein I, Edelstein J, Sarma R, Sanmarco M, Selvester RH. The electrocardiogram in obesity. *J Electrocardiol.* 1982;15:115–118.
103. Master AM, Oppenheimer ET. A study of obesity: circulatory, roentgen-ray and electrocardiographic investigations. *JAMA.* 1929;92:1652–1656.
104. Nomura A, Zareba W, Moss AJ. Obesity does not influence electrocardiographic parameters in coronary patients. *Am J Cardiol.* 2000;85:106–8, A9.
105. Alpert MA, Terry BE, Hamm CR, Fan TM, Cohen MV, Massey CV, Painter JA. Effect of weight loss on the ECG of normotensive morbidly obese patients. *Chest.* 2001;119:507–510.
106. Pidlich J, Pfeffel F, Zwiauer K, Schneider B, Schmidinger H. The effect of weight reduction on the surface electrocardiogram: a prospective trial in obese children and adolescents. *Int J Obes Relat Metab Disord.* 1997;21:1018–1023.
107. Starr JW, Wagner GS, Behar VS, Walston A II, Greenfield JC Jr. Vectorcardiographic criteria for the diagnosis of inferior myocardial infarction. *Circulation.* 1974;49:829–836.
108. Benjamin EJ, Levy D. Why is left ventricular hypertrophy so predictive of morbidity and mortality? *Am J Med Sci.* 1999;317:168–175.
109. Alpert MA, Alexander JK. *The Heart and Lung in Obesity.* Armonk: Futura Publishing Company, 1998.
110. Nath A, Alpert MA, Terry BE, Kelly DL. Sensitivity and specificity of electrocardiographic criteria for left and right ventricular hypertrophy in morbid obesity. *Am J Cardiol.* 1988;62:126–130.
111. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, Phillips MC. Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. *J Am Coll Cardiol.* 1985;6:572–580.
112. Abergel E, Tase M, Menard J, Chatellier G. Influence of obesity on the diagnostic value of electrocardiographic criteria for detecting left ventricular hypertrophy. *Am J Cardiol.* 1996;77:739–744.
113. Pringle TH, Scobie IN, Murray RG, Kesson CM, Maccuish AC. Prolongation of the QT interval during therapeutic starvation: a substrate for malignant arrhythmias. *Int J Obes.* 1983;7:253–261.
114. Sandhofer F, Dienst F, Bolzano K, et al. Severe cardiovascular complication associated with prolonged starvation. *BMJ.* 1973;1:462–463.
115. Garnett ES, Barnard DL, Ford J, Goodbody RA, Woodehouse MA. Gross fragmentation of cardiac myofibrils after therapeutic starvation for obesity. *Lancet.* 1969;1:914–916.
116. Rasmussen LH, Andersen T. The relationship between QTc changes and nutrition during weight loss after gastroplasty. *Acta Med Scand.* 1985;217:271–275.
117. Sours HE, Frattali VP, Brand CD, Feldman RA, Forbes AL, Swanson RC, Paris AL. Sudden death associated with very low calorie weight reduction regimens. *Am J Clin Nutr.* 1981;34:453–461.
118. Isner JM, Sours HE, Paris AL, Ferrans VJ, Roberts WC. Sudden, unexpected death in avid dieters using the liquid-protein-modified-fast diet. Observations in 17 patients and the role of the prolonged QT interval. *Circulation.* 1979;60:1401–1412.
119. Saphir O, Corrigan M. Fatty infiltration of the myocardium. *Arch Intern Med.* 1933;52:410–428.
120. Quain R. Fatty diseases of the heart. *Medico-Chirurgical Transactions.* 1850;33:121–196.
121. House AA, Walley VM. Right heart failure due to ventricular adiposity: ‘adipositas cordis’: an old diagnosis revisited. *Can J Cardiol.* 1996;12:485–489.
122. Pratt JH. On the causes of cardiac insufficiency. *Bull Johns Hopkins Hosp.* 1904;15:301–309.
123. Master AM. Fatty degeneration of the heart. *Arch Intern Med.* 1923;22:221–231.
124. Alpert MA, Lambert CR, Terry BE, Kelly DL, Panayiotou H, Mukerji V, Massey CV, Cohen MV. Effect of weight loss on left ventricular mass in nonhypertensive morbidly obese patients. *Am J Cardiol.* 1994;73:918–921.
125. Alpert MA, Kelly DL. Value and limitations of echocardiography assessment of obese patients. *Echocardiography.* 1986;3:261–272.
126. Ansari A, Rholi AO. Pseudopericardial effusion: echocardiographic and computed tomographic correlations. *Clin Cardiol.* 1986;9:551–555.
127. Savage DD, Garrison RJ, Brand F, Anderson SJ, Castelli WP, Kannel WB, Feinleib M. Prevalence and correlates of posterior extra echocardiographic spaces in a free-living population based sample (the Framingham study). *Am J Cardiol.* 1983;51:1207–1212.
128. Prior JT. Lipomatous hypertrophy of the cardiac interatrial septum: a lesion resembling hibernoma, lipoblastomatosis and infiltrating lipoma. *Arch Pathol.* 1964;78:11–15.
129. Page DL. Lipomatous hypertrophy of the cardiac interatrial septum: its development and probable clinical significance. *Hum Pathol.* 1970;1:151–163.
130. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG. Diastolic dysfunction in type 2 diabetes men without hypertension or coronary artery disease: importance of the Valsalva maneuver in screening patients. *Diabetes Care.* 2001;24:5–10.
131. Dumesnil JG, Gaudreault G, Honos GN, Kingma JG Jr. Use of Valsalva maneuver to unmask left ventricular diastolic function abnormalities by

- Doppler echocardiography in patients with coronary artery disease or systemic hypertension. *Am J Cardiol.* 1991;68:515–519.
132. Peterson LR, Waggoner AD, Schechtman KB, Meyer T, Gropler RJ, Barzilai B, Davila-Roman VG. Alterations in left ventricular structure and function in young healthy obese women: assessment by echocardiography and tissue Doppler imaging. *J Am Coll Cardiol.* 2004;43:1399–1404.
 133. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol.* 1992;20:1251–1260.
 134. Lauer MS, Anderson KM, Larson MG, Levy D. A new method for indexing left ventricular mass for differences in body size. *Am J Cardiol.* 1994;74:487–491.
 135. Daniels SR, Kimball TR, Morrison JA, Khoury P, Witt S, Meyer RA. Effect of lean body mass, fat mass, blood pressure, and sexual maturation on left ventricular mass in children and adolescents. Statistical, biological, and clinical significance. *Circulation.* 1995;92:3249–3254.
 136. Hense HW, Gneiting B, Muscholl M, Broeckel U, Kuch B, Doering A, Riegger GA, Schunkert H. The associations of body size and body composition with left ventricular mass: impacts for indexation in adults. *J Am Coll Cardiol.* 1998;32:451–457.
 137. de Divitiis O, Fazio S, Petitto M, Maddalena G, Contaldo F, Mancini M. Obesity and cardiac function. *Circulation.* 1981;64:477–482.
 138. Nakajima T, Fujioka S, Tokunaga K, Matsuzawa Y, Tarui S. Correlation of intraabdominal fat accumulation and left ventricular performance in obesity. *Am J Cardiol.* 1989;64:369–373.
 139. Sugeran HJ, Sugeran EL, Wolfe L, Kellum JM Jr, Schweitzer MA, DeMaria EJ. Risks and benefits of gastric bypass in morbidly obese patients with severe venous stasis disease. *Ann Surg.* 2001;234:41–46.
 140. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med.* 2002;162:1182–1189.
 141. Hansson PO, Eriksson H, Welin L, Svardsudd K, Wilhelmsen L. Smoking and abdominal obesity: risk factors for venous thromboembolism among middle-aged men: 'the study of men born in 1913.' *Arch Intern Med.* 1999;159:1886–1890.
 142. Goldhaber SZ, Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Willett WC, Hennekens CH. A prospective study of risk factors for pulmonary embolism in women. *JAMA.* 1997;277:642–645.
 143. Blaszyk H, Wollan PC, Witkiewicz AK, Bjornsson J. Death from pulmonary thromboembolism in severe obesity: lack of association with established genetic and clinical risk factors. *Virchows Arch.* 1999;434:529–532.
 144. Blaszyk H, Bjornsson J. Factor V Leiden and morbid obesity in fatal postoperative pulmonary embolism. *Arch Surg.* 2000;135:1410–1413.
 145. Arcaro G, Zamboni M, Rossi L, Turcato E, Covi G, Armellini F, Bosello O, Lechi A. Body fat distribution predicts the degree of endothelial dysfunction in uncomplicated obesity. *Int J Obes Relat Metab Disord.* 1999;23:936–942.
 146. Lee KU. Oxidative stress markers in Korean subjects with insulin resistance syndrome. *Diabetes Res Clin Pract.* 2001;54 Suppl 2:S29–S33.
 147. Keaney JF Jr, Larson MG, Vasan RS, Wilson PW, Lipinska I, Corey D, Massaro JM, Sutherland P, Vita JA, Benjamin EJ; Framingham Study. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. *Arterioscler Thromb Vasc Biol.* 2003;23:434–439.
 148. Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH. Weight and blood pressure: findings in hypertension screening of 1 million Americans. *JAMA.* 1978;240:1607–1610.
 149. Brown CD, Higgins M, Donato KA, Rohde FC, Garrison R, Obarzanek E, Ernst ND, Horan M. Body mass index and the prevalence of hypertension and dyslipidemia. *Obes Res.* 2000;8:605–619.
 150. Nielsen PE, Janniche H. The accuracy of auscultatory measurement of arm blood pressure in very obese subjects. *Acta Med Scand.* 1974;195:403–409.
 151. King GE. Errors in clinical measurement of blood pressure in obesity. *Clin Sci.* 1967;32:223–237.
 152. Kirkendall WM, Feinleib M, Freis ED, Mark AL. Recommendations for human blood pressure determination by sphygmomanometers: subcommittee of the AHA Postgraduate Education Committee. *Circulation.* 1980;62:1146A–1155A.
 153. Johnson AL, Cornoni JC, Cassel JC, Tyroler HA, Heyden S, Hames CG. Influence of race, sex and weight on blood pressure behavior in young adults. *Am J Cardiol.* 1975;35:523–530.
 154. Voors AW, Webber LS, Frerichs RR, Berenson GS. Body height and body mass as determinants of basal blood pressure in children: the Bogalusa Heart Study. *Am J Epidemiol.* 1977;106:101–108.
 155. Bjorntorp P. Classification of obese patients and complications related to the distribution of surplus fat. *Nutrition.* 1990;6:131–137.
 156. Bjorntorp P. Obesity and adipose tissue distribution as risk factors for the development of disease: a review. *Infusionstherapie.* 1990;17:24–27.
 157. Poirier P, Lemieux I, Mauriege P, Dewailly E, Blanchet C, Bergeron J, Despres JP. Impact of waist circumference on the relationship between blood pressure and insulin: the Quebec Health Survey. *Hypertension.* 2005;45:363–367.
 158. Muller DC, Elahi D, Pratley RE, Tobin JD, Andres R. An epidemiological test of the hyperinsulinemia-hypertension hypothesis. *J Clin Endocrinol Metab.* 1993;76:544–548.
 159. Reisin E. Weight reduction in the management of hypertension: epidemiologic and mechanistic evidence. *Can J Physiol Pharmacol.* 1986;64:818–824.
 160. Ferrannini E. The haemodynamics of obesity: a theoretical analysis. *J Hypertens.* 1992;10:1417–1423.
 161. Reaven GM. Banting lecture 1988: role of insulin resistance in human disease. *Diabetes.* 1988;37:1595–1607.
 162. Poirier P, Despres JP. Waist circumference, visceral obesity, and cardiovascular risk. *J Cardiopulm Rehabil.* 2003;23:161–169.
 163. Hansen BC. The metabolic syndrome X. *Ann N Y Acad Sci.* 1999;892:1–24.
 164. Saad MF, Lillioja S, Nyomba BL, Castillo C, Ferraro R, De Gregorio M, Ravussin E, Knowler WC, Bennett PH, Howard BV. Racial differences in the relation between blood pressure and insulin resistance. *N Engl J Med.* 1991;324:733–739.
 165. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med.* 2003;163:427–436.
 166. Landsberg L, Troisi R, Parker D, Young JB, Weiss ST. Obesity, blood pressure, and the sympathetic nervous system. *Ann Epidemiol.* 1991;1:295–303.
 167. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206–1252.
 168. Tsutsu N, Nuno K, Kodama T, Nomiya M, Iwase M, Fujishima M. Lack of association between blood pressure and insulin in patients with insulinoma. *J Hypertens.* 1990;8:479–482.
 169. Hall JE, Brands MW, Mizelle HL, Gaillard CA, Hildebrandt DA. Chronic intrarenal hyperinsulinemia does not cause hypertension. *Am J Physiol.* 1991;260:F663–F669.
 170. Bastard JP, Jardel C, Delattre J, Hainque B, Bruckert E, Oberlin F. Evidence for a link between adipose tissue interleukin-6 content and serum C-reactive protein concentrations in obese subjects. *Circulation.* 1999;99:2221–2222.
 171. Frohlich M, Imhof A, Berg G, Hutchinson WL, Pepys MB, Boeing H, Muehle R, Brenner H, Koenig W. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care.* 2000;23:1835–1839.
 172. Schotte DE, Stunkard AJ. The effects of weight reduction on blood pressure in 301 obese patients. *Arch Intern Med.* 1990;150:1701–1704.
 173. Novi RF, Porta M, Lamberto M, Molinatti GM. Reductions of body weight and blood pressure in obese hypertensive patients treated by diet. A retrospective study. *Panminerva Med.* 1989;31:13–15.
 174. Staessen J, Fagard R, Amery A. The relationship between body weight and blood pressure. *J Hum Hypertens.* 1988;2:207–217.
 175. Pontiroli AE, Pizzocri P, Saibene A, Girola A, Koprivic D, Fragasso G. Left ventricular hypertrophy and QT interval in obesity and in hypertension: effects of weight loss and of normalisation of blood pressure. *Int J Obes Relat Metab Disord.* 2004;28:1118–1123.

176. Sjostrom CD, Peltonen M, Wedel H, Sjostrom L. Differentiated long-term effects of intentional weight loss on diabetes and hypertension. *Hypertension*. 2000;36:20–25.
177. Phillipson EA. Sleep apnea: a major public health problem. *N Engl J Med*. 1993;328:1271–1273.
178. Bearpark H, Elliott L, Grunstein R, Cullen S, Schneider H, Althaus W, Sullivan C. Snoring and sleep apnea: a population study in Australian men. *Am J Respir Crit Care Med*. 1995;151:1459–1465.
179. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328:1230–1235.
180. Strollo PJ Jr, Rogers RM. Obstructive sleep apnea. *N Engl J Med*. 1996;334:99–104.
181. Vgontzas AN, Tan TL, Bixler EO, Martin LF, Shubert D, Kales A. Sleep apnea and sleep disruption in obese patients. *Arch Intern Med*. 1994;154:1705–1711.
182. Narkiewicz K, van de Borne PJ, Cooley RL, Dyken ME, Somers VK. Sympathetic activity in obese subjects with and without obstructive sleep apnea. *Circulation*. 1998;98:772–776.
183. Viner S, Szalai JP, Hoffstein V. Are history and physical examination a good screening test for sleep apnea? *Ann Intern Med*. 1991;115:356–359.
184. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA*. 2000;283:1829–1836.
185. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, Somers VK. Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation*. 2002;105:2462–2464.
186. Partinen M, Jamieson A, Guilleminault C. Long-term outcome for obstructive sleep apnea syndrome patients. Mortality. *Chest*. 1988;94:1200–1204.
187. Kessler R, Chaouat A, Weitzenblum E, Oswald M, Ehrhart M, Apprill M, Krieger J. Pulmonary hypertension in the obstructive sleep apnoea syndrome: prevalence, causes and therapeutic consequences. *Eur Respir J*. 1996;9:787–794.
188. Laaban JP, Cassuto D, Orvoen-Frija E, Iliou MC, Mundler O, Leger D, Oppert JM. Cardiorespiratory consequences of sleep apnoea syndrome in patients with massive obesity. *Eur Respir J*. 1998;11:20–27.
189. Marquis K, Maltais F, Duguay V, Bezeau AM, LeBlanc P, Jobin J, Poirier P. The metabolic syndrome in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil*. 2005;25:226–232.
190. Amad KH, Brennan JC, Alexander JK. The cardiac pathology of chronic exogenous obesity. *Circulation*. 1965;32:740–745.
191. James TN, Frame B, Coates EO. De subitaneis mortibus, 3: Pickwickian syndrome. *Circulation*. 1973;48:1311–1320.
192. Sugerman HJ, Baron PL, Fairman RP, Evans CR, Vetrovec GW. Hemodynamic dysfunction in obesity hypoventilation syndrome and the effects of treatment with surgically induced weight loss. *Ann Surg*. 1988;207:604–613.
193. Abbott RD, Behrens GR, Sharp DS, Rodriguez BL, Burchfiel CM, Ross GW, Yano K, Curb JD. Body mass index and thromboembolic stroke in nonsmoking men in older middle age: the Honolulu Heart Program. *Stroke*. 1994;25:2370–2376.
194. Rhoads GG, Kagan A. The relation of coronary disease, stroke, and mortality to weight in youth and in middle age. *Lancet*. 1983;1:492–495.
195. Shinton R, Shipley M, Rose G. Overweight and stroke in the Whitehall study. *J Epidemiol Community Health*. 1991;45:138–142.
196. Rexrode KM, Hennekens CH, Willett WC, Colditz GA, Stampfer MJ, Rich-Edwards JW, Speizer FE, Manson JE. A prospective study of body mass index, weight change, and risk of stroke in women. *JAMA*. 1997;277:1539–1545.
197. Lapidus L, Bengtsson C, Larsson B, et al. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *BMJ (Clin Res Ed)*. 1984;289:1257–1261.
198. Folsom AR, Prineas RJ, Kaye SA, Munger RG. Incidence of hypertension and stroke in relation to body fat distribution and other risk factors in older women. *Stroke*. 1990;21:701–706.
199. Terry RB, Page WF, Haskell WL. Waist/hip ratio, body mass index and premature cardiovascular disease mortality in US Army veterans during a twenty-three year follow-up study. *Int J Obes Relat Metab Disord*. 1992;16:417–423.
200. Walker SP, Rimm EB, Ascherio A, Kawachi I, Stampfer MJ, Willett WC. Body size and fat distribution as predictors of stroke among US men. *Am J Epidemiol*. 1996;144:1143–1150.
201. Pyorala M, Miettinen H, Laakso M, Pyorala K. Hyperinsulinemia and the risk of stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. *Stroke*. 1998;29:1860–1866.
202. Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR, Buring JE, Manson JE. Body mass index and the risk of stroke in men. *Arch Intern Med*. 2002;162:2557–2562.
203. Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massaro JM, D'Agostino RB, Franzblau C, Wilson PW. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. *Stroke*. 2001;32:2575–2579.
204. Sriram K, Benkovic SA, Miller DB, O'Callaghan JP. Obesity exacerbates chemically induced neurodegeneration. *Neuroscience*. 2002;115:1335–1346.
205. McGill HC Jr. Fatty streaks in the coronary arteries and aorta. *Lab Invest*. 1968;18:560–564.
206. Skalen K, Gustafsson M, Rydberg EK, Hulthen LM, Wiklund O, Innerarity TL, Boren J. Subendothelial retention of atherogenic lipoproteins in early atherosclerosis. *Nature*. 2002;417:750–754.
207. Joseph LJ, Ryan AS, Sorkin J, Mangano C, Brendle DC, Corretti MC, Gardner AW, Katzell LI. Body fat distribution and flow-mediated endothelium-dependent vasodilation in older men. *Int J Obes Relat Metab Disord*. 2002;26:663–669.
208. Bots ML, Hofman A, Grobbee DE. Increased common carotid intima-media thickness: adaptive response or a reflection of atherosclerosis? Findings from the Rotterdam Study. *Stroke*. 1997;28:2442–2447.
209. Spence JD. Ultrasound measurement of carotid plaque as a surrogate outcome for coronary artery disease. *Am J Cardiol*. 2002;89:10B–15B.
210. Heiss G, Sharrett AR, Barnes R, Chambless LE, Szklo M, Alzola C. Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. *Am J Epidemiol*. 1991;134:250–256.
211. Ciccone M, Vettor R, Pannaciuoli N, Minenna A, Bellacicco M, Rizzon P, Giorgino R, De Pergola G. Plasma leptin is independently associated with the intima-media thickness of the common carotid artery. *Int J Obes Relat Metab Disord*. 2001;25:805–810.
212. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation*. 1997;96:1432–1437.
213. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults: Cardiovascular Health Study Collaborative Research Group. *N Engl J Med*. 1999;340:14–22.
214. Freedman DS, Dietz WH, Tang R, Mensah GA, Bond MG, Urbina EM, Srinivasan S, Berenson GS. The relation of obesity throughout life to carotid intima-media thickness in adulthood: the Bogalusa Heart Study. *Int J Obes Relat Metab Disord*. 2004;28:159–166.
215. Bogaty P, Poirier P, Simard S, Boyer L, Solymoss S, Dagenais GR. Biological profiles in subjects with recurrent acute coronary events compared with subjects with long-standing stable angina. *Circulation*. 2001;103:3062–3068.
216. Bogaty P, Robitaille NM, Solymoss S, Boyer L, Auger D, Labbe L, Simard S, Rail J, Genest J Jr, Turgeon J. Atherogenic, hemostatic, and other potential risk markers in subjects with previous isolated myocardial infarction compared with long-standing uncomplicated stable angina. *Am Heart J*. 1998;136:884–893.
217. McGill HC Jr, McMahan CA, Herderick EE, Malcom GT, Tracy RE, Strong JP. Origin of atherosclerosis in childhood and adolescence. *Am J Clin Nutr*. 2000;72:1307S–1315S.
218. Berenson GS. Bogalusa Heart Study: a long-term community study of a rural biracial (black/white) population. *Am J Med Sci*. 2001;322:267–274.
219. Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea. *JAMA*. 1953;152:1090–1093.
220. McGill HC Jr, McMahan CA, Malcom GT, Oalmann MC, Strong JP. Relation of glycohemoglobin and adiposity to atherosclerosis in youth. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arterioscler Thromb Vasc Biol*. 1995;15:431–440.
221. Zieske AW, Malcom GT, Strong JP. Natural history and risk factors of atherosclerosis in children and youth: the PDAY study. *Pediatr Pathol Mol Med*. 2002;21:213–237.
222. McGill HC Jr, McMahan CA, Herderick EE, Zieske AW, Malcom GT, Tracy RE, Strong JP. Pathobiological Determinants of Atherosclerosis

- in Youth (PDAY) Research Group. Obesity accelerates the progression of coronary atherosclerosis in young men. *Circulation*. 2002;105:2712–2718.
223. Kortelainen ML, Sarkioja T. Visceral fat and coronary pathology in male adolescents. *Int J Obes Relat Metab Disord*. 2001;25:228–232.
 224. Kannel WB. The Framingham Study: historical insight on the impact of cardiovascular risk factors in men versus women. *J Genet Specif Med*. 2002;5:27–37.
 225. Kortelainen ML. Myocardial infarction and coronary pathology in severely obese people examined at autopsy. *Int J Obes Relat Metab Disord*. 2002;26:73–79.
 226. Rabkin SW, Mathewson FA, Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26 year observation period: the Manitoba Study. *Am J Cardiol*. 1977;39:452–458.
 227. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*. 1983;67:968–977.
 228. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, Speizer FE, Hennekens CH. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med*. 1990;322:882–889.
 229. Dagenais GR, Yi Q, Mann JF, Bosch J, Pogue J, Yusuf S. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. *Am Heart J*. 2005;149:54–60.
 230. Kragelund C, Hassager C, Hildebrandt P, Torp-Pedersen C, Kober L; TRACE study group. Impact of obesity on long-term prognosis following acute myocardial infarction. *Int J Cardiol*. 2005;98:123–131.
 231. Gal RA, Gunasekera J, Massardo T, Shalev Y, Port SC. Long-term prognostic value of a normal dipyridamole thallium-201 perfusion scan. *Clin Cardiol*. 1991;14:971–974.
 232. Ferraro S, Perrone-Filardi P, Desiderio A, Betocchi S, D'Alto M, Liguori L, Trimigliozzi P, Turco S, Chiariello M. Left ventricular systolic and diastolic function in severe obesity: a radionuclide study. *Cardiology*. 1996;87:347–353.
 233. Freedman N, Schechter D, Klein M, Marciano R, Rozenman Y, Chisin R. SPECT attenuation artifacts in normal and overweight persons: insights from a retrospective comparison of Rb-82 positron emission tomography and Tl-201 SPECT myocardial perfusion imaging. *Clin Nucl Med*. 2000;25:1019–1023.
 234. Prvulovich EM, Lonn AH, Bomanji JB, Jarritt PH, Ell PJ. Transmission scanning for attenuation correction of myocardial 201Tl images in obese patients. *Nucl Med Commun*. 1997;18:207–218.
 235. Barnden LR, Ong PL, Rowe CC. Simultaneous emission transmission tomography using technetium-99m for both emission and transmission. *Eur J Nucl Med*. 1997;24:1390–1397.
 236. McNulty PH, Ettinger SM, Field JM, Gilchrist IC, Kozak M, Chambers CE, Gascho JA. Cardiac catheterization in morbidly obese patients. *Catheter Cardiovasc Interv*. 2002;56:174–177.
 237. Madu EC. Transesophageal dobutamine stress echocardiography in the evaluation of myocardial ischemia in morbidly obese subjects. *Chest*. 2000;117:657–661.
 238. Barbeau GR, Arsenault F, Dugas L, Simard S, Lariviere MM. Evaluation of the ulnopalmar arterial arches with pulse oximetry and plethysmography: comparison with the Allen's test in 1010 patients. *Am Heart J*. 2004;147:489–493.
 239. Eisenstein EL, Shaw LK, Nelson CL, Anstrom KJ, Hakim Z, Mark DB. Obesity and long-term clinical and economic outcomes in coronary artery disease patients. *Obes Res*. 2002;10:83–91.
 240. Gruberg L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, Ahmed LM, Kent KM, Pichard AD, Suddath WO, Satler LF, Lindsay J Jr. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol*. 2002;39:578–584.
 241. Lakka TA, Lakka HM, Salonen R, Kaplan GA, Salonen JT. Abdominal obesity is associated with accelerated progression of carotid atherosclerosis in men. *Atherosclerosis*. 2001;154:497–504.
 242. Otsuka Y, Miyazaki S, Okumura H, Yasuda S, Daikoku S, Morii I, Sutani Y, Goto Y, Nonogi H. Abnormal glucose tolerance, not small vessel diameter, is a determinant of long-term prognosis in patients treated with balloon coronary angioplasty. *Eur Heart J*. 2000;21:1790–1796.
 243. St Pierre J, Lemieux I, Vohl MC, Perron P, Tremblay G, Despres JP, Gaudet D. Contribution of abdominal obesity and hypertriglyceridemia to impaired fasting glucose and coronary artery disease. *Am J Cardiol*. 2002;90:15–18.
 244. Korpilahti K, Syvanne M, Engblom E, Hamalainen H, Puukka P, Ronnema T. Components of the insulin resistance syndrome are associated with progression of atherosclerosis in non-grafted arteries 5 years after coronary artery bypass surgery. *Eur Heart J*. 1998;19:711–719.
 245. Kowalska I, Prokop J, Bachorzewska-Gajewska H, Telejko B, Kinalskali I, Kochman W, Musial W. Disturbances of glucose metabolism in men referred for coronary arteriography: postload glycemia as predictor for coronary atherosclerosis. *Diabetes Care*. 2001;24:897–901.
 246. Qiao Q, Pyorala K, Pyorala M, Nissinen A, Lindstrom J, Tilvis R, Tuomilehto J. Two-hour glucose is a better risk predictor for incident coronary heart disease and cardiovascular mortality than fasting glucose. *Eur Heart J*. 2002;23:1267.
 247. Marik P, Varon J. The obese patient in the ICU. *Chest*. 1998;113:492–498.
 248. Ascione R, Angelini GD. Is obesity still a risk factor for patients undergoing coronary surgery? *Ital Heart J*. 2003;4:824–828.
 249. Rockx MA, Fox SA, Stitt LW, Lehnhardt KR, McKenzie FN, Quantz MA, Menkis AH, Novick RJ. Is obesity a predictor of mortality, morbidity and readmission after cardiac surgery? *Can J Surg*. 2004;47:34–38.
 250. Moulton MJ, Creswell LL, Mackey ME, Cox JL, Rosenbloom M. Obesity is not a risk factor for significant adverse outcomes after cardiac surgery. *Circulation*. 1996;94:II-87–II-92.
 251. Birkmeyer NJ, Charlesworth DC, Hernandez F, Leavitt BJ, Marrin CA, Morton JR, Olmstead EM, O'Connor GT. Obesity and risk of adverse outcomes associated with coronary artery bypass surgery: Northern New England Cardiovascular Disease Study Group. *Circulation*. 1998;97:1689–1694.
 252. Kuduvali M, Grayson AD, Oo AY, Fabri BM, Rashid A. Risk of morbidity and in-hospital mortality in obese patients undergoing coronary artery bypass surgery. *Eur J Cardiothorac Surg*. 2002;22:787–793.
 253. Rose DK, Cohen MM, Wigglesworth DF, DeBoer DP. Critical respiratory events in the postanesthesia care unit: patient, surgical, and anesthetic factors. *Anesthesiology*. 1994;81:410–418.
 254. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med*. 2001;161:996–1002.
 255. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med*. 2002;347:305–313.
 256. Chen YT, Vaccarino V, Williams CS, Butler J, Berkman LF, Krumholz HM. Risk factors for heart failure in the elderly: a prospective community-based study. *Am J Med*. 1999;106:605–612.
 257. Wilhelmsen L, Rosengren A, Eriksson H, Lappas G. Heart failure in the general population of men: morbidity, risk factors and prognosis. *J Intern Med*. 2001;249:253–261.
 258. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol*. 2001;38:789–795.
 259. Alla F, Briancon S, Juilliere Y, Mertes PM, Villemot JP, Zannad F. Differential clinical prognostic classifications in dilated and ischemic advanced heart failure: the EPICAL study. *Am Heart J*. 2000;139:895–904.
 260. Osman AF, Mehra MR, Lavie CJ, Nunez E, Milani RV. The incremental prognostic importance of body fat adjusted peak oxygen consumption in chronic heart failure. *J Am Coll Cardiol*. 2000;36:2126–2131.
 261. Lissin LW, Gauri AJ, Froelicher VF, Ghayoumi A, Myers J, Giacomini J. The prognostic value of body mass index and standard exercise testing in male veterans with congestive heart failure. *J Card Fail*. 2002;8:206–215.
 262. Davos CH, Doehner W, Rauchhaus M, Ciccoira M, Francis DP, Coats AJ, Clark AL, Anker SD. Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. *J Card Fail*. 2003;9:29–35.
 263. Lavie CJ, Osman AF, Milani RV, Mehra MR. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. *Am J Cardiol*. 2003;91:891–894.
 264. Mosterd A, Cost B, Hoes AW, de Bruijne MC, Deckers JW, Hofman A, Grobbee DE. The prognosis of heart failure in the general population: the Rotterdam Study. *Eur Heart J*. 2001;22:1318–1327.
 265. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ,

- Packer M, Silver MA, Stevenson LW, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure); International Society for Heart and Lung Transplantation; Heart Failure Society of America. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. *Circulation*. 2001;104:2996–3007.
266. Remme WJ, Swedberg K, Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J*. 2001;22:1527–1560.
267. Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, Kosiborod M, Portnay EL, Sokol SI, Bader F, Krumholz HM. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med*. 2005;165:55–61.
268. Grady KL, White-Williams C, Naftel D, Costanzo MR, Pitts D, Rayburn B, VanBakel A, Jaski B, Bourge R, Kirklin J. Are preoperative obesity and cachexia risk factors for post heart transplant morbidity and mortality: a multi-institutional study of preoperative weight-height indices: Cardiac Transplant Research Database (CTRD) Group. *J Heart Lung Transplant*. 1999;18:750–763.
269. Leung RS, Bradley TD. Sleep apnea and cardiovascular disease. *Am J Respir Crit Care Med*. 2001;164:2147–2165.
270. Kannel WB, Plehn JF, Cupples LA. Cardiac failure and sudden death in the Framingham Study. *Am Heart J*. 1988;115:869–875.
271. Brown DW, Giles WH, Greenlund KJ, Valdez R, Croft JB. Impaired fasting glucose, diabetes mellitus, and cardiovascular disease risk factors are associated with prolonged QTc duration: results from the Third National Health and Nutrition Examination Survey. *J Cardiovasc Risk*. 2001;8:227–233.
272. el-Gamal A, Gallagher D, Nawras A, Gandhi P, Gomez J, Allison DB, Steinberg JS, Shumacher B, Blank R, Heymsfield SB. Effects of obesity on QT, RR, and QTc intervals. *Am J Cardiol*. 1995;75:956–959.
273. Mshui ME, Saikawa T, Ito K, Hara M, Sakata T. QT interval and QT dispersion before and after diet therapy in patients with simple obesity. *Proc Soc Exp Biol Med*. 1999;220:133–138.
274. Fukushige T, Yoshinaga M, Shimago A, Nishi J, Kono Y, Nomura Y, Miyata K, Imamura M, Shibata T, Nagashima M, Niimura I. Effect of age and overweight on the QT interval and the prevalence of long QT syndrome in children. *Am J Cardiol*. 2002;89:395–398.
275. Frank S, Colliver JA, Frank A. The electrocardiogram in obesity: statistical analysis of 1,029 patients. *J Am Coll Cardiol*. 1986;7:295–299.
276. Peiris AN, Thakur RK, Sothmann MS, Kok FJ, Vandenbroucke JP, Pool J. Relationship of regional fat distribution and obesity to electrocardiographic parameters in healthy premenopausal women. *South Med J*. 1991;84:961–965.
277. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. *Circulation*. 1991;84:1516–1523.
278. Corbi GM, Carbone S, Ziccardi P, Giugliano G, Marfella R, Nappo F, Paolisso G, Esposito K, Giugliano D. FFAs and QT intervals in obese women with visceral adiposity: effects of sustained weight loss over 1 year. *J Clin Endocrinol Metab*. 2002;87:2080–2083.
279. Girola A, Enrini R, Garbetta F, Tufano A, Caviezel F. QT dispersion in uncomplicated human obesity. *Obes Res*. 2001;9:71–77.
280. Esposito K, Nicoletti G, Marzano S, Gualdiro P, Carusone C, Marfella R, Beneduce F, Giugliano D. Autonomic dysfunction associates with prolongation of QT intervals and blunted night BP in obese women with visceral obesity. *J Endocrinol Invest*. 2002;25:RC32–RC35.
281. Signal-averaged electrocardiography. *J Am Coll Cardiol*. 1996;27:238–249.
282. Lalani AP, Kanna B, John J, Ferrick KJ, Huber MS, Shapiro LE. Abnormal signal-averaged electrocardiogram (SAECG) in obesity. *Obes Res*. 2000;8:20–28.
283. Marfella R, De Angelis L, Nappo F, Manzella D, Siniscalchi M, Paolisso G, Giugliano D. Elevated plasma fatty acid concentrations prolong cardiac repolarization in healthy subjects. *Am J Clin Nutr*. 2001;73:27–30.
284. Abraham R, Riemersma RA, Wood D, Elton R, Oliver MF. Adipose fatty acid composition and the risk of serious ventricular arrhythmias in acute myocardial infarction. *Am J Cardiol*. 1989;63:269–272.
285. D'Amico M, Marfella R, Nappo F, Di Filippo C, De Angelis L, Berrino L, Rossi F, Giugliano D. High glucose induces ventricular instability and increases vasomotor tone in rats. *Diabetologia*. 2001;44:464–470.
286. Marfella R, Nappo F, De Angelis L, Siniscalchi M, Rossi F, Giugliano D. The effect of acute hyperglycaemia on QTc duration in healthy man. *Diabetologia*. 2000;43:571–575.
287. Peterson HR, Rothschild M, Weinberg CR, Fell RD, McLeish KR, Pfeifer MA. Body fat and the activity of the autonomic nervous system. *N Engl J Med*. 1988;318:1077–1083.
288. Hirsch J, Leibel RL, Mackintosh R, Aguirre A. Heart rate variability as a measure of autonomic function during weight change in humans. *Am J Physiol*. 1991;261:R1418–R1423.
289. Poirier P, Hernandez TL, Weil KM, Shepard TJ, Eckel RH. Impact of diet-induced weight loss on the cardiac autonomic nervous system in severe obesity. *Obes Res*. 2003;11:1040–1047.
290. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J*. 1987;113:1489–1494.
291. Seccareccia F, Pannozzo F, Dima F, Minoprio A, Menditto A, Lo Noce C, Giampaoli S; Malattie Cardiovascolari Aterosclerotiche Istituto Superiore di Sanita Project. Heart rate as a predictor of mortality: the MATISS project. *Am J Public Health*. 2001;91:1258–1263.
292. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet*. 1998;351:478–484.
293. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, Sullivan M, Wedel H; Swedish Obese Subjects Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med*. 2004;351:2683–2693.
294. Backman L, Freyschuss U, Hallberg D, Melcher A. Cardiovascular function in extreme obesity. *Acta Med Scand*. 1973;193:437–446.
295. MacMahon SW, Wilcken DE, Macdonald GJ. The effect of weight reduction on left ventricular mass: a randomized controlled trial in young, overweight hypertensive patients. *N Engl J Med*. 1986;314:334–339.
296. Himeno E, Nishino K, Nakashima Y, Kuroiwa A, Ikeda M. Weight reduction regresses left ventricular mass regardless of blood pressure level in obese subjects. *Am Heart J*. 1996;131:313–319.
297. Tuck ML, Sowers J, Dornfeld L, Kledzik G, Maxwell M. The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. *N Engl J Med*. 1981;304:930–933.
298. Sasson Z, Rasooly Y, Bhesania T, Rasooly I. Insulin resistance is an important determinant of left ventricular mass in the obese. *Circulation*. 1993;88:1431–1436.
299. Harp JB, Henry SA, DiGirolamo M. Dietary weight loss decreases serum angiotensin-converting enzyme activity in obese adults. *Obes Res*. 2002;10:985–990.
300. Lantigua RA, Amatruda JM, Biddle TL, Forbes GB, Lockwood DH. Cardiac arrhythmias associated with a liquid protein diet for the treatment of obesity. *N Engl J Med*. 1980;303:735–738.
301. Singh BN, Gaarder TD, Kanegae T, Goldstein M, Montgomerie JZ, Mills H. Liquid protein diets and torsade de pointes. *JAMA*. 1978;240:115–119.
302. From the Centers for Disease Control and Prevention. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: US Department of Health and Human Services interim public health recommendations. *JAMA*. 1997;278:1729–1731.
303. Robioli PA, Rigolin VH, Wilson JS, Harrison JK, Sanders LL, Bashore TM, Feldman JM. Carcinoid heart disease: correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. *Circulation*. 1995;92:790–795.
304. Redfield MM, Nicholson WJ, Edwards WD, Tajik AJ. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. *Ann Intern Med*. 1992;117:50–52.
305. Ryan DH, Bray GA, Helmecke F, Sander G, Volaufova J, Greenway F, Subramaniam P, Glancy DL. Serial echocardiographic and clinical evaluation of valvular regurgitation before, during, and after treatment with

- fenfluramine or dexfenfluramine and mazindol or phentermine. *Obes Res.* 1999;7:313–322.
306. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, Schaff HV. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med.* 1997;337:581–588.
 307. Weissman NJ, Tighe JFJ, Gottdiener JS, Gwynne JT. An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo: Sustained-Release Dexfenfluramine Study Group. *N Engl J Med.* 1998;339:725–732.
 308. Khan MA, Herzog CA, St Peter JV, Hartley GG, Madlon-Kay R, Dick CD, Asinger RW, Vessey JT. The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. *N Engl J Med.* 1998;339:713–718.
 309. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C, Wouters E, Aubier M, Simonneau G, Begaud B. Appetite-suppressant drugs and the risk of primary pulmonary hypertension: International Primary Pulmonary Hypertension Study Group. *N Engl J Med.* 1996;335:609–616.
 310. Jick H, Vasilakis C, Weinrauch LA, Meier CR, Jick SS, Derby LE. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. *N Engl J Med.* 1998;339:719–724.
 311. Weissman NJ, Panza JA, Tighe JF, Gwynne JT. Natural history of valvular regurgitation 1 year after discontinuation of dexfenfluramine therapy: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 2001;134:267–273.
 312. Mast ST, Jollis JG, Ryan T, Anstrom KJ, Crary JL. The progression of fenfluramine-associated valvular heart disease assessed by echocardiography. *Ann Intern Med.* 2001;134:261–266.
 313. Cannistra LB, Cannistra A. Regression of multivalvular regurgitation after the cessation of fenfluramine and phentermine treatment. *N Engl J Med.* 1998;339:771.
 314. Gardin JM, Schumacher D, Constantine G, Davis KD, Leung C, Reid CL. Valvular abnormalities and cardiovascular status following exposure to dexfenfluramine or phentermine/fenfluramine. *JAMA.* 2000;283:1703–1709.
 315. Gardin JM, Weissman NJ, Leung C, Panza JA, Fernicola D, Davis KD, Constantine GD, Reid CL. Clinical and echocardiographic follow-up of patients previously treated with dexfenfluramine or phentermine/fenfluramine. *JAMA.* 2001;286:2011–2014.
 316. Palmieri V, Arnett DK, Roman MJ, Liu JE, Bella JN, Oberman A, Kitzman DW, Hopkins PN, Morgan D, de Simone G, Devereux RB. Appetite suppressants and valvular heart disease in a population-based sample: the HyperGEN study. *Am J Med.* 2002;112:710–715.
 317. Davidoff R, McTiernan A, Constantine G, Davis KD, Balady GJ, Mendes LA, Rudolph RE, Bowen DJ. Echocardiographic examination of women previously treated with fenfluramine: long-term follow-up of a randomized, double-blind, placebo-controlled trial. *Arch Intern Med.* 2001;161:1429–1436.
 318. Sjostrom L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, Krempf M. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients: European Multicentre Orlistat Study Group. *Lancet.* 1998;352:167–172.
 319. James WP, Astrup A, Finer N, Hilsted J, Kopelman P, Rossner S, Saris WH, Van Gaal LF. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group: Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet.* 2000;356:2119–2125.
 320. McNeely W, Goa KL. Sibutramine: a review of its contribution to the management of obesity. *Drugs.* 1998;56:1093–1124.
 321. Bach DS, Rissanen AM, Mendel CM, Shepherd G, Weinstein SP, Kelly F, Seaton TB, Patel B, Pekkarinen TA, Armstrong WF. Absence of cardiac valve dysfunction in obese patients treated with sibutramine. *Obes Res.* 1999;7:363–369.
 322. Zannad F, Gille B, Grentzinger A, Bruntz JF, Hammadi M, Boivin JM, Hanotin C, Igau B, Drouin P. Effects of sibutramine on ventricular dimensions and heart valves in obese patients during weight reduction. *Am Heart J.* 2002;144:508–515.
 323. Atkinson RL. Use of drugs in the treatment of obesity. *Annu Rev Nutr.* 1997;17:383–403.
 324. Wang F, Schultz AB, Musich S, McDonald T, Hirschland D, Edington DW. The relationship between National Heart, Lung, and Blood Institute Weight Guidelines and concurrent medical costs in a manufacturing population. *Am J Health Promot.* 2003;17:183–189.
 325. Cornier MA, Tate CW, Grunwald GK, Bessesen DH. Relationship between waist circumference, body mass index, and medical care costs. *Obes Res.* 2002;10:1167–1172.
 326. Narbro K, Agren G, Jonsson E, Naslund I, Sjostrom L, Peltonen M; Swedish Obese Subjects Intervention Study. Pharmaceutical costs in obese individuals: comparison with a randomly selected population sample and long-term changes after conventional and surgical treatment: the SOS intervention study. *Arch Intern Med.* 2002;162:2061–2069.
 327. Agren G, Narbro K, Naslund I, Sjostrom L, Peltonen M. Long-term effects of weight loss on pharmaceutical costs in obese subjects: a report from the SOS intervention study. *Int J Obes Relat Metab Disord.* 2002;26:184–192.
 328. Sampalis JS, Liberman M, Auger S, Christou NV. The impact of weight reduction surgery on health-care costs in morbidly obese patients. *Obes Surg.* 2004;14:939–947.
 329. Mitchell BM, Gutin B, Kapuku G, Barbeau P, Humphries MC, Owens S, Vemulapalli S, Allison J. Left ventricular structure and function in obese adolescents: relations to cardiovascular fitness, percent body fat, and visceral adiposity, and effects of physical training. *Pediatrics.* 2002;109:E73.
 330. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med.* 2002;347:1483–1492.
 331. Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr.* 1999;69:373–380.
 332. Gregg EW, Gerzoff RB, Thompson TJ, Williamson DF. Intentional weight loss and death in overweight and obese US adults 35 years of age and older. *Ann Intern Med.* 2003;138:383–389.
 333. Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective study of intentional weight loss and mortality in never-smoking overweight US white women aged 40–64 years. *Am J Epidemiol.* 1995;141:1128–1141.
 334. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care.* 2000;23:1499–1504.